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# METHODS AND COMPOSITIONS USING IMMUNOMODULATORY COMPOUNDS FOR TREATMENT AND MANAGEMENT OF CANCERS AND OTHER DISEASES

This application claims the benefit of U.S. provisional application nos. 60/380,842, filed May 17, 2002, and 60/424,600, filed November 6, 2002, the entireties of which are incorporated herein by reference.

## 1. FIELD OF THE INVENTION

This invention relates to methods of treating, preventing and/or managing specific cancers, and other diseases including, but not limited to, those associated with, or characterized by, undesired angiogenesis, by the administration of one or more immunomodulatory compounds alone or in combination with other therapeutics. In particular, the invention encompasses the use of specific combinations, or "cocktails," of drugs and other therapy, *e.g.*, radiation to treat these specific cancers, including those refractory to conventional therapy. The invention also relates to pharmaceutical compositions and dosing regimens.

## 2. BACKGROUND OF THE INVENTION

### 2.1 PATHOBIOLOGY OF CANCER AND OTHER DISEASES

Cancer is characterized primarily by an increase in the number of abnormal cells derived from a given normal tissue, invasion of adjacent tissues by these abnormal cells, or lymphatic or blood-borne spread of malignant cells to regional lymph nodes and to distant sites (metastasis). Clinical data and molecular biologic studies indicate that cancer is a multistep process that begins with minor preneoplastic changes, which may under certain conditions progress to neoplasia. The neoplastic lesion may evolve clonally and develop an increasing capacity for invasion, growth, metastasis, and heterogeneity, especially under conditions in which the neoplastic cells escape the host's immune surveillance. Roitt, I., Brostoff, J and Kale, D., *Immunology*, 17.1-17.12 (3rd ed., Mosby, St. Louis, Mo., 1993).

There is an enormous variety of cancers which are described in detail in the medical literature. Examples includes cancer of the lung, colon, rectum, prostate, breast, brain, and intestine. The incidence of cancer continues to climb as the general population ages, as new cancers develop, and as susceptible populations (*e.g.*, people infected with AIDS or excessively exposed to sunlight) grow. A tremendous demand therefore exists for new methods and compositions that can be used to treat patients with cancer.

Many types of cancers are associated with new blood vessel formation, a process known as angiogenesis. Several of the mechanisms involved in tumor-induced angiogenesis have been elucidated. The most direct of these mechanisms is the secretion by the tumor cells of cytokines with angiogenic properties. Examples of these cytokines include acidic and basic fibroblastic growth factor (a,b-FGF), angiogenin, vascular endothelial growth factor (VEGF), and TNF-$\alpha$. Alternatively, tumor cells can release angiogenic peptides through the production of proteases and the subsequent breakdown of the extracellular matrix where some cytokines are stored (*e.g.*, b-FGF). Angiogenesis can also be induced indirectly through the recruitment of inflammatory cells (particularly macrophages) and their subsequent release of angiogenic cytokines (*e.g.*, TNF-$\alpha$, bFGF).

A variety of other diseases and disorders are also associated with, or characterized by, undesired angiogenesis. For example, enhanced or unregulated angiogenesis has been implicated in a number of diseases and medical conditions including, but not limited to, ocular neovascular diseases, choroidal neovascular diseases, retina neovascular diseases, rubeosis (neovascularization of the angle), viral diseases, genetic diseases, inflammatory diseases, allergic diseases, and autoimmune diseases. Examples of such diseases and conditions include, but are not limited to: diabetic retinopathy; retinopathy of prematurity; corneal graft rejection; neovascular glaucoma; retrolental fibroplasia; and proliferative vitreoretinopathy.

Accordingly, compounds that can control angiogenesis or inhibit the production of certain cytokines, including TNF-$\alpha$, may be useful in the treatment and prevention of various diseases and conditions.

## 2.2 METHODS OF TREATING CANCER

Current cancer therapy may involve surgery, chemotherapy, hormonal therapy and/or radiation treatment to eradicate neoplastic cells in a patient (see, for example, Stockdale, 1998, *Medicine*, vol. 3, Rubenstein and Federman, eds., Chapter 12, Section IV). Recently, cancer therapy could also involve biological therapy or immunotherapy. All of these approaches pose significant drawbacks for the patient. Surgery, for example, may be contraindicated due to the health of a patient or may be unacceptable to the patient. Additionally, surgery may not completely remove neoplastic tissue. Radiation therapy is only effective when the neoplastic tissue exhibits a higher sensitivity to radiation than normal tissue. Radiation therapy can also often elicit serious side effects. Hormonal therapy is rarely given as a single agent. Although hormonal therapy can be effective, it is often used to prevent or delay recurrence of cancer after other treatments have removed the

majority of cancer cells. Biological therapies and immunotherapies are limited in number and may produce side effects such as rashes or swellings, flu-like symptoms, including fever, chills and fatigue, digestive tract problems or allergic reactions.

With respect to chemotherapy, there are a variety of chemotherapeutic agents available for treatment of cancer. A majority of cancer chemotherapeutics act by inhibiting DNA synthesis, either directly, or indirectly by inhibiting the biosynthesis of deoxyribonucleotide triphosphate precursors, to prevent DNA replication and concomitant cell division. Gilman et al., *Goodman and Gilman's: The Pharmacological Basis of Therapeutics*, Tenth Ed. (McGraw Hill, New York).

Despite availability of a variety of chemotherapeutic agents, chemotherapy has many drawbacks. Stockdale, *Medicine*, vol. 3, Rubenstein and Federman, eds., ch. 12, sect. 10, 1998. Almost all chemotherapeutic agents are toxic, and chemotherapy causes significant, and often dangerous side effects including severe nausea, bone marrow depression, and immunosuppression. Additionally, even with administration of combinations of chemotherapeutic agents, many tumor cells are resistant or develop resistance to the chemotherapeutic agents. In fact, those cells resistant to the particular chemotherapeutic agents used in the treatment protocol often prove to be resistant to other drugs, even if those agents act by different mechanism from those of the drugs used in the specific treatment. This phenomenon is referred to as pleiotropic drug or multidrug resistance. Because of the drug resistance, many cancers prove refractory to standard chemotherapeutic treatment protocols.

Other diseases or conditions associated with, or characterized by, undesired angiogenesis are also difficult to treat. However, some compounds such as protamine, hepain and steroids have been proposed to be useful in the treatment of certain specific diseases. Taylor et al., *Nature* 297:307 (1982); Folkman et al., *Science* 221:719 (1983); and U.S. Pat. Nos. 5,001,116 and 4,994,443. Thalidomide and certain derivatives of it have also been proposed for the treatment of such diseases and conditions. U.S. patent nos. 5,593,990, 5,629,327, 5,712,291, 6,071,948 and 6,114,355 to D'Amato.

Still, there is a significant need for safe and effective methods of treating, preventing and managing cancer and other diseases and conditions, particularly for diseases that are refractory to standard treatments, such as surgery, radiation therapy, chemotherapy and hormonal therapy, while reducing or avoiding the toxicities and/or side effects associated with the conventional therapies.

## 2.3 IMIDS™

A number of studies have been conducted with the aim of providing compounds that can safely and effectively be used to treat diseases associated with abnormal production of TNF-α. *See, e.g.*, Marriott, J.B., *et al.*, *Expert Opin. Biol. Ther.* 1(4):1-8 (2001); G.W. Muller, *et al.*, Journal of Medicinal Chemistry 39(17): 3238-3240 (1996); and G.W. Muller, *et al.*, Bioorganic & Medicinal Chemistry Letters 8: 2669-2674 (1998). Some studies have focused on a group of compounds selected for their capacity to potently inhibit TNF-α production by LPS stimulated PBMC. L.G. Corral, *et al.*, Ann. Rheum. Dis. 58:(Suppl I) 1107-1113 (1999). These compounds, which are referred to as IMiDs™ (Celgene Corporation) or Immunomodulatory Drugs, show not only potent inhibition of TNF-α but also marked inhibition of LPS induced monocyte IL1ß and IL12 production. LPS induced IL6 is also inhibited by immunomodulatory compounds, *albeit* partially. These compounds are potent stimulators of LPS induced IL10. *Id.* Particular examples of IMiD™s include, but are not limited to, the substituted 2-(2,6-dioxopiperidin-3-yl) phthalimides and substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindoles described in United States Patent Nos. 6,281,230 and 6,316,471, both to G.W. Muller, *et al.*

## 3. SUMMARY OF THE INVENTION

This invention encompasses methods of treating and preventing certain types of cancer, including primary and metastatic cancer, as well as cancers that are refractory or resistant to conventional chemotherapy. The methods comprise administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof. The invention also encompasses methods of managing certain cancers (*e.g.*, preventing or prolonging their recurrence, or lengthening the time of remission) which comprise administering to a patient in need of such management a prophylactically effective amount of an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

In particular methods of the invention, an immunomodulatory compound is administered in combination with a therapy conventionally used to treat, prevent or manage cancer. Examples of such conventional therapies include, but are not limited to, surgery, chemotherapy, radiation therapy, hormonal therapy, biological therapy and immunotherapy.

This invention also encompasses methods of treating, managing or preventing diseases and disorders other than cancer that are associated with, or characterized by,

undesired angiogenesis, which comprise administering to a patient in need of such treatment, management or prevention a therapeutically or prophylactically effective amount of an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

In other methods of the invention, an immunomodulatory compound is administered in combination with a therapy conventionally used to treat, prevent or manage diseases or disorders associated with, or characterized by, undesired angiogenesis. Examples of such conventional therapies include, but are not limited to, surgery, chemotherapy, radiation therapy, hormonal therapy, biological therapy and immunotherapy.

This invention encompasses pharmaceutical compositions, single unit dosage forms, dosing regimens and kits which comprise an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, and a second, or additional, active agent. Second active agents include specific combinations, or "cocktails," of drugs.

## 4. BRIEF DESCRIPTION OF FIGURE

Figure 1 shows a comparison of the effects of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revimid™) and thalidomide in inhibiting the proliferation of multiple myeloma (MM) cell lines in an *in vitro* study. The uptake of [$^3$H]-thymidine by different MM cell lines (MM.1S, Hs Sultan, U266 and RPMI-8226) was measured as an indicator of the cell proliferation.

## 5. DETAILED DESCRIPTION OF THE INVENTION

A first embodiment of the invention encompasses methods of treating, managing, or preventing cancer which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

In particular methods encompassed by this embodiment, the immunomodulatory compound is administered in combination with another drug ("second active agent") or method of treating, managing, or preventing cancer. Second active agents include small molecules and large molecules (*e.g.*, proteins and antibodies), examples of which are provided herein, as well as stem cells. Methods, or therapies, that can be used in combination with the administration of the immunomodulatory compound include, but are not limited to, surgery, blood transfusions, immunotherapy, biological therapy, radiation

therapy, and other non-drug based therapies presently used to treat, prevent or manage cancer.

Another embodiment of the invention encompasses methods of treating, managing or preventing diseases and disorders other than cancer that are characterized by undesired angiogenesis. These methods comprise the administration of a therapeutically or prophylactically effective amount of an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

Examples of diseases and disorders associated with, or characterized by, undesired angiogenesis include, but are not limited to, inflammatory diseases, autoimmune diseases, viral diseases, genetic diseases, allergic diseases, bacterial diseases, ocular neovascular diseases, choroidal neovascular diseases, retina neovascular diseases, and rubeosis (neovascularization of the angle).

In particular methods encompassed by this embodiment, the immunomodulatory compound is administer in combination with a second active agent or method of treating, managing, or preventing the disease or condition. Second active agents include small molecules and large molecules (*e.g.*, proteins and antibodies), examples of which are provided herein, as well as stem cells. Methods, or therapies, that can be used in combination with the administration of the immunomodulatory compound include, but are not limited to, surgery, blood transfusions, immunotherapy, biological therapy, radiation therapy, and other non-drug based therapies presently used to treat, prevent or manage disease and conditions associated with, or characterized by, undesired angiogenesis.

The invention also encompasses pharmaceutical compositions (*e.g.*, single unit dosage forms) that can be used in methods disclosed herein. Particular pharmaceutical compositions comprise an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, and a second active agent.

## 5.1 IMMUNOMODULATORY COMPOUNDS

Compounds used in the invention include immunomodulatory compounds that are racemic, stereomerically enriched or stereomerically pure, and pharmaceutically acceptable salts, solvates, hydrates, stereoisomers, clathrates, and prodrugs thereof. Preferred compounds used in the invention are small organic molecules having a molecular weight less than about 1,000 g/mol, and are not proteins, peptides, oligonucleotides, oligosaccharides or other macromolecules.

As used herein and unless otherwise indicated, the terms "immunomodulatory compounds" and "IMiDs™" (Celgene Corporation) encompasses small organic molecules that markedly inhibit TNF-α, LPS induced monocyte IL1ß and IL12, and partially inhibit IL6 production. Specific immunomodulatory compounds are discussed below.

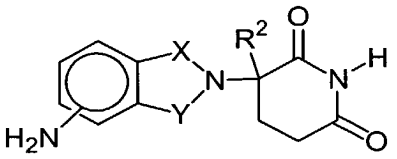
TNF-α is an inflammatory cytokine produced by macrophages and monocytes during acute inflammation. TNF-α is responsible for a diverse range of signaling events within cells. TNF-α may play a pathological role in cancer. Without being limited by theory, one of the biological effects exerted by the immunomodulatory compounds of the invention is the reduction of synthesis of TNF-α. Immunomodulatory compounds of the invention enhance the degradation of TNF-α mRNA.

Further, without being limited by theory, immunomodulatory compounds used in the invention may also be potent co-stimulators of T cells and increase cell proliferation dramatically in a dose dependent manner. Immunomodulatory compounds of the invention may also have a greater co-stimulatory effect on the CD8+ T cell subset than on the CD4+ T cell subset. In addition, the compounds preferably have anti-inflammatory properties, and efficiently co-stimulate T cells.

Specific examples of immunomodulatory compounds of the invention, include, but are not limited to, cyano and carboxy derivatives of substituted styrenes such as those disclosed in U.S. patent no. 5,929,117; 1-oxo-2-(2,6-dioxo-3-fluoropiperidin-3yl) isoindolines and 1,3-dioxo-2-(2,6-dioxo-3-fluoropiperidine-3-yl) isoindolines such as those described in U.S. patent no. 5,874,448; the tetra substituted 2-(2,6-dioxopiperdin-3-yl)-1-oxoisoindolines described in U.S. patent no. 5,798,368; 1-oxo and 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl) isoindolines (*e.g.*, 4-methyl derivatives of thalidomide and EM-12), including, but not limited to, those disclosed in U.S. patent no. 5,635,517; and a class of non-polypeptide cyclic amides disclosed in U.S. patent nos. 5,698,579 and 5,877,200; analogs and derivatives of thalidomide, including hydrolysis products, metabolites, derivatives and precursors of thalidomide, such as those described in U.S. patent nos. 5,593,990, 5,629,327, and 6,071,948 to D'Amato; aminothalidomide, as well as analogs, hydrolysis products, metabolites, derivatives and precursors of aminothalidomide, and substituted 2-(2,6-dioxopiperidin-3-yl) phthalimides and substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindoles such as those described in U.S. patent nos. 6,281,230 and 6,316,471; isoindole-imide compounds such as those described in U.S. patent application no. 09/972,487 filed on October 5, 2001, U.S. patent application no. 10/032,286 filed on December 21, 2001, and International Application No. PCT/US01/50401 (International Publication No. WO 02/059106). The entireties of each of the patents and patent

applications identified herein are incorporated herein by reference. Immunomodulatory compounds of the invention do not include thalidomide.

Other specific immunomodulatory compounds of the invention include, but are not limited to, 1-oxo-and 1,3 dioxo-2-(2,6-dioxopiperidin-3-yl) isoindolines substituted with amino in the benzo ring as described in U.S. Patent no. 5,635,517 which is incorporated herein by reference. These compounds have the structure I:



I

in which one of X and Y is C=O, the other of X and Y is C=O or $CH_2$, and $R^2$ is hydrogen or lower alkyl, in particular methyl. Specific immunomodulatory compounds include, but are not limited to:

1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline;

1-oxo-2-(2,6-dioxopiperidin-3-yl)-5-aminoisoindoline;

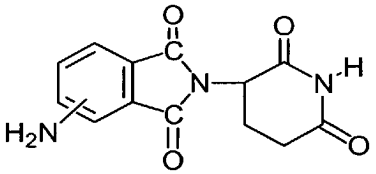
1-oxo-2-(2,6-dioxopiperidin-3-yl)-6-aminoisoindoline;

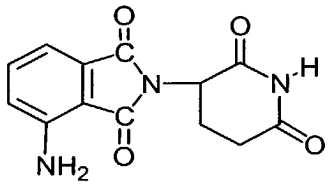
1-oxo-2-(2,6-dioxopiperidin-3-yl)-7-aminoisoindoline;

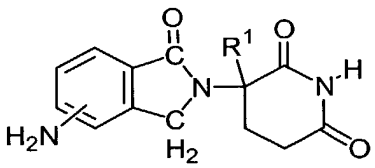
1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline; and

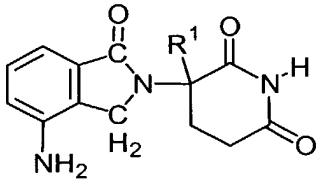
1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-5-aminoisoindoline.

Other specific immunomodulatory compounds of the invention belong to a class of substituted 2-(2,6-dioxopiperidin-3-yl) phthalimides and substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindoles, such as those described in U.S. patent nos. 6,281,230; 6,316,471; 6,335,349; and 6,476,052, and International Patent Application No. PCT/US97/13375 (International Publication No. WO 98/03502), each of which is incorporated herein by reference. Compounds representative of this class are of the formulas:



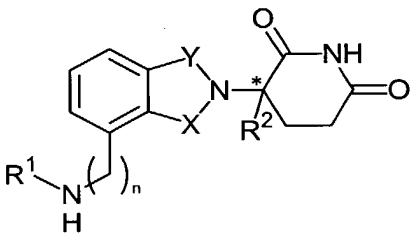






wherein $R^1$ is hydrogen or methyl. In a separate embodiment, the invention encompasses the use of enantiomerically pure forms (*e.g.* optically pure (R) or (S) enantiomers) of these compounds.

Still other specific immunomodulatory compounds of the invention belong to a class of isoindole-imides disclosed in U.S. patent application nos. 10/032,286 and 09/972,487, and International Application No. PCT/US01/50401 (International Publication No. WO 02/059106), each of which are incorporated herein by reference. Representative compounds are of formula II:



II

and pharmaceutically acceptable salts, hydrates, solvates, clathrates, enantiomers, diastereomers, racemates, and mixtures of stereoisomers thereof, wherein:

one of X and Y is C=O and the other is $CH_2$ or C=O;

$R^1$ is H, $(C_1–C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, benzyl, aryl, $(C_0$-$C_4)$alkyl–$(C_1$-$C_6)$heterocycloalkyl, $(C_0$-$C_4)$alkyl–$(C_2$-$C_5)$heteroaryl, $C(O)R^3$, $C(S)R^3$, $C(O)OR^4$, $(C_1$-$C_8)$alkyl–$N(R^6)_2$, $(C_1$-$C_8)$alkyl–$OR^5$, $(C_1$-$C_8)$alkyl–$C(O)OR^5$, $C(O)NHR^3$, $C(S)NHR^3$, $C(O)NR^3R^{3'}$, $C(S)NR^3R^{3'}$ or $(C_1$-$C_8)$alkyl–$O(CO)R^5$;

$R^2$ is H, F, benzyl, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, or $(C_2$-$C_8)$alkynyl;

$R^3$ and $R^{3'}$ are independently $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$cycloalkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, benzyl, aryl, $(C_0$-$C_4)$alkyl–$(C_1$-$C_6)$heterocycloalkyl, $(C_0$-$C_4)$alkyl–$(C_2$-$C_5)$heteroaryl, $(C_0$-$C_8)$alkyl–$N(R^6)_2$, $(C_1$-$C_8)$alkyl–$OR^5$, $(C_1$-$C_8)$alkyl–$C(O)OR^5$, $(C_1$-$C_8)$alkyl–$O(CO)R^5$, or $C(O)OR^5$;

$R^4$ is $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_4)$alkyl–$OR^5$, benzyl, aryl, $(C_0$-$C_4)$alkyl–$(C_1$-$C_6)$heterocycloalkyl, or $(C_0$-$C_4)$alkyl–$(C_2$-$C_5)$heteroaryl;

$R^5$ is $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, benzyl, aryl, or $(C_2\text{-}C_5)$heteroaryl;

each occurrence of $R^6$ is independently H, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, benzyl, aryl, $(C_2\text{-}C_5)$heteroaryl, or $(C_0\text{-}C_8)$alkyl–C(O)O–$R^5$ or the $R^6$ groups can join to form a heterocycloalkyl group;

n is 0 or 1; and

* represents a chiral-carbon center.

In specific compounds of formula II, when n is 0 then $R^1$ is $(C_3\text{-}C_7)$cycloalkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, benzyl, aryl, $(C_0\text{-}C_4)$alkyl–$(C_1\text{-}C_6)$heterocycloalkyl, $(C_0\text{-}C_4)$alkyl-$(C_2\text{-}C_5)$heteroaryl, C(O)$R^3$, C(O)O$R^4$, $(C_1\text{-}C_8)$alkyl–N$(R^6)_2$, $(C_1\text{-}C_8)$alkyl–O$R^5$, $(C_1\text{-}C_8)$alkyl–C(O)O$R^5$, C(S)NH$R^3$, or $(C_1\text{-}C_8)$alkyl–O(CO)$R^5$;

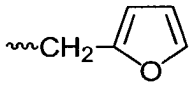
$R^2$ is H or $(C_1\text{-}C_8)$alkyl; and

$R^3$ is $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, benzyl, aryl, $(C_0\text{-}C_4)$alkyl–$(C_1$ –$C_6)$heterocycloalkyl, $(C_0\text{-}C_4)$alkyl–$(C_2\text{-}C_5)$heteroaryl, $(C_5\text{-}C_8)$alkyl–N$(R^6)_2$ ; $(C_0\text{-}C_8)$alkyl–NH–C(O)O–$R^5$; $(C_1\text{-}C_8)$alkyl–O$R^5$, $(C_1\text{-}C_8)$alkyl–C(O)O$R^5$, $(C_1\text{-}C_8)$alkyl–O(CO)$R^5$, or C(O)O$R^5$; and the other variables have the same definitions.

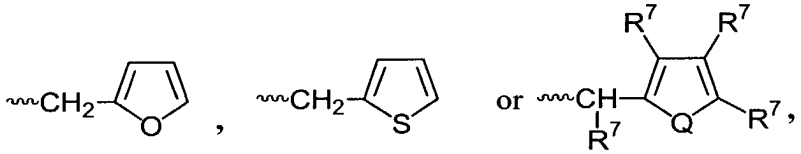
In other specific compounds of formula II, $R^2$ is H or $(C_1\text{-}C_4)$alkyl.

In other specific compounds of formula II, $R^1$ is $(C_1\text{-}C_8)$alkyl or benzyl.

In other specific compounds of formula II, $R^1$ is H, $(C_1\text{-}C_8)$alkyl, benzyl, $CH_2OCH_3$, $CH_2CH_2OCH_3$, or



In another embodiment of the compounds of formula II, $R^1$ is



wherein Q is O or S, and each occurrence of $R^7$ is independently H, $(C_1\text{-}C_8)$alkyl, benzyl, $CH_2OCH_3$, or $CH_2CH_2OCH_3$.

In other specific compounds of formula II, $R^1$ is C(O)$R^3$.

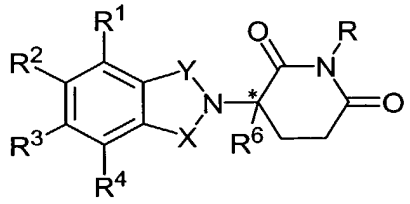
In other specific compounds of formula II, $R^3$ is $(C_0\text{-}C_4)$alkyl–$(C_2\text{-}C_5)$heteroaryl, $(C_1\text{-}C_8)$alkyl, aryl, or $(C_0\text{-}C_4)$alkyl–O$R^5$.

In other specific compounds of formula II, heteroaryl is pyridyl, furyl, or thienyl.

In other specific compounds of formula II, $R^1$ is C(O)O$R^4$.

In other specific compounds of formula II, the H of C(O)NHC(O) can be replaced with $(C_1\text{-}C_4)$alkyl, aryl, or benzyl.

Still other specific immunomodulatory compounds of the invention belong to a class of isoindole-imides disclosed in U.S. patent application no. 09/781,179, International Publication No. WO 98/54170, and United States Patent No. 6,395,754, each of which are incorporated herein by reference. Representative compounds are of formula III:



III

and pharmaceutically acceptable salts, hydrates, solvates, clathrates, enantiomers, diastereomers, racemates, and mixtures of stereoisomers thereof, wherein:

one of X and Y is C=O and the other is $CH_2$ or C=O;

R is H or $CH_2OCOR'$;

(i) each of $R^1$, $R^2$, $R^3$, or $R^4$, independently of the others, is halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms or (ii) one of $R^1$, $R^2$, $R^3$, or $R^4$ is nitro or $-NHR^5$ and the remaining of $R^1$, $R^2$, $R^3$, or $R^4$ are hydrogen;

$R^5$ is hydrogen or alkyl of 1 to 8 carbons

$R^6$ hydrogen, alkyl of 1 to 8 carbon atoms, benzo, chloro, or fluoro;

R' is $R^7$-$CHR^{10}$-$N(R^8R^9)$;

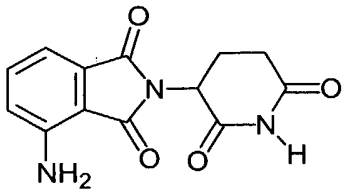
$R^7$ is m-phenylene or p-phenylene or $-(C_n H_{2n})-$ in which n has a value of 0 to 4;

each of $R^8$ and $R^9$ taken independently of the other is hydrogen or alkyl of 1 to 8 carbon atoms, or $R^8$ and $R^9$ taken together are tetramethylene, pentamethylene, hexamethylene, or $-CH_2CH_2[X]X_1CH_2CH_2-$ in which $[X]X_1$ is -O-, -S-, or -NH-;

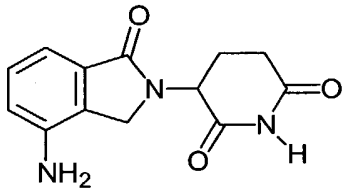
$R^{10}$ is hydrogen, alkyl of to 8 carbon atoms, or phenyl; and

* represents a chiral-carbon center.

The most preferred immunomodulatory compounds of the invention are 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione and 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione. The compounds can be obtained via standard, synthetic methods (*see e.g.*, United States Patent No. 5,635,517, incorporated herein by reference). The compounds are available from Celgene Corporation, Warren, NJ. 4-(Amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione (ACTIMID™) has the following chemical structure:



The compound 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (REVIMID™) has the following chemical structure:



Compounds of the invention can either be commercially purchased or prepared according to the methods described in the patents or patent publications disclosed herein. Further, optically pure compounds can be asymmetrically synthesized or resolved using known resolving agents or chiral columns as well as other standard synthetic organic chemistry techniques.

As used herein and unless otherwise indicated, the term "pharmaceutically acceptable salt" encompasses non-toxic acid and base addition salts of the compound to which the term refers. Acceptable non-toxic acid addition salts include those derived from organic and inorganic acids or bases know in the art, which include, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulphonic acid, acetic acid, tartaric acid, lactic acid, succinic acid, citric acid, malic acid, maleic acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid, embolic acid, enanthic acid, and the like.

Compounds that are acidic in nature are capable of forming salts with various pharmaceutically acceptable bases. The bases that can be used to prepare pharmaceutically acceptable base addition salts of such acidic compounds are those that form non-toxic base addition salts, *i.e.,* salts containing pharmacologically acceptable cations such as, but not limited to, alkali metal or alkaline earth metal salts and the calcium, magnesium, sodium or potassium salts in particular. Suitable organic bases include, but are not limited to, N,N-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumaine (N-methylglucamine), lysine, and procaine.

As used herein and unless otherwise indicated, the term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (*in vitro* or *in vivo*) to provide the compound. Examples of prodrugs include, but are not limited to, derivatives of immunomodulatory compounds of the invention that

comprise biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Other examples of prodrugs include derivatives of immunomodulatory compounds of the invention that comprise -NO, $-NO_2$, -ONO, or $-ONO_2$ moieties. Prodrugs can typically be prepared using well-known methods, such as those described in 1 *Burger's Medicinal Chemistry and Drug Discovery*, 172-178, 949-982 (Manfred E. Wolff *ed.*, 5th ed. 1995), and *Design of Prodrugs* (H. Bundgaard ed., Elselvier, New York 1985).

As used herein and unless otherwise indicated, the terms "biohydrolyzable amide," "biohydrolyzable ester," "biohydrolyzable carbamate," "biohydrolyzable carbonate," "biohydrolyzable ureide," "biohydrolyzable phosphate" mean an amide, ester, carbamate, carbonate, ureide, or phosphate, respectively, of a compound that either: 1) does not interfere with the biological activity of the compound but can confer upon that compound advantageous properties *in vivo*, such as uptake, duration of action, or onset of action; or 2) is biologically inactive but is converted *in vivo* to the biologically active compound. Examples of biohydrolyzable esters include, but are not limited to, lower alkyl esters, lower acyloxyalkyl esters (such as acetoxylmethyl, acetoxyethyl, aminocarbonyloxymethyl, pivaloyloxymethyl, and pivaloyloxyethyl esters), lactonyl esters (such as phthalidyl and thiophthalidyl esters), lower alkoxyacyloxyalkyl esters (such as methoxycarbonyl-oxymethyl, ethoxycarbonyloxyethyl and isopropoxycarbonyloxyethyl esters), alkoxyalkyl esters, choline esters, and acylamino alkyl esters (such as acetamidomethyl esters). Examples of biohydrolyzable amides include, but are not limited to, lower alkyl amides, $\alpha$-amino acid amides, alkoxyacyl amides, and alkylaminoalkylcarbonyl amides. Examples of biohydrolyzable carbamates include, but are not limited to, lower alkylamines, substituted ethylenediamines, amino acids, hydroxyalkylamines, heterocyclic and heteroaromatic amines, and polyether amines.

Various immunomodulatory compounds of the invention contain one or more chiral centers, and can exist as racemic mixtures of enantiomers or mixtures of diastereomers. This invention encompasses the use of stereomerically pure forms of such compounds, as well as the use of mixtures of those forms. For example, mixtures comprising equal or unequal amounts of the enantiomers of a particular immunomodulatory compounds of the invention may be used in methods and compositions of the invention. These isomers may be asymmetrically synthesized or resolved using standard techniques such as chiral columns or chiral resolving agents. *See, e.g.*, Jacques, J., *et al., Enantiomers, Racemates and Resolutions* (Wiley-Interscience, New York, 1981); Wilen, S. H., *et al., Tetrahedron*

33:2725 (1977); Eliel, E. L., *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, S. H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

As used herein and unless otherwise indicated, the term "stereomerically pure" means a composition that comprises one stereoisomer of a compound and is substantially free of other stereoisomers of that compound. For example, a stereomerically pure composition of a compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure composition of a compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, more preferably greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, even more preferably greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, and most preferably greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound. As used herein and unless otherwise indicated, the term "stereomerically enriched" means a composition that comprises greater than about 60% by weight of one stereoisomer of a compound, preferably greater than about 70% by weight, more preferably greater than about 80% by weight of one stereoisomer of a compound. As used herein and unless otherwise indicated, the term "enantiomerically pure" means a stereomerically pure composition of a compound having one chiral center. Similarly, the term "stereomerically enriched" means a stereomerically enriched composition of a compound having one chiral center.

It should be noted that if there is a discrepancy between a depicted structure and a name given that structure, the depicted structure is to be accorded more weight. In addition, if the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it.

## 5.2 SECOND ACTIVE AGENTS

Immunomodulatory compounds can be combined with other pharmacologically active compounds ("second active agents") in methods and compositions of the invention. It is believed that certain combinations work synergistically in the treatment of particular

types of cancer and certain diseases and conditions associated with, or characterized by, undesired angiogenesis. Immunomodulatory compounds can also work to alleviate adverse effects associated with certain second active agents, and some second active agents can be used to alleviate adverse effects associated with immunomodulatory compounds.

One or more second active ingredients or agents can be used in the methods and compositions of the invention together with an immunomodulatory compound. Second active agents can be large molecules (*e.g.*, proteins) or small molecules (*e.g.*, synthetic inorganic, organometallic, or organic molecules).

Examples of large molecule active agents include, but are not limited to, hematopoietic growth factors, cytokines, and monoclonal and polyclonal antibodies. Typical large molecule active agents are biological molecules, such as naturally occurring or artificially made proteins. Proteins that are particularly useful in this invention include proteins that stimulate the survival and/or proliferation of hematopoietic precursor cells and immunologically active poietic cells *in vitro* or *in vivo*. Others stimulate the division and differentiation of committed erythroid progenitors in cells *in vitro* or *in vivo*. Particular proteins include, but are not limited to: interleukins, such as IL-2 (including recombinant IL-II ("rIL2") and canarypox IL-2), IL-10, IL-12, and IL-18; interferons, such as interferon alfa-2a, interferon alfa-2b, interferon alfa-n1, interferon alfa-n3, interferon beta-I a, and interferon gamma-I b; GM-CF and GM-CSF; and EPO.

Particular proteins that can be used in the methods and compositions of the invention include, but are not limited to: filgrastim, which is sold in the United States under the trade name Neupogen® (Amgen, Thousand Oaks, CA); sargramostim, which is sold in the United States under the trade name Leukine® (Immunex, Seattle, WA); and recombinant EPO, which is sold in the United States under the trade name Epogen® (Amgen, Thousand Oaks, CA).

Recombinant and mutated forms of GM-CSF can be prepared as described in U.S. patent nos. 5,391,485; 5,393,870; and 5,229,496; all of which are incorporated herein by reference. Recombinant and mutated forms of G-CSF can be prepared as described in U.S. patent nos. 4,810,643; 4,999,291; 5,528,823; and 5,580,755; all of which are incorporated herein by reference.

This invention encompasses the use of native, naturally occurring, and recombinant proteins. The invention further encompasses mutants and derivatives (*e.g.*, modified forms) of naturally occurring proteins that exhibit, *in vivo*, at least some of the pharmacological activity of the proteins upon which they are based. Examples of mutants include, but are

not limited to, proteins that have one or more amino acid residues that differ from the corresponding residues in the naturally occurring forms of the proteins. Also encompassed by the term "mutants" are proteins that lack carbohydrate moieties normally present in their naturally occurring forms (*e.g.*, nonglycosylated forms). Examples of derivatives include, but are not limited to, pegylated derivatives and fusion proteins, such as proteins formed by fusing IgG1 or IgG3 to the protein or active portion of the protein of interest. *See, e.g.*, Penichet, M.L. and Morrison, S.L., *J. Immunol. Methods* 248:91-101 (2001).

Antibodies that can be used in combination with compounds of the invention include monoclonal and polyclonal antibodies. Examples of antibodies include, but are not limited to, trastuzumab (Herceptin®), rituximab (Rituxan®),bevacizumab (Avastin™), pertuzumab (Omnitarg™), tositumomab (Bexxar®), edrecolomab (Panorex®), and G250. Compounds of the invention can also be combined with, or used in combination with, anti-TNF-$\alpha$ antibodies.

Large molecule active agents may be administered in the form of anti-cancer vaccines. For example, vaccines that secrete, or cause the secretion of, cytokines such as IL-2, G-CSF, and GM-CSF can be used in the methods, pharmaceutical compositions, and kits of the invention. *See, e.g.*, Emens, L.A., *et al.*, *Curr. Opinion Mol. Ther.* 3(1):77-84 (2001).

In one embodiment of the invention, the large molecule active agent reduces, eliminates, or prevents an adverse effect associated with the administration of an immunomodulatory compound. Depending on the particular immunomodulatory compound and the disease or disorder begin treated, adverse effects can include, but are not limited to, drowsiness and somnolence, dizziness and orthostatic hypotension, neutropenia, infections that result from neutropenia, increased HIV-viral load, bradycardia, Stevens-Johnson Syndrome and toxic epidermal necrolysis, and seizures (*e.g.*, grand mal convulsions). A specific adverse effect is neutropenia.

Second active agents that are small molecules can also be used to alleviate adverse effects associated with the administration of an immunomodulatory compound. However, like some large molecules, many are believed to be capable of providing a synergistic effect when administered with (*e.g.*, before, after or simultaneously) an immunomodulatory compound. Examples of small molecule second active agents include, but are not limited to, anti-cancer agents, antibiotics, immunosuppressive agents, and steroids.

Examples of anti-cancer agents include, but are not limited to: acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin;

ametantrone acetate; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; celecoxib (COX-2 inhibitor); chlorambucil; cirolemycin; cisplatin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; dactinomycin; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; docetaxel; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; ilmofosine; iproplatin; irinotecan; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran; paclitaxel; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; taxotere; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine

tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; and zorubicin hydrochloride.

Other anti-cancer drugs include, but are not limited to: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorlns; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin; diphenyl spiromustine; docetaxel; docosanol; dolasetron; doxifluridine; doxorubicin; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene;

idramantone; ilmofosine; ilomastat; imatinib (*e.g.*, Gleevec®), imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim;Erbitux, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; oblimersen (Genasense®); $O^6$-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII

retinamide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer.

Specific second active agents include, but are not limited to, oblimersen (Genasense®), remicade, docetaxel, celecoxib, melphalan, dexamethasone (Decadron®), steroids, gemcitabine, cisplatinum, temozolomide, etoposide, cyclophosphamide, temodar, carboplatin, procarbazine, gliadel, tamoxifen, topotecan, methotrexate, Arisa®, taxol, taxotere, fluorouracil, leucovorin, irinotecan, xeloda, CPT-11, interferon alpha, pegylated interferon alpha (*e.g.*, PEG INTRON-A), capecitabine, cisplatin, thiotepa, fludarabine, carboplatin, liposomal daunorubicin, cytarabine, doxetaxol, pacilitaxel, vinblastine, IL-2, GM-CSF, dacarbazine, vinorelbine, zoledronic acid, palmitronate, biaxin, busulphan, prednisone, bisphosphonate, arsenic trioxide, vincristine, doxorubicin (Doxil®), paclitaxel, ganciclovir, adriamycin, estramustine sodium phosphate (Emcyt®), sulindac, and etoposide.

## 5.3 METHODS OF TREATMENTS AND PREVENTION

Methods of this invention encompass methods of treating, preventing and/or managing various types of cancer and diseases and disorders associated with, or characterized by, undesired angiogenesis. As used herein, unless otherwise specified, the term "treating" refers to the administration of a compound of the invention or other additional active agent after the onset of symptoms of the particular disease or disorder. As used herein, unless otherwise specified, the term "preventing" refers to the administration

prior to the onset of symptoms, particularly to patients at risk of cancer, and other diseases and disorders associated with, or characterized by, undesired angiogenesis. The term "prevention" includes the inhibition of a symptom of the particular disease or disorder. Patients with familial history of cancer and diseases and disorders associated with, or characterized by, undesired angiogenesis are preferred candidates for preventive regimens. As used herein and unless otherwise indicated, the term "managing" encompasses preventing the recurrence of the particular disease or disorder in a patient who had suffered from it, and/or lengthening the time a patient who had suffered from the disease or disorder remains in remission.

As used herein, the term "cancer" includes, but is not limited to, solid tumors and blood born tumors. The term "cancer" refers to disease of skin tissues, organs, blood, and vessels, including, but not limited to, cancers of the bladder, bone or blood, brain, breast, cervix, chest, colon, endrometrium, esophagus, eye, head, kidney, liver, lymph nodes, lung, mouth, neck, ovaries, pancreas, prostate, rectum, stomach, testis, throat, and uterus. Specific cancers include, but are not limited to, advanced malignancy, amyloidosis, neuroblastoma, meningioma, hemangiopericytoma, multiple brain metastase, glioblastoma multiforms, glioblastoma, brain stem glioma, poor prognosis malignant brain tumor, malignant glioma, recurrent malignant giolma, anaplastic astrocytoma, anaplastic oligodendroglioma, neuroendocrine tumor, rectal adenocarcinoma, Dukes C & D colorectal cancer, unresectable colorectal carcinoma, metastatic hepatocellular carcinoma, Kaposi's sarcoma, karotype acute myeloblastic leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-Cell lymphoma, cutaneous B-Cell lymphoma, diffuse large B-Cell lymphoma, low grade follicular lymphoma, malignant melanoma, malignant mesothelioma, malignant pleural effusion mesothelioma syndrome, peritoneal carcinoma, papillary serous carcinoma, gynecologic sarcoma, soft tissue sarcoma, scelroderma, cutaneous vasculitis, Langerhans cell histiocytosis, leiomyosarcoma, fibrodysplasia ossificans progressive, hormone refractory prostate cancer, resected high-risk soft tissue sarcoma, unrescectable hepatocellular carcinoma, Waldenstrom's macroglobulinemia, smoldering myeloma, indolent myeloma, fallopian tube cancer, androgen independent prostate cancer, androgen dependent stage IV non-metastatic prostate cancer, hormone-insensitive prostate cancer, chemotherapy-insensitive prostate cancer, papillary thyroid carcinoma, follicular thyroid carcinoma, medullary thyroid carcinoma, and leiomyoma. In a specific embodiment, the cancer is metastatic. In another embodiment, the cancer is refractory or resistance to chemotherapy or radiation; in particular, refractory to thalidomide.

As used herein to refer to diseases and conditions other than cancer, the terms "diseases or disorders associated with, or characterized by, undesired angiogenesis," "diseases or disorders associated with undesired angiogenesis," and "diseases or disorders characterized by undesired angiogenesis" refer to diseases, disorders and conditions that are caused, mediated or attended by undesired, unwanted or uncontrolled angiogenesis, including, but not limited to, inflammatory diseases, autoimmune diseases, genetic diseases, allergic diseases, bacterial diseases, ocular neovascular diseases, choroidal neovascular diseases, and retina neovascular diseases.

Examples of such diseases or disorders associated with undesired angiogenesis include, but are not limited to, diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, proliferative vitreoretinopathy, trachoma, myopia, optic pits, epidemnic keratoconjunctivitis, atopic keratitis, superior limbic keratitis, pterygium keratitis sicca, sjogrens, acne rosacea, phylectenulosis, syphilis, lipid degeneration, bacterial ulcer, fungal ulcer, Herpes simplex infection, Herpes zoster infection, protozoan infection, Kaposi sarcoma, Mooren ulcer, Terrien's marginal degeneration, mariginal keratolysis, rheumatoid arthritis, systemic lupus, polyarteritis, trauma, Wegeners sarcoidosis, Scleritis, Steven's Johnson disease, periphigoid radial keratotomy, sickle cell anemia, sarcoid, pseudoxanthoma elasticum, Pagets disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic uveitis, chronic vitritis, Lyme's disease, Eales disease, Bechets disease, retinitis, choroiditis, presumed ocular histoplasmosis, Bests disease, Stargarts disease, pars planitis, chronic retinal detachment, hyperviscosity syndromes, toxoplasmosis, rubeosis, sarcodisis, sclerosis, soriatis, psoriasis, primary sclerosing cholangitis, proctitis, primary biliary srosis, idiopathic pulmonary fibrosis, and alcoholic hepatitis.

In specific embodiments of the invention, diseases or disorders associated with undesired angiogenesis do not include congestive heart failure, cardiomyopathy, pulmonary edema, endotoxin-mediated septic shock, acute viral myocarditis, cardiac allograft rejection, myocardial infarction, HIV, hepatitis, adult respiratory distress syndrome, bone-resorption disease, chronic obstructive pulmonary diseases, chronic pulmonary inflammatory disease, dermatitis, cystic fibrosis, septic shock, sepsis, endotoxic shock, hemodynamic shock, sepsis syndrome, post ischemic reperfusion injury, meningitis, psoriasis, fibrotic disease, cachexia, graft rejection, rheumatoid spondylitis, osteoporosis, Crohn's disease, ulcerative colitis, inflammatory-bowel disease, multiple sclerosis, systemic lupus erythrematosus,

erythema nodosum leprosum in leprosy, radiation damage, asthma, hyperoxic alveolar injury, malaria, mycobacterial infection, and opportunistic infections resulting from HIV.

This invention encompasses methods of treating patients who have been previously treated for cancer or diseases or disorders associated with, or characterized by, undesired angiogenesis, but are non-responsive to standard therapies, as well as those who have not previously been treated. The invention also encompasses methods of treating patients regardless of patient's age, although some diseases or disorders are more common in certain age groups. The invention further encompasses methods of treating patients who have undergone surgery in an attempt to treat the disease or condition at issue, as well as those who have not. Because patients with cancer and diseases and disorders characterized by undesired angiogenesis have heterogenous clinical manifestations and varying clinical outcomes, the treatment given to a patient may vary, depending on his/her prognosis. The skilled clinician will be able to readily determine without undue experimentation specific secondary agents, types of surgery, and types of non-drug based standard therapy that can be effectively used to treat an individual patient with cancer and other diseases or disorders.

Methods encompassed by this invention comprise administering one or more immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, to a patient (*e.g.*, a human) suffering, or likely to suffer, from cancer or a disease or disorder mediated by undesired angiogenesis.

In one embodiment of the invention, an immunomodulatory compound of the invention can be administered orally and in single or divided daily doses in an amount of from about 0.10 to about 150 mg/day. In a particular embodiment, 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione (Actimid™) may be administered in an amount of from about 0.1 to about 1 mg per day, or alternatively from about 0.1 to about 5 mg every other day. In a preferred embodiment, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl -piperidine-2,6-dione (Revimid™) may be administered in an amount of from about 5 to 25 mg per day, or alternatively from about 10 to about 50 mg every other day.

In a specific embodiment, 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione (Actimid™) may be administered in an amount of about 1, 2, or 5 mg per day to patients with relapsed multiple myeloma. In a particular embodiment, 3-(4-amino-1-oxo -1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revimid™) may be administered initially in an amount of 5 mg/day and the dose can be escalated every week to 10, 20, 25, 30 and 50 mg/day. In a specific embodiment, Revimid™ can be administered in an amount of up to

about 30 mg/day to patients with solid tumor. In a particular embodiment, Revimid™ can be administered in an amount of up to about 40 mg/day to patients with glioma.

### 5.3.1 COMBINATION THERAPY WITH A SECOND ACTIVE AGENT

Specific methods of the invention comprise administering an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, in combination with one or more second active agents, and/or in combination with radiation therapy, blood transfusions, or surgery. Examples of immunomodulatory compounds of the invention are disclosed herein (*see, e.g.*, section 5.1). Examples of second active agents are also disclosed herein (*see, e.g.*, section 5.2).

Administration of the immunomodulatory compounds and the second active agents to a patient can occur simultaneously or sequentially by the same or different routes of administration. The suitability of a particular route of administration employed for a particular active agent will depend on the active agent itself (*e.g.*, whether it can be administered orally without decomposing prior to entering the blood stream) and the disease being treated. A preferred route of administration for an immunomodulatory compound of the invention is orally. Preferred routes of administration for the second active agents or ingredients of the invention are known to those of ordinary skill in the art. *See, e.g.*, *Physicians' Desk Reference*, 1755-1760 (56th ed., 2002).

In one embodiment of the invention, the second active agent is administered intravenously or subcutaneously and once or twice daily in an amount of from about 1 to about 1000 mg, from about 5 to about 500 mg, from about 10 to about 350 mg, or from about 50 to about 200 mg. The specific amount of the second active agent will depend on the specific agent used, the type of disease being treated or managed, the severity and stage of disease, and the amount(s) of immunomodulatory compounds of the invention and any optional additional active agents concurrently administered to the patient. In a particular embodiment, the second active agent is oblimersen (Genasense®), GM-CSF, G-CSF, EPO, taxotere, irinotecan, dacarbazine, transretinoic acid, topotecan, pentoxifylline, ciprofloxacin, dexamethasone, vincristine, doxorubicin, COX-2 inhibitor, IL2, IL8, IL18, IFN, Ara-C, vinorelbine, or a combination thereof.

In a particular embodiment, GM-CSF, G-CSF or EPO is administered subcutaneously during about five days in a four or six week cycle in an amount of from about 1 to about 750 mg/m$^2$/day, preferably in an amount of from about 25 to about 500

mg/m$^2$/day, more preferably in an amount of from about 50 to about 250 mg/m$^2$/day, and most preferably in an amount of from about 50 to about 200 mg/m$^2$/day. In a certain embodiment, GM-CSF may be administered in an amount of from about 60 to about 500 mcg/m$^2$ intravenously over 2 hours, or from about 5 to about 12 mcg/m$^2$/day subcutaneously. In a specific embodiment, G-CSF may be administered subcutaneously in an amount of about 1 mcg/kg/day initially and can be adjusted depending on rise of total granulocyte counts. The maintenance dose of G-CSF may be administered in an amount of about 300 (in smaller patients) or 480 mcg subcutaneously. In a certain embodiment, EPO may be administered subcutaneously in an amount of 10,000 Unit 3 times per week.

In another embodiment, Revimid™ in an amount of about 25 mg/d and dacarbazine in an amount of about from 200 to 1,000 mg/m$^2$/d are administered to patients with metastatic malignant melanoma. In a specific embodiment, Revimid™ is administered in an amount of from about 5 to about 25 mg/d to patients with metastatic malignant melanoma whose disease has progressed on treatment with dacarbazine, IL-2 or IFN. In a specific embodiment, Revimid™ is administered to patients with relapsed or refractory multiple myeloma in an amount of about 15 mg/d twice a day or about 30 mg/d four times a day in a combination with dexamethasone.

In another embodiment, an immunomodulatory compound is administered with melphalan and dexamethasone to patients with amyloidosis. In a specific embodiment, an immunomodulatory compound of the invention and steroids can be administered to patients with amyloidosis.

In another embodiment, an immunomodulatory compound is administered with gemcitabine and cisplatinum to patients with locally advanced or metastatic transitional cell bladder cancer.

In another embodiment, an immunomodulatory compound is administered in combination with a second active ingredient as follows: temozolomide to pediatric patients with relapsed or progressive brain tumors or recurrent neuroblastoma; celecoxib, etoposide and cyclophosphamide for relapsed or progressive CNS cancer; temodar to patients with recurrent or progressive meningioma, malignant meningioma, hemangiopericytoma, multiple brain metastases, relapased brain tumors, or newly diagnosed glioblastoma multiforms; irinotecan to patients with recurrent glioblastoma; carboplatin to pediatric patients with brain stem glioma; procarbazine to pediatric patients with progressive malignant gliomas; cyclophosphamide to patients with poor prognosis malignant brain tumors, newly diagnosed or recurrent glioblastoma multiforms; Gliadel® for high grade

recurrent malignant gliomas; temozolomide and tamoxifen for anaplastic astrocytoma; or topotecan for gliomas, glioblastoma, anaplastic astrocytoma or anaplastic oligodendroglioma.

In another embodiment, an immunomodulatory compound is administered with methotrexate and cyclophosphamide to patients with metastatic breast cancer.

In another embodiment, an immunomodulatory compound is administered with temozolomide to patients with neuroendocrine tumors.

In another embodiment, an immunomodulatory compound is administered with gemcitabine to patients with recurrent or metastatic head or neck cancer. In another embodiment, an immunomodulatory compound is administered with gemcitabine to patients with pancreatic cancer.

In another embodiment, an immunomodulatory compound is administered to patients with colon cancer in combination with Arisa®, taxol and/or taxotere.

In another embodiment, an immunomodulatory compound is administered with capecitabine to patients with refractory colorectal cancer or patients who fail first line therapy or have poor performance in colon or rectal adenocarcinoma.

In another embodiment, an immunomodulatory compound is administered in combination with fluorouracil, leucovorin, and irinotecan to patients with Dukes C & D colorectal cancer or to patients who have been previously treated for metastatic colorectal cancer.

In another embodiment, an immunomodulatory compound is administered to patients with refractory colorectal cancer in combination with capecitabine, xeloda, and/or CPT-11.

In another embodiment, an immunomodulatory compound of the invention is administered with capecitabine and irinotecan to patients with refractory colorectal cancer or to patients with unresectable or metastatic colorectal carcinoma.

In another embodiment, an immunomodulatory compound is administered alone or in combination with interferon alpha or capecitabine to patients with unresectable or metastatic hepatocellular carcinoma; or with cisplatin and thiotepa to patients with primary or metastatic liver cancer.

In another embodiment, an immunomodulatory compound is administered in combination with pegylated interferon alpha to patients with Kaposi's sarcoma.

In another embodiment, an immunomodulatory compound is administered in combination with fludarabine, carboplatin, and/or topotecan to patients with refractory or relapsed or high-risk acuted myelogenous leukemia.

In another embodiment, an immunomodulatory compound is administered in combination with liposomal daunorubicin, topotecan and/or cytarabine to patients with unfavorable karotype acute myeloblastic leukemia.

In another embodiment, an immunomodulatory compound is administered in combination with gemcitabine and irinotecan to patients with non-small cell lung cancer. In one embodiment, an immunomodulatory compound is administered in combination with carboplatin and irinotecan to patients with non-small cell lung cancer. In one embodiment, an immunomodulatory compound is administered with doxetaxol to patients with non-small cell lung cancer who have been previously treated with carbo/VP 16 and radiotherapy.

In another embodiment, an immunomodulatory compound is administered in combination with carboplatin and/or taxotere, or in combination with carboplatin, pacilitaxel and/or thoracic radiotherapy to patients with non-small cell lung cancer. In a specific embodiment, an immunomodulatory compound is administered in combination with taxotere to patients with stage IIIB or IV non-small cell lung cancer.

In another embodiment, an immunomodulatory compound of the invention is administered in combination with oblimersen (Genasense®) to patients with small cell lung cancer.

In another embodiment, an immunomodulatory compound is administered alone or in combination with a second active ingredient such as vinblastine or fludarabine to patients with various types of lymphoma, including, but not limited to, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-Cell lymphoma, cutaneous B-Cell lymphoma, diffuse large B-Cell lymphoma or relapsed or refractory low grade follicular lymphoma.

In another embodiment, an immunomodulatory compound is administered in combination with taxotere, IL-2, IFN, GM-CSF, and/or dacarbazine to patients with various types or stages of melanoma.

In another embodiment, an immunomodulatory compound is administered alone or in combination with vinorelbine to patients with malignant mesothelioma, or stage IIIB non-small cell lung cancer with pleural implants or malignant pleural effusion mesothelioma syndrome.

In another embodiment, an immunomodulatory compound is administered to patients with various types or stages of multiple myeloma in combination with

dexamethasone, zoledronic acid, palmitronate, GM-CSF, biaxin, vinblastine, melphalan, busulphan, cyclophosphamide, IFN, palmidronate, prednisone, bisphosphonate, celecoxib, arsenic trioxide, PEG INTRON-A, vincristine, or a combination thereof.

In another embodiment, an immunomodulatory compound is administered to patients with relapsed or refractory multiple myeloma in combination with doxorubicin (Doxil®), vincristine and/or dexamethasone (Decadron®).

In another embodiment, an immunomodulatory compound is administered to patients with various types or stages of ovarian cancer such as peritoneal carcinoma, papillary serous carcinoma, refractory ovarian cancer or recurrent ovarian cancer, in combination with taxol, carboplatin, doxorubicin, gemcitabine, cisplatin, xeloda, paclitaxel, dexamethasone, or a combination thereof.

In another embodiment, an immunomodulatory compound is administered to patients with various types or stages of prostate cancer, in combination with xeloda, 5 FU/LV, gemcitabine, irinotecan plus gemcitabine, cyclophosphamide, vincristine, dexamethasone, GM-CSF, celecoxib, taxotere, ganciclovir, paclitaxel, adriamycin, docetaxel, estramustine, Emcyt, or a combination thereof.

In another embodiment, an immunomodulatory compound is administered to patients with various types or stages of renal cell cancer, in combination with capecitabine, IFN, tamoxifen, IL-2, GM-CSF, Celebrex®, or a combination thereof.

In another embodiment, an immunomodulatory compound is administered to patients with various types or stages of gynecologic, uterus or soft tissue sarcoma cancer in combination with IFN, a COX-2 inhibitor such as Celebrex®, and/or sulindac.

In another embodiment, an immunomodulatory compound is administered to patients with various types or stages of solid tumors in combination with celebrex, etoposide, cyclophosphamide, docetaxel, apecitabine, IFN, tamoxifen, IL-2, GM-CSF, or a combination thereof.

In another embodiment, an immunomodulatory compound is administered to patients with scelroderma or cutaneous vasculitis in combination with celebrex, etoposide, cyclophosphamide, docetaxel, apecitabine, IFN, tamoxifen, IL-2, GM-CSF, or a combination thereof.

This invention also encompasses a method of increasing the dosage of an anti-cancer drug or agent that can be safely and effectively administered to a patient, which comprises administering to a patient (*e.g.*, a human) an immunomodulatory compound of the invention, or a pharmaceutically acceptable derivative, salt, solvate, clathrate, hydrate, or

prodrug thereof. Patients that can benefit by this method are those likely to suffer from an adverse effect associated with anti-cancer drugs for treating a specific cancer of the skin, subcutaneous tissue, lymph nodes, brain, lung, liver, bone, intestine, colon, heart, pancreas, adrenal, kidney, prostate, breast, colorectal, or combinations thereof. The administration of an immunomodulatory compound of the invention alleviates or reduces adverse effects which are of such severity that it would otherwise limit the amount of anti-cancer drug.

In one embodiment, an immunomodulatory compound of the invention can be administered orally and daily in an amount of from about 0.1 to about 150 mg, and preferably from about 1 to about 50 mg, more preferably from about 2 to about 25 mg prior to, during, or after the occurrence of the adverse effect associated with the administration of an anti-cancer drug to a patient. In a particular embodiment, an immunomodulatory compound of the invention is administered in combination with specific agents such as heparin, aspirin, coumadin, or G-CSF to avoid adverse effects that are associated with anti-cancer drugs such as but not limited to neutropenia or thrombocytopenia.

In one embodiment, an immunomodulatory compound of the invention can be administered to patients with diseases and disorders associated with, or characterized by, undesired angiogenesis in combination with additional active ingredients including but not limited to anti-cancer drugs, anti-inflammatories, antihistamines, antibiotics, and steroids.

In another embodiment, this invention encompasses a method of treating, preventing and/or managing cancer, which comprises administering an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, in conjunction with (*e.g.* before, during, or after) conventional therapy including, but not limited to, surgery, immunotherapy, biological therapy, radiation therapy, or other non-drug based therapy presently used to treat, prevent or manage cancer. The combined use of the immunomodulatory compounds of the invention and conventional therapy may provide a unique treatment regimen that is unexpectedly effective in certain patients. Without being limited by theory, it is believed that immunomodulatory compounds of the invention may provide additive or synergistic effects when given concurrently with conventional therapy.

As discussed elsewhere herein, the invention encompasses a method of reducing, treating and/or preventing adverse or undesired effects associated with conventional therapy including, but not limited to, surgery, chemotherapy, radiation therapy, hormonal therapy, biological therapy and immunotherapy. One or more immunomodulatory compounds of the

invention and other active ingredient can be administered to a patient prior to, during, or after the occurrence of the adverse effect associated with conventional therapy.

In one embodiment, an immunomodulatory compound of the invention can be administered in an amount of from about 0.1 to about 150 mg, and preferably from about 1 to about 25 mg, more preferably from about 2 to about 10 mg orally and daily alone, or in combination with a second active agent disclosed herein (*see, e.g.*, section 5.2), prior to, during, or after the use of conventional therapy.

In a specific embodiment of this method, an immunomodulatory compound of the invention and doxetaxol are administered to patients with non-small cell lung cancer who were previously treated with carbo/VP 16 and radiotherapy.

### 5.3.2 USE WITH TRANSPLANTATION THERAPY

Compounds of the invention can be used to reduce the risk of Graft Versus Host Disease (GVHD). Therefore, the invention encompasses a method of treating, preventing and/or managing cancer, which comprises administering the immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, in conjunction with transplantation therapy.

As those of ordinary skill in the art are aware, the treatment of cancer is often based on the stages and mechanism of the disease. For example, as inevitable leukemic transformation develops in certain stages of cancer, transplantation of peripheral blood stem cells, hematopoietic stem cell preparation or bone marrow may be necessary. The combined use of the immunomodulatory compound of the invention and transplantation therapy provides a unique and unexpected synergism. In particular, an immunomodulatory compound of the invention exhibits immunomodulatory activity that may provide additive or synergistic effects when given concurrently with transplantation therapy in patients with cancer.

An immunomodulatory compound of the invention can work in combination with transplantation therapy reducing complications associated with the invasive procedure of transplantation and risk of GVHD. This invention encompasses a method of treating, preventing and/or managing cancer which comprises administering to a patient (*e.g.*, a human) an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, before, during, or after the transplantation of umbilical cord blood, placental blood, peripheral blood stem cell, hematopoietic stem cell preparation or bone marrow. Examples of stem cells suitable for use in the methods of the invention are disclosed in U.S. provisional patent application

no. 60/372,348, filed April 12, 2002 by R. Hariri *et al.*, the entirety of which is incorporated herein by reference.

In one embodiment of this method, an immunomodulatory compound of the invention is administered to patients with multiple myeloma before, during, or after the transplantation of autologous peripheral blood progenitor cell.

In another embodiment, an immunomodulatory compound is administered to patients with relapsing multiple myeloma after the stem cell transplantation.

In another embodiment, an immunomodulatory compound and prednisone are administered as maintenance therapy to patients with multiple myeloma following the transplantation of autologous stem cell.

In another embodiment, an immunomodulatory compound and dexamethasone are administered as salvage therapy for low risk post transplantation to patients with multiple myeloma.

In another embodiment, an immunomodulatory compound and dexamethasone are administered as maintenance therapy to patients with multiple myeloma following the transplantation of autologous bone marrow.

In another embodiment, an immunomodulatory compound is administered following the administration of high dose of melphalan and the transplantation of autologous stem cell to patients with chemotherapy responsive multiple myeloma.

In another embodiment, an immunomodulatory compound and PEG INTRO-A are administered as maintenance therapy to patients with multiple myeloma following the transplantation of autologous CD34-selected peripheral stem cell.

In another embodiment, an immunomodulatory compound is administered with post transplant consolidation chemotherapy to patients with newly diagnosed multiple myeloma to evaluate anti-angiogenesis.

In another embodiment, an immunomodulatory compound and dexamethasone are administered as maintenance therapy after DCEP consolidation, following the treatment with high dose of melphalan and the transplantation of peripheral blood stem cell to 65 years of age or older patients with multiple myeloma.

### 5.3.3 CYCLING THERAPY

In certain embodiments, the prophylactic or therapeutic agents of the invention are cyclically administered to a patient. Cycling therapy involves the administration of an active agent for a period of time, followed by a rest for a period of time, and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one

or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment.

Consequently, in one specific embodiment of the invention, an immunomodulatory compound of the invention is administered daily in a single or divided doses in a four to six week cycle with a rest period of about a week or two weeks. The invention further allows the frequency, number, and length of dosing cycles to be increased. Thus, another specific embodiment of the invention encompasses the administration of an immunomodulatory compound of the invention for more cycles than are typical when it is administered alone. In yet another specific embodiment of the invention, an immunomodulatory compound of the invention is administered for a greater number of cycles that would typically cause dose-limiting toxicity in a patient to whom a second active ingredient is not also being administered.

In one embodiment, an immunomodulatory compound of the invention is administered daily and continuously for three or four weeks at a dose of from about 0.1 to about 150 mg/d followed by a break of one or two weeks. Actimid™ is preferably administered daily and continuously at an initial dose of 0.1 to 5 mg/d with dose escalation (every week) by 1 to 10 mg/d to a maximum dose of 50 mg/d for as long as therapy is tolerated. In a particular embodiment, Revimid™ is administered in an amount of about 5, 10, or 25mg/day, preferably in an amount of about 10 mg/day for three to four weeks, followed by one week or two weeks of rest in a four or six week cycle.

In one embodiment of the invention, an immunomodulatory compound of the invention and a second active ingredient are administered orally, with administration of an immunomodulatory compound of the invention occurring 30 to 60 minutes prior to a second active ingredient, during a cycle of four to six weeks. In another embodiment of the invention, the combination of an immunomodulatory compound of the invention and a second active ingredient is administered by intravenous infusion over about 90 minutes every cycle. In a specific embodiment, one cycle comprises the administration of from about 10 to about 25 mg/day of Revimid™ and from about 50 to about 200 mg/m$^2$/day of a second active ingredient daily for three to four weeks and then one or two weeks of rest. In another specific embodiment, each cycle comprises the administration of from about 5 to about 10 mg/day of Actimid™ and from about 50 to about 200 mg/m$^2$/day of a second active ingredient for 3 to 4 weeks followed by one or two weeks of rest. Typically, the number of cycles during which the combinatorial treatment is administered to a patient will

be from about one to about 24 cycles, more typically from about two to about 16 cycles, and even more typically from about four to about three cycles.

## 5.4 PHARMACEUTICAL COMPOSITIONS AND DOSAGE FORMS

Pharmaceutical compositions can be used in the preparation of individual, single unit dosage forms. Pharmaceutical compositions and dosage forms of the invention comprise an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof. Pharmaceutical compositions and dosage forms of the invention can further comprise one or more excipients.

Pharmaceutical compositions and dosage forms of the invention can also comprise one or more additional active ingredients. Consequently, pharmaceutical compositions and dosage forms of the invention comprise the active ingredients disclosed herein (*e.g.*, an immunomodulatory compound and a second active agent). Examples of optional second, or additional, active ingredients are disclosed herein (*see, e.g.*, section 5.2).

Single unit dosage forms of the invention are suitable for oral, mucosal (*e.g.*, nasal, sublingual, vaginal, buccal, or rectal), parenteral (*e.g.*, subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial), topical (*e.g.*, eye drops or other ophthalmic preparations), transdermal or transcutaneous administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; powders; aerosols (*e.g.*, nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (*e.g.*, aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or a water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient; eye drops or other ophthalmic preparations suitable for topical administration; and sterile solids (*e.g.*, crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

The composition, shape, and type of dosage forms of the invention will typically vary depending on their use. For example, a dosage form used in the acute treatment of a disease may contain larger amounts of one or more of the active ingredients it comprises than a dosage form used in the chronic treatment of the same disease. Similarly, a parenteral dosage form may contain smaller amounts of one or more of the active ingredients it comprises than an oral dosage form used to treat the same disease. These and

other ways in which specific dosage forms encompassed by this invention will vary from one another will be readily apparent to those skilled in the art. *See, e.g., Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA (1990).

Typical pharmaceutical compositions and dosage forms comprise one or more excipients. Suitable excipients are well known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a patient. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms. The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form. For example, the decomposition of some active ingredients may be accelerated by some excipients such as lactose, or when exposed to water. Active ingredients that comprise primary or secondary amines are particularly susceptible to such accelerated decomposition. Consequently, this invention encompasses pharmaceutical compositions and dosage forms that contain little, if any, lactose other mono- or di-saccharides. As used herein, the term "lactose-free" means that the amount of lactose present, if any, is insufficient to substantially increase the degradation rate of an active ingredient.

Lactose-free compositions of the invention can comprise excipients that are well known in the art and are listed, for example, in the *U.S. Pharmacopeia* (USP) 25-NF20 (2002). In general, lactose-free compositions comprise active ingredients, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. Preferred lactose-free dosage forms comprise active ingredients, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

This invention further encompasses anhydrous pharmaceutical compositions and dosage forms comprising active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (*e.g.*, 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. *See, e.g.*, Jens T. Carstensen, *Drug Stability: Principles & Practice*, 2d. Ed., Marcel Dekker, NY, NY, 1995, pp. 379-80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or

humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine are preferably anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are preferably packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (*e.g.*, vials), blister packs, and strip packs.

The invention further encompasses pharmaceutical compositions and dosage forms that comprise one or more compounds that reduce the rate by which an active ingredient will decompose. Such compounds, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers.

Like the amounts and types of excipients, the amounts and specific types of active ingredients in a dosage form may differ depending on factors such as, but not limited to, the route by which it is to be administered to patients. However, typical dosage forms of the invention comprise an immunomodulatory compound of the invention or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof in an amount of from about 0.10 to about 150 mg. Typical dosage forms comprise an immunomodulatory compound of the invention or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof in an amount of about 0.1, 1, 2, 5, 7.5, 10, 12.5, 15, 17.5, 20, 25, 50, 100, 150 or 200 mg. In a particular embodiment, a preferred dosage form comprises 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione (Actimid™) in an amount of about 1, 2, 5, 10, 25 or 50mg. In a specific embodiment, a preferred dosage form comprises 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revimid™) in an amount of about 5, 10, 25 or 50mg. Typical dosage forms comprise the second active ingredient in an amount of 1 to about 1000 mg, from about 5 to about 500 mg, from about 10 to about 350 mg, or from about 50 to about 200 mg. Of course, the specific amount of the anti-cancer drug will depend on the specific agent

used, the type of cancer being treated or managed, and the amount(s) of an immunomodulatory compound of the invention and any optional additional active agents concurrently administered to the patient.

### 5.4.1 ORAL DOSAGE FORMS

Pharmaceutical compositions of the invention that are suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets (*e.g.*, chewable tablets), caplets, capsules, and liquids (*e.g.*, flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. *See generally*, *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA (1990).

Typical oral dosage forms of the invention are prepared by combining the active ingredients in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (*e.g.*, powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid excipients are employed. If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as powder or granules, optionally mixed with an excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

Examples of excipients that can be used in oral dosage forms of the invention include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not

limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (*e.g.*, Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101, AVICEL-PH-103 AVICEL RC-581, AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, PA), and mixtures thereof. An specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103™ and Starch 1500 LM.

Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions of the invention is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

Disintegrants are used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms of the invention. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, preferably from about 1 to about 5 weight percent of disintegrant.

Disintegrants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums, and mixtures thereof.

Lubricants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL200, manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, TX), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, MA), and mixtures thereof. If used at all, lubricants are typically used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

A preferred solid oral dosage form of the invention comprises an immunomodulatory compound of the invention, anhydrous lactose, microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin.

### 5.4.2 DELAYED RELEASE DOSAGE FORMS

Active ingredients of the invention can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled-release.

All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum

amount of time. Advantages of controlled-release formulations include extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled-release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (*e.g.*, adverse) effects.

Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

### 5.4.3 PARENTERAL DOSAGE FORMS

Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial. Because their administration typically bypasses patients' natural defenses against contaminants, parenteral dosage forms are preferably sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

Suitable vehicles that can be used to provide parenteral dosage forms of the invention are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms of the invention. For example, cyclodextrin and its derivatives can be used to increase the solubility of an

immunomodulatory compound of the invention and its derivatives. *See, e.g.*, U.S. Patent No. 5,134,127, which is incorporated herein by reference.

### 5.4.4 TOPICAL AND MUCOSAL DOSAGE FORMS

Topical and mucosal dosage forms of the invention include, but are not limited to, sprays, aerosols, solutions, emulsions, suspensions, eye drops or other ophthalmic preparations, or other forms known to one of skill in the art. *See, e.g.*, *Remington's Pharmaceutical Sciences*, 16th and 18th eds., Mack Publishing, Easton PA (1980 & 1990); and *Introduction to Pharmaceutical Dosage Forms*, 4th ed., Lea & Febiger, Philadelphia (1985). Dosage forms suitable for treating mucosal tissues within the oral cavity can be formulated as mouthwashes or as oral gels.

Suitable excipients (*e.g.*, carriers and diluents) and other materials that can be used to provide topical and mucosal dosage forms encompassed by this invention are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind, typical excipients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof to form solutions, emulsions or gels, which are non-toxic and pharmaceutically acceptable. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well known in the art. *See, e.g.*, *Remington's Pharmaceutical Sciences*, 16th and 18th eds., Mack Publishing, Easton PA (1980 & 1990).

The pH of a pharmaceutical composition or dosage form may also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. Different salts, hydrates or solvates of the active ingredients can be used to further adjust the properties of the resulting composition.

### 5.4.5 KITS

Typically, active ingredients of the invention are preferably not administered to a patient at the same time or by the same route of administration. This invention therefore

encompasses kits which, when used by the medical practitioner, can simplify the administration of appropriate amounts of active ingredients to a patient.

A typical kit of the invention comprises a dosage form of an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt salt, solvate, hydrate, stereoisomer, prodrug, or clathrate thereof. Kits encompassed by this invention can further comprise additional active ingredients such as oblimersen (Genasense®), melphalan, G-CSF, GM-CSF, EPO, topotecan, dacarbazine, irinotecan, taxotere, IFN, COX-2 inhibitor, pentoxifylline, ciprofloxacin, dexamethasone, IL2, IL8, IL18, Ara-C, vinorelbine, isotretinoin, 13 cis-retinoic acid, or a pharmacologically active mutant or derivative thereof, or a combination thereof. Examples of the additional active ingredients include, but are not limited to, those disclosed herein (*see, e.g.*, section 5.2).

Kits of the invention can further comprise devices that are used to administer the active ingredients. Examples of such devices include, but are not limited to, syringes, drip bags, patches, and inhalers.

Kits of the invention can further comprise cells or blood for transplantation as well as pharmaceutically acceptable vehicles that can be used to administer one or more active ingredients. For example, if an active ingredient is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in which the active ingredient can be dissolved to form a particulate-free sterile solution that is suitable for parenteral administration. Examples of pharmaceutically acceptable vehicles include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

## 6. EXAMPLES

Certain embodiments of the invention are illustrated by the following non-limiting examples.

### 6.1 MODULATION OF CYTOKINE PRODUCTION

A series of non-clinical pharmacology and toxicology studies have been performed to support the clinical evaluation of an immunomodulatory compound of the invention in human subjects. These studies were performed in accordance with internationally

recognized guidelines for study design and in compliance with the requirements of Good Laboratory Practice (GLP), unless otherwise noted.

Inhibition of TNF-$\alpha$ production following LPS-stimulation of human PBMC and human whole blood by 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione (Actimid™), 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione and thalidomide (Revimid™) was investigated *in vitro* (Muller *et al.*, *Bioorg. Med. Chem. Lett.* 9:1625-1630, 1999). The $IC_{50}$'s of 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione for inhibiting production of TNF-$\alpha$ following LPS-stimulation of PBMC and human whole blood were ~24 nM (6.55 ng/mL) and ~25 nM (6.83 ng/mL), respectively. *In vitro* studies suggest a pharmacological activity profile for 3-(4-amino-1-oxo-1,3-dihydro -isoindol-2-yl)-piperidine-2,6-dione that is similar to, but at least 200 times more potent than, thalidomide. *In vitro* studies have also demonstrated that concentrations of 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione of 2.73 to 27.3 ng/mL (0.01 to 0.1 $\mu$M) achieved 50% inhibition of the proliferation of MM.IS and Hs Sultan cells.

The $IC_{50}$'s of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione for inhibiting production of TNF-$\alpha$ following LPS-stimulation of PBMC and human whole blood were ~100 nM (25.9 ng/mL) and ~480 nM (103.6 ng/mL), respectively. Thalidomide, in contrast, had an $IC_{50}$ of ~194 $\mu$M (50.2 $\mu$g/mL) for inhibiting production of TNF-$\alpha$ following LPS-stimulation of PBMC. *In vitro* studies suggest a pharmacological activity profile for 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione that is similar to, but 50 to 2000 times more potent than, thalidomide. It has been shown that the compound is approximately 50-100 times more potent than thalidomide in stimulating the proliferation of T-cells following primary induction by T-cell receptor (TCR) activation. 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione is also approximately 50 to 100 times more potent than thalidomide in augmenting the production of IL-2 and IFN-$\gamma$ following TCR activation of PBMC (IL-2) or T-cells (IFN-$\gamma$). In addition, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione exhibited dose-dependent inhibition of LPS-stimulated production of the pro-inflammatory cytokines TNF-$\alpha$, IL-1$\beta$, and IL-6 by PBMC while it increased production of the anti-inflammatory cytokine IL-10.

## 6.2 INHIBITION OF MM CELL PROLIFERATION

The ability of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revimid™) and thalidomide for comparison to effect the proliferation of MM cell lines has been investigated in an *in vitro* study. Uptake [$^3$H]-thymidine by different MM cell lines

(MM.1S, Hs Sultan, U266 and RPMI-8226) was measured as an indicator of cell proliferation. Cells were incubated in the presence of compounds for 48 hours; [$^3$H]-thymidine was included for the last 8 hours of the incubation period. Addition of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione to MM.1S and Hs Sultan cells resulted in 50% inhibition of cell proliferation at concentrations of 0.4 $\mu$m and 1 $\mu$m, respectively. In contrast, addition of thalidomide at concentrations up to 100 $\mu$m resulted in only 15% and 20% inhibition of cell proliferation in MM.1S and Hs Sultan cells, respectively. These data are summarized in Figure 1.

### 6.3 TOXICOLOGY STUDIES

The effects of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revimid™) on cardiovascular and respiratory function are investigated in anesthetized dogs. Two groups of Beagle dogs (2/sex/group) are used. One group receives three doses of vehicle only and the other receives three ascending doses of 3-(4-amino-1-oxo-1,3 -dihydro-isoindol-2-yl)-piperidine-2,6-dione (2, 10, and 20 mg/kg). In all cases, doses of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione or vehicle are successively administered *via* infusion through the jugular vein separated by intervals of at least 30 minutes.

The cardiovascular and respiratory changes induced by 3-(4-amino-1 -oxo-1,3 -dihydro-isoindol-2-yl)-piperidine-2,6-dione are minimal at all doses when compared to the vehicle control group. The only statistically significant difference between the vehicle and treatment groups is a small increase in arterial blood pressure (from 94 mmHg to 101 mmHg) following administration of the low dose of 3-(4-amino-1-oxo-1,3 -dihydro -isoindol-2-yl)-piperidine-2,6-dione. This effect lasts approximately 15 minutes and is not seen at higher doses. Deviations in femoral blood flow, respiratory parameters, and Qtc interval are common to both the control and treated groups and are not considered treatment-related.

### 6.4 CYCLING THERAPY IN PATIENTS

In a specific embodiment, an immunomodulatory compound of the invention are cyclically administered to patients with cancer. Cycling therapy involves the administration of a first agent for a period of time, followed by a rest for a period of time and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment.

In a specific embodiment, prophylactic or therapeutic agents are administered in a cycle of about 4 to 6 weeks, about once or twice every day. One cycle can comprise the administration of a therapeutic on prophylactic agent for three to four weeks and at least a week or two weeks of rest. The number of cycles administered is from about one to about 24 cycles, more typically from about two to about 16 cycles, and more typically from about four to about eight cycles.

For example, in a cycle of four weeks, on day 1, the administration of 25 mg/d of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione is started. On day 22, the administration of the compound is stopped for a week of rest. On day 29, the administration of 25 mg/d 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidin-2,6-dione is begun.

## 6.5 CLINICAL STUDIES IN PATIENTS

### 6.5.1 TREATMENT OF RELAPSED MULTIPLE MYELOMA

4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione (Actimid™) was administered to patients with relapsed/refractory multiple myeloma. The study was conducted in compliance with Good Clinical Practices. Patients were at least 18 years old, had been diagnosed with multiple myeloma (with paraprotein in serum and/or urine), and were considered refractory to treatment after at least two cycles of treatment, or have relapsed after two cycles of treatment.

Patients who have progressive disease, according to the Southwest Oncology Group (SWOG) criteria, on their prior regimen are considered treatment refractory. Relapse following remission is defined as >25% increase in M component from baseline levels; reappearance of the M paraprotein that had previously disappeared; or a definite increase in the size and number of lytic bone lesions recognized on radiographs. Patients may have had prior therapy with thalidomide, provided they were able to tolerate the treatment. A Zubrod performance status of 0 to 2 is required for all patients.

4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione is administered to patients at doses of 1, 2, 5, or 10 mg/day for up to four weeks; at each dose level, three patients are initially enrolled. Dosing occurs at approximately the same time each morning; all doses are administered in the fasted state (no eating for at least two hours prior to dosing and two hours after dosing). 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione doses are administered in an ascending fashion such that patients in the first cohort receive the lowest dose of 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione (1 mg/day) and escalation to the next higher dose level occurs only following the establishment of

safety and tolerability at the current dose. If one out of three patients at any dose level experience dose limiting toxicity (DLT), three additional patients are enrolled at that dose. If none of the three additional patients experience DLT, escalation to the next dose level occurs; dose escalations continue in a similar fashion until the MTD is established or the maximum daily dose (10 mg/day) is attained. However, if one of the three additional patients enrolled experiences DLT, the MTD has been reached. If two or more of the three additional patients enrolled experience DLT, the MTD is judged to have been exceeded and three additional patients are enrolled at the preceding dose level to confirm the MTD. Once the MTD has been identified, four additional patients are enrolled at that dose level so that a total of 10 patients is treated at the MTD.

Blood sampling for analysis of pharmacokinetic parameters is performed on Days 1 and 28 according to the following sampling schedule: pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, and 24 hours post-dose. An additional blood sample is collected at each weekly visit for the determination of 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione levels. Total urine collections are also made with urine pooled according to the following time intervals post-dose: 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours. Safety assessments are made by monitoring adverse events, vital signs, ECGs, clinical laboratory evaluations (blood chemistry, hematology, lymphocyte phenotyping, and urinalysis), and physical examination at specific times during the study.

Results of interim pharmacokinetic analyses obtained following single- and multiple-dose administration of 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione to multiple myeloma patients are presented below in Tables 1 and 2. These data show that 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione was steadily absorbed at all dose levels in relapsed multiple myeloma patients. Maximum plasma concentrations occurred at a median $T_{max}$ of between 2.5 and 2.8 hours post-dose at Day 1 and between 3 and 4 hours post-dose at Week 4. At all doses, plasma concentrations declined in a monophasic manner after reaching $C_{max}$. The start of the elimination phase occurred between 3 and 10 hours post-dose at Day 1 and Week 4, respectively.

These data also showed that after 4 weeks of dosing, 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione accumulated to a small extent (mean accumulation ratios ~1.02 to 1.52 and ~0.94 to 1.62 for $C_{max}$ and $AUC_{(0-\tau)}$, respectively). There was almost a dose proportional increase in $AUC_{(0-\tau)}$ and $C_{max}$ values with increasing dose. A five-fold higher dose of 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione produced a 3.2- and 2.2-fold increase in $C_{max}$ at Day 1 and Week 4, respectively. Similarly, a 5-fold

increase in dose resulted in a 3.6- and 2.3-fold increase in $AUC_{(0-\tau)}$, at Day 1 and Week 4, respectively.

Table 1

Pharmacokinetic parameters of Actimid™ in relapsed multiple myeloma patients

| Parameter | | 1 mg (N=6) | 2 mg (N=2) | 5 mg (N=3) |
|---|---|---|---|---|
| **Day 1** | | | | |
| $C_{max}$ | ng/mL | 15.03 (4.04) | 24.4* (12.1) | 48.56 (14.03) |
| $t_{max}$ | h | 3.3 (2.6) | 2.7* (0.3) | 2.3 (0.3) |
| $AUC_{(0-\infty)}$ | ng.h/mL | 152.90 (36.62) | 279.18 (51.10) | 593.10 (335.23) |
| $AUC_{(0-\tau)}$ | | 134.21 (27.14) | 249.57 (29.26) | 520.94 (267.32) |
| t½ | h | 7.3 (3.4) | 6.3 (1.4) | 6.5 (2.2) |
| CL/F | mL/min | 114.75 (29.20) | 121.43 (22.22) | 182.31 (117.06) |
| Vz/f | L | 69.55 (44.97) | 65.31 (2.80) | 87.24 (22.61) |

t = 24 hours N/A = not available

Table 2

Pharmacokinetic parameters of Actimid™ following multiple oral doses(1, 2, and 5 mg/day) in relapsed multiple myeloma patients

| Parameter | | 1 mg (N=5) | 2 mg (N=2) | 5 mg (N=3) |
|---|---|---|---|---|
| **Week 4** | | | | |
| $C_{max}$ | ng/mL | 23.20 (7.48) | 30.05* (15.64) | 58.07 (38.08) |
| $t_{max}$ | h | 3.6 (1.5) | 2.8* (0.3) | 5.0 (2.6) |
| $AUC_{(0-\infty)}$ | ng.h/mL | N/A | N/A | N/A |
| $AUC_{(0-\tau)}$ | | 239.31 (122.59) | 269.36 (186.34) | 597.24 (354.23) |
| t½ | h | 6.2* (0.6) | 7.7 (2.8) | 7.8 (4.0) |
| CL/F | mL/min | 87.85 (48.48) | 162.68 (112.54) | 207.50 (175.41) |
| Vz/f | L | 41.35* (8.84) | 95.04 (35.39) | 103.95 (27.25) |

$\tau$ = 24 hours
N/A = not available
* N = 3 patients

### 6.5.2 TREATMENT OF RELAPSED MULTIPLE MYELOMA

Two Phase 1 clinical studies of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl) -piperidine-2,6-dione (Revimid™) have been conducted to identify the maximum tolerated dose (MTD) in patientswith refractory or relapsed multiple myeloma. These studies have also characterized the safety profile of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl) -piperidine-2,6-dione when ascending doses of 3-(4-amino-1-oxo-1,3-dihydro-isoindol -2-yl)-piperidine-2,6-dione were given orally for up to 4 weeks. Patients started 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl) -piperidine -2,6-dione treatment at 5 mg/day

with subsequent escalation to 10, 25, and 50 mg/day. Patients were enrolled for 28 days at their assigned dose, with the option of extended treatment for those who did not exhibit disease progression or experience dose limiting toxicity (DLT). Patients were evaluated for adverse events at each visit and the severity of these events was graded according to the National Cancer Institute (NCI) Common Toxicity Criteria. Patients were discontinued if they experienced DLT (Grade 3 or greater non-hematological, or Grade 4 hematological toxicity).

In this study, 27 patients were enrolled. All patients had relapsed multiple myeloma and 18 (72%) were refractory to salvage therapy. Among these patients, 15 had undergone prior autologous stem cell transplantation and 16 patients had received prior thalidomide treatment. The median number of prior regimens was 3 (range 2 to 6).

Blood and urine samples were collected for analysis of pharmacokinetic parameters on Days 1 and 28. Blood samples were collected according to the following sampling schedule: pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, and 24 hours post-dose. In addition, a blood sample was collected at each weekly clinic visit for 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione determination. Total urine was collected and pooled according to the following time intervals post-dose: 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours. Response to treatment was assessed by M-protein quantification (by immunoelectrophoresis) from serum and a 24-hour urine collection, with creatinine clearance and 24-hour protein calculations undertaken at screening, baseline, Weeks 2 and 4, and monthly thereafter (or upon early termination). Bone marrow aspirations and/or tissue biopsy are also performed at Months 3, 6 and 12 if a patient's paraprotein serum concentration or 24-hour urine protein excretion declined to the next lower level, based on best response criteria. Preliminary results for the 28-day treatment period are summarized below.

Preliminary pharmacokinetic analyses based on these two studies indicated that AUC and $C_{max}$ values increase proportionally with dose following single and multiple doses in multiple myeloma patients (as was seen in healthy volunteers). Further, there was no evidence of accumulation with multiple dosing as single dose $AUC_{(0-\infty)}$ was comparable to multiple dose $AUC_{0-\tau}$ following the same dose of 3-(4-amino-1-oxo-1,3-dihydro -isoindol-2-yl)-piperidine-2,6-dione. Similar to healthy volunteer studies, double peaks were observed. Exposure in multiple myeloma patients appeared to be slightly higher based on $C_{max}$ and AUC values as compared to healthy male volunteers while clearance in multiple myeloma patients was lower than it was in healthy volunteers, consistent with their

poorer renal function (both as a consequence of their age and their disease). Finally, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione half-live in patients was shorter than in healthy volunteers (mean 8 hours, ranging up to 17 hours).

In this study, the first cohort of 3 patients was treated for 28 days at 5 mg/day without any dose limiting toxicity (DLT). The second cohort of 3 patients subsequently commenced therapy at 10 mg/day. Patients in the second 10 mg/day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione cohort tolerated treatment well.

### 6.5.3 TREATMENT OF SOLID TUMORS

Study with 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revimid™) was conducted in patients with varying types of solid tumors, including malignant melanoma (13), carcinoma of the pancreas (2), carcinoid-unknown primary (1), renal carcinoma (1), breast carcinoma (1) and NSCLC (2). Patients received 5 mg/day 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione for seven days and are subsequently escalated every seven days to 10 mg/day, 25 mg/day, and 50 mg/day for a total of 4 weeks of treatment. Patients who, experienced clinical benefit were permitted to continue on treatment as Named Patients.

The study initially enrolled 20 patients and was subsequently amended to enroll 16 additional patients (adrenal carcinoma, NSCLC, malignant mesothelioma, breast cancer, malignant melanoma (8), renal cell cancer (4)) at a higher dose. The 16 additional patients were given weekly escalating doses of 25 mg/day, 50 mg/day, 75 mg/day, 100 mg/day, 125 mg/day, and 150 mg/day over a 6-week period with continuing treatment for an additional six weeks.

The study of Phase 1 study was designed to determine a maximum tolerated dose (MTD) of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione in patients with refractory solid tumors and/or lymphoma, as well as to characterize the pharmacokinetic and side effect profiles of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl) -piperidine-2,6-dione in this patient population. The study design dictates that at least 3 patients must be enrolled at a dose level and have completed 28 days of treatment prior to enrollment of patients at the next higher dose level. Patients in the first cohort began dosing at 5 mg/day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine- 2,6-dione. Patients will be escalated to 10, 20, 25, and 30 mg/day provided there is no toxicity.

In this study, the MTD is defined as the highest dose level in which fewer than two of six patients treated did not experience Grade 3 or greater non-hematological toxicity or Grade 4 or greater hematological toxicity. If, at any given dose level in either study, one

out of three patients experiences toxicity, three additional patients must be treated at that particular dose. If, however, two out of six patients experience DLT, the MTD is judged to have been exceeded. No further dose escalations are to occur and additional patients are to be enrolled at the previous dose level. The dose of 3-(4-amino-1-oxo-1,3-dihydro-isoindol -2-yl)-piperidine-2,6-dione administered is escalated until the MTD is achieved or the maximum daily dose of is reached.

No DLTs were reported in the initial group of 20 patients enrolled in the study. Thirteen of the original 20 trial patients, along with 2 non-trial patients, continued on treatment as named patients at doses up to 150 mg/day.

### 6.5.4 TREATMENT OF GLIOMAS

This study was performed to find toxicity in patients with recurrent, high-grade gliomas. The study is designed such that patients are given increasingly higher doses of 3-(4-amino-1-oxo-1,3-dihydro-isoindol -2-yl)-piperidine-2,6-dione until a maximum tolerated dose (MTD) is established. The study also seeks to obtain preliminary toxicity information and pharmacokinetic data on 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl) -piperidine-2,6-dione, as well as to develop exploratory data concerning surrogate end points of angiogenic activity *in vivo* using functional neuro-imaging studies, and *in vitro* assays of serum angiogenic peptides.

Patients enrolled in the first cohort receive 2.5 mg/m$^2$/day for a 4-week cycle. During each 4-week cycle of therapy, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl) -piperidine-2,6-dione administered once daily for 3 weeks followed by a week of rest. Patients who complete a treatment cycle may receive another cycle of 3-(4-amino-1 -oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione treatment if two criteria are met. First, the patient must have stable disease or have experienced a partial response or complete response, or the patient is benefiting from the therapy with 3-(4-amino-1-oxo-1,3-dihydro -isoindol-2-yl)-piperidine-2,6-dione as evidenced by a decrease in tumor-related symptoms such as neurological deficits. Second, the patient must have recovered from toxicity related to 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl) -piperidine-2,6-dione which occurred in the prior cycle by Day 42 or sooner (28-day cycle plus limit of 2 weeks to recover) as evidenced by a return to Grade $\leq$ 1 toxicity level. Patients who experience DLT in the previous cycle should have their dose modified. DLT is defined as an non-hematological event Grade $\geq$ 3 toxicity or hematological event of Grade 4 toxicity thought to be related to the study medication. Patients who experience DLT in the first cycle and have no response to therapy are removed from the study.

3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl) -piperidine-2,6-dione doses are subsequently escalated to 5, 8, 11, 15, and 20 mg/m$^2$/day to a maximum total daily dose of 40 mg. Patients continue to receive 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine -2,6-dione on a 4-week cycle per dose level until one of the off-study criteria are met.

Three patients are enrolled in each cohort. If at least one DLT occurs, three additional patients are added to the cohort at that particular dose level. If two DLTs occur, the MTD, defined as the dose at which fewer than one-third of patients at each dose level experiences DLT has been exceeded and four more patients are treated at the previous dose.

Patients who experience DLT during the first 4-week cycle are removed from the study, except if they have a response to therapy. For patients who have completed their first 4-week cycle of without DLT, but who subsequently experience Grade 3 or 4 hematological and/or nonhematological toxicity, treatment is suspended for a minimum of a week. If the toxicity resolves to < Grade 2 within three weeks, the patient is treated at two dose levels lower than the dose that caused the toxicity (or a 50% reduction if the patient was treated at the first or second dose level). Patients in whom Grade 3 or 4 toxicity does not resolve to < Grade 1 within three weeks, or those who have another Grade 3 toxicity at the reduced dose are removed from the study.

Pharmacokinetic sampling is performed prior the first dose of 3-(4-amino-1-oxo-1,3 -dihydro-isoindol-2-yl)-piperidine-2,6-dione (Day 1) and 0.5, 1, 2, 4, 6, 8, 24, and 48 hours thereafter. Sampling is also conducted pre-dose on Days 7 and 21 and 0.5, 1, 2, 4, 6, 8, and 24 post-dose on Day 21 to evaluate steady-state 3-(4-amino-1-oxo-1,3-dihydro-isoindol -2-yl)-piperidine-2,6-dione levels.

### 6.5.5 TREATMENT OF METASTATIC MELANOMA

Patients with metastatic melanoma were started on 3-(4-amino-1-oxo-1,3-dihydro -isoindol-2-yl)-piperidine-2,6-dione (Revmid™) at 5 mg/day for seven days. The dose was then increased every seven days to 10 mg/day, 25 mg/day, and 50 mg/day, respectively, for a total of four weeks on therapy. Five of the 13 melanoma patients who were treated under this regimen either showed disease stabilization or a partial response in the first four weeks of treatment. Tumor response was seen in cutaneous and subcutaneous lesions (five patients), lymph nodes (two patients), and liver (one patient). The duration of response was approximately six months. The result suggests that the compound appears is a promising new anti-cancer agent and has both antiangiogenic and immunomodulatory properties.

### 6.5.6 TREATMENT OF RELAPSED OR REFRACTORY MULTIPLE MYELOMA

Patients with relapsed and refractory Dune-Salmon stage III multiple myeloma, who have either failed at least three previous regimens or presented with poor performance status, neutropenia or thrombocytopenia, are treated with up to four cycles of combination of melphalan (50 mg intravenously), an immunomodulatory compound of the invention (about 1 to 150 mg orally daily), and dexamethasone (40 mg/day orally on days 1 to 4) every four to six weeks. Maintenance treatment consisting of daily an immunomodulatory compound of the invention and monthly dexamethasone are continued until the disease progression. The therapy using an immunomodulatory compound of the invention in combination with melphalan and dexamethasone is highly active and generally tolerated in heavily pretreated multiple myeloma patients whose prognosis is otherwise poor.

The embodiments of the invention described above are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope of the invention and are encompassed by the appended claims.

## CLAIMS

What is claimed is:

1. A method of treating, managing or preventing a specific cancer, which comprises administering to a patient in need of such treatment, management or prevention a therapeutically or prophylactically effective amount of an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

2. A method of treating, managing or preventing a specific cancer, which comprises administering to a patient in need of such treatment, management or prevention a therapeutically or prophylactically effective amount of an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, and a therapeutically or prophylactically effective amount of a second active ingredient, radiation therapy, hormonal therapy, biological therapy or immunotherapy.

3. A method of treating, managing or preventing a disease associated with undesired angiogenesis, which comprises administering to a patient in need of such treatment, management or prevention a therapeutically or prophylactically effective amount of an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

4. A method of treating, managing or preventing a disease associated with undesired angiogenesis, which comprises administering to a patient in need of such treatment, management or prevention a therapeutically or prophylactically effective amount of an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, and a therapeutically or prophylactically effective amount of a second active ingredient.

5. The method of claim 1, wherein the cancer is advanced malignancy, amyloidosis, neuroblastoma, meningioma, hemangiopericytoma, multiple brain metastase, glioblastoma multiforms, glioblastoma, brain stem glioma, poor prognosis malignant brain tumor, malignant glioma, anaplastic astrocytoma, anaplastic oligodendroglioma, neuroendocrine tumor, rectal adenocarcinoma, Dukes C & D colorectal cancer, unresectable colorectal carcinoma, metastatic hepatocellular carcinoma, Kaposi's sarcoma, karotype acute myeloblastic leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous

T-Cell lymphoma, cutaneous B-Cell lymphoma, diffuse large B-Cell lymphoma, low grade follicular lymphoma, malignant melanoma, malignant mesothelioma, malignant pleural effusion mesothelioma syndrome, peritoneal carcinoma, papillary serous carcinoma, gynecologic sarcoma, soft tissue sarcoma, scelroderma, cutaneous vasculitis, Langerhans cell histiocytosis, leiomyosarcoma, fibrodysplasia ossificans progressive, hormone refractory prostate cancer, resected high-risk soft tissue sarcoma, unrescectable hepatocellular carcinoma, Waldenstrom's macroglobulinemia, smoldering myeloma, indolent myeloma, fallopian tube cancer, androgen independent prostate cancer, androgen dependent stage IV non-metastatic prostate cancer, hormone-insensitive prostate cancer, chemotherapy-insensitive prostate cancer, papillary thyroid carcinoma, follicular thyroid carcinoma, medullary thyroid carcinoma, or leiomyoma.

6. The method of claim 2, wherein the cancer is advanced malignancy, amyloidosis, locally advanced bladder cancer, metastatic transitional cell bladder cancer, relapsed brain tumor, progressive brain tumor, neuroblastoma, meningioma, hemangiopericytoma, multiple brain metastase, glioblastoma multiforms, glioblastoma, brain stem glioma, poor prognosis malignant brain tumor, malignant glioma, anaplastic astrocytoma, anaplastic oligodendroglioma, metastatic breast cancer, neuroendocrine tumor, rectal adenocarcinoma, Dukes C & D colorectal cancer, unresectable colorectal carcinoma, metastatic hepatocellular carcinoma, Kaposi's sarcoma, karotype acute myeloblastic leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-Cell lymphoma, cutaneous B-Cell lymphoma, diffuse large B-Cell lymphoma, low grade follicular lymphoma, malignant melanoma, malignant mesothelioma, stage IIIB non-small cell lung cancer, malignant pleural effusion mesothelioma syndrome, mutiple myeloma, peritoneal carcinoma, papillary serous carcinoma, gynecologic sarcoma, soft tissue sarcoma, scelroderma, cutaneous vasculitis, Langerhans cell histiocytosis, leiomyosarcoma, fibrodysplasia ossificans progressive, hormone refractory prostate cancer, resected high-risk soft tissue sarcoma, unrescectable hepatocellular carcinoma, Waldenstrom's macroglobulinemia, smoldering myeloma, indolent myeloma, fallopian tube cancer, androgen independent prostate cancer, androgen dependent stage IV non-metastatic prostate cancer, hormone-insensitive prostate cancer, chemotherapy-insensitive prostate cancer, papillary thyroid carcinoma, follicular thyroid carcinoma, medullary thyroid carcinoma, or leiomyoma.

7. The method of claim 3 or 4, wherein the disease or disorder is diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, neovascular glaucoma,

retrolental fibroplasia, proliferative vitreoretinopathy, trachoma, myopia, optic pits, epidemnic keratoconjunctivitis, atopic keratitis, superior limbic keratitis, pterygium keratitis sicca, sjogrens, acne rosacea, phylectenulosis, syphilis, lipid degeneration, bacterial ulcer, fungal ulcer, Herpes simplex infection, Herpes zoster infection, protozoan infection, Kaposi sarcoma, Mooren ulcer, Terrien's marginal degeneration, mariginal keratolysis, rheumatoid arthritis, systemic lupus, polyarteritis, trauma, Wegeners sarcoidosis, Scleritis, Steven's Johnson disease, periphigoid radial keratotomy, sickle cell anemia, sarcoid, pseudoxanthoma elasticum, Pagets disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic uveitis, chronic vitritis, Lyme's disease, Eales disease, Bechets disease, retinitis, choroiditis, presumed ocular histoplasmosis, Bests disease, Stargarts disease, pars planitis, chronic retinal detachment, hyperviscosity syndromes, toxoplasmosis, sclerosing cholangitis, or rubeosis.

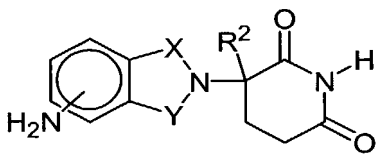
8. The method of claim 2 or 4, wherein the second active ingredient is hematopoietic growth factor, cytokine, anti-cancer agent, antibiotic, cox-2 inhibitor, immunomodulatory agent, immunosuppressive agent, corticosteroid, or a pharmacologically active mutant or derivative thereof.

9. The method of claim 8, wherein the second active ingredient is oblimersen, melphalan, G-CSF, GM-CSF, EPO, topotecan, pentoxifylline, taxotere, iritotecan, a COX-2 inhibitor, ciprofloxacin, dexamethasone, doxorubicin, vincristine, IL 2, IFN, dacarbazine, Ara-C, vinorelbine, isotretinoin, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, or a pharmacologically active mutant or derivative thereof.

10. The method of one of claims 1-4, wherein the immunomodulatory compound is 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione.

11. The method of one of claims 1-4, wherein the immunomodulatory compound is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione.

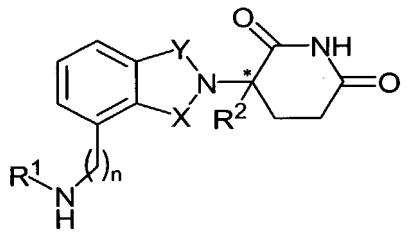
12. The method of one of claims 1-4, wherein the immunomodulatory compound is of formula (I):



(I)

wherein one of X and Y is C=O, the other of X and Y is C=O or $CH_2$, and $R^2$ is hydrogen or lower alkyl.

13. The method of one of claims 1-4, wherein the immunomodulatory compound is of formula (II):



(II)

wherein

one of X and Y is C=O and the other is $CH_2$ or C=O;

$R^1$ is H, $(C_1–C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $C(O)R^3$, $C(S)R^3$, $C(O)OR^4$, $(C_1–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–$OR^5$, $(C_1–C_8)$alkyl–$C(O)OR^5$, $C(O)NHR^3$, $C(S)NHR^3$, $C(O)NR^3R^{3'}$, $C(S)NR^3R^{3'}$ or $(C_1–C_8)$alkyl–$O(CO)R^5$;

$R^2$ is H, F, benzyl, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, or $(C_2–C_8)$alkynyl;

$R^3$ and $R^{3'}$ are independently $(C_1–C_8)$alkyl, $(C_3–C_7)$cycloalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl, $(C_0–C_8)$alkyl–$N(R^6)_2$, $(C_1–C_8)$alkyl–$OR^5$, $(C_1–C_8)$alkyl–$C(O)OR^5$, $(C_1–C_8)$alkyl–$O(CO)R^5$, or $C(O)OR^5$;

$R^4$ is $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, $(C_1–C_4)$alkyl–$OR^5$, benzyl, aryl, $(C_0–C_4)$alkyl–$(C_1–C_6)$heterocycloalkyl, or $(C_0–C_4)$alkyl–$(C_2–C_5)$heteroaryl;

$R^5$ is $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, or $(C_2–C_5)$heteroaryl;

each occurrence of $R^6$ is independently H, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl, benzyl, aryl, $(C_2–C_5)$heteroaryl, or $(C_0–C_8)$alkyl–$C(O)O–R^5$ or the $R^6$ groups join to form a heterocycloalkyl group;

n is 0 or 1; and

* represents a chiral-carbon center.

14. The method of one of claims 1-4, wherein the immunomodulatory compound is a cyano or carboxy derivative of a substituted styrene, 1-oxo-2-(2,6-dioxo-3-fluoropiperidin-3yl) isoindoline, 1,3-dioxo-2-(2,6-dioxo-3-fluoropiperidine-3-yl) isoindoline, or tetra substituted 2-(2,6-dioxopiperdin-3-yl)-1-oxoisoindoline.

15. The method of claim 14, wherein the immunomodulatory compound is enantiomerically pure.

16. A pharmaceutical composition comprising an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, and a second active ingredient, wherein the second active ingredient is hematopoietic growth factor, cytokine, anti-cancer agent, antibiotic, cox-2 inhibitor, immunomodulatory agent, immunosuppressive agent, corticosteroid, or a pharmacologically active mutant or derivative thereof.

17. A pharmaceutical composition comprising an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, and a second active ingredient, wherein the second active ingredient is oblimersen, melphalan, G-CSF, GM-CSF, EPO, a cox-2 inhibitor, topotecan, pentoxifylline, ciprofloxacin, taxotere, iritotecan, dexamethasone, doxorubicin, vincristine, IL 2, IFN, dacarbazine, Ara-C, vinorelbine, isotretinoin, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, or a pharmacologically active mutant or derivative thereof.

18. The pharmaceutical composition of claim 16 or 17, wherein the immunomodulatory compound is enantiomerically pure.

19. A kit comprising:

a pharmaceutical composition comprising an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof; and

a pharmaceutical composition comprising hematopoietic growth factor, cytokine, anti-cancer agent, antibiotic, a cox-2 inhibitor, immunomodulatory agent, immunosuppressive agent, corticosteroid, or a pharmacologically active mutant or derivative thereof, or a combination thereof.

20. A kit comprising:

a pharmaceutical composition comprising an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof; and

a pharmaceutical composition comprising oblimersen, melphalan, G-CSF, GM-CSF, EPO, a cox-2 inhibitor, topotecan, pentoxifylline, taxotere, iritotecan, ciprofloxacin, dexamethasone, doxorubicin, vincristine, IL 2, IFN, dacarbazine, Ara-C, vinorelbine, isotretinoin, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, or a pharmacologically active mutant or derivative thereof, or a combination thereof.

21. A kit comprising:

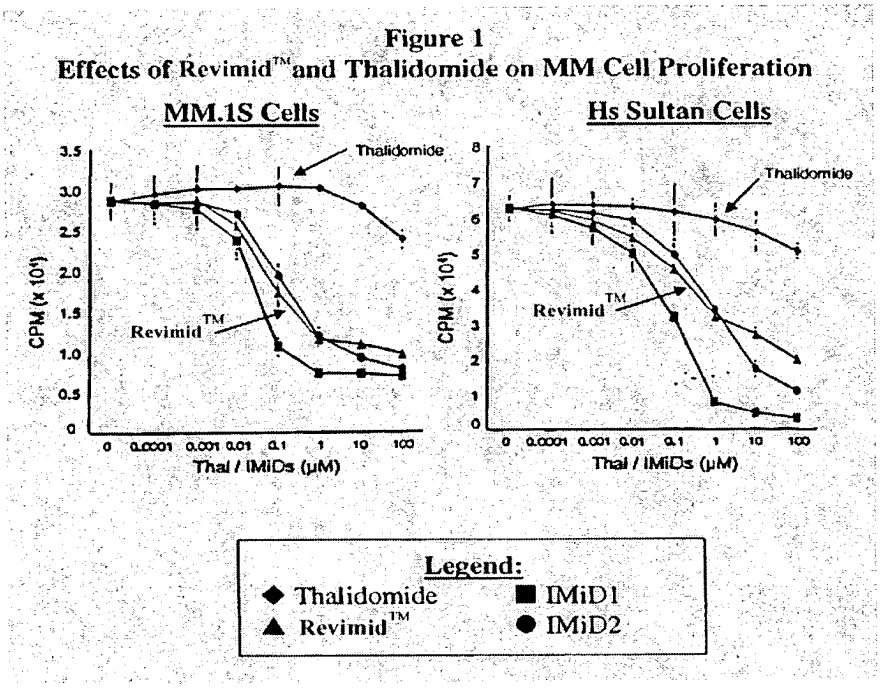
a pharmaceutical composition comprising an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof; and

umbilical cord blood, placental blood, peripheral blood stem cell, hematopoietic stem cell preparation or bone marrow.

## ABSTRACT

Methods of treating, preventing and/or managing cancer as well as and diseases and disorders associated with, or characterized by, undesired angiogenesis are disclosed. Specific methods encompass the administration of an immunomodulatory compound alone or in combination with a second active ingredient. The invention further relates to methods of reducing or avoiding adverse side effects associated with chemotherapy, radiation therapy, hormonal therapy, biological therapy or immunotherapy which comprise the administration of an immunomodulatory compound. Pharmaceutical compositions, single unit dosage forms, and kits suitable for use in methods of the invention are also disclosed.

**Figure 1**
**Effects of Revimid™ and Thalidomide on MM Cell Proliferation**



7-9-04 1614 JRW

**EXPRESS MAIL NO. EV475140930US**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Application of: Jerome B. Zeldis

Group Art Unit: 1614

Serial No.: 10/438,213

Examiner: To be assigned

Filed: May 15, 2003

Attorney Docket No.: 501872-999073
(Formerly 9516-074-999)

For: METHODS AND COMPOSITIONS USING IMMUNOMODULATORY COMPOUNDS FOR TREATMENT AND MANAGEMENT OF CANCERS AND OTHER DISEASES

**PRELIMINARY AMENDMENT**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Prior to examination on the merits, please enter the following amendments and remarks into the file of the above-captioned application.

**Amendments to the Claims** are reflected in the listing of the claims that begins on page 2 of this paper.

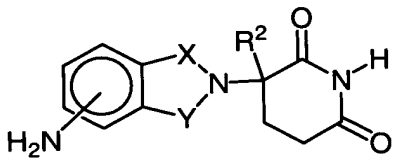
**Remarks** begin on page 6 of this paper.

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of the Claims:**

Claims 1-21. (canceled without prejudice)

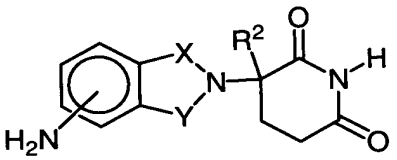
22. (new) A method of treating prostate cancer, which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I):



(I)

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, wherein one of X and Y is C=O, the other of X and Y is C=O or $CH_2$, and $R^2$ is hydrogen or lower alkyl.

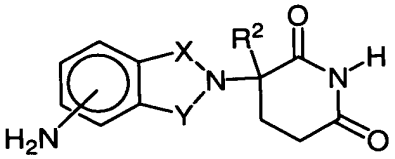
23. (new) A method of treating metastatic melanoma, which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I):



(I)

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, wherein one of X and Y is C=O, the other of X and Y is C=O or $CH_2$, and $R^2$ is hydrogen or lower alkyl.

24. (new) A method of treating multiple myeloma, which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I):



(I)

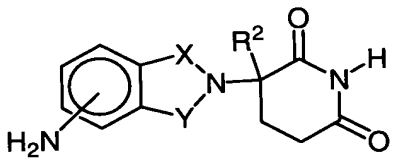
or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, wherein one of X and Y is C=O, the other of X and Y is C=O or $CH_2$, and $R^2$ is hydrogen or lower alkyl.

25. (new) The method of claim 22, wherein the prostate cancer is hormone refractory prostate cancer, hormone-insensitive prostate cancer, androgen independent prostate cancer, androgen dependent stage IV non-metastatic prostate cancer, or chemotherapy-insensitive prostate cancer.

26. (new) The method of claim 24, wherein the multiple myeloma is smoldering myeloma, indolent myeloma, chemotherapy responsive multiple myeloma, refractory myeloma, relapsed myeloma, or relapsed and refractory Dune-Salmon stage III multiple myeloma.

27. (new) The method of claim 22, 23 or 24, wherein $R^2$ is hydrogen.

28. (new) The method of claim 22, 23 or 24, wherein the compound has formula (I):




(I)

wherein one of X and Y is C=O, the other of X and Y is C=O or $CH_2$, and $R^2$ is hydrogen or lower alkyl.

29. (new) The method of claim 22, 23 or 24, wherein the compound is a pharmaceutically acceptable salt.

30. (new) The method of claim 22, 23 or 24, wherein the compound is a pharmaceutically acceptable solvate.

31. (new) The method of claim 22, 23 or 24, wherein the compound is a pharmaceutically acceptable stereoisomer.

32. (new) The method of claim 31, wherein the stereoisomer is an enantiomerically pure R isomer.

33. (new) The method of claim 31, wherein the stereoisomer is an enantiomerically pure S isomer.

34. (new) The method of claim 22, 23 or 24, wherein the compound is 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione.

35. (new) The method of claim 22, 23 or 24, wherein the compound is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione.

36. (new) The method of claim 22, which further comprises administering a therapeutically effective amount of a second active agent.

37. (new) The method of claim 23, which further comprises administering a therapeutically effective amount of a second active agent.

38. (new) The method of claim 24, which further comprises administering a therapeutically effective amount of a second active agent.

39. (new) The method of claim 36, 37 or 38, wherein the second active agent is hematopoietic growth factor, a cytokine, or an anti-cancer agent.

40. (new) The method of claim 39, wherein the second active agent is G-CSF, GM-CSF, EPO, IL 2, IFN, or a pharmacologically active mutant or derivative thereof.

41. (new) The method of claim 39, wherein the second active agent is oblimersen, melphalan, topotecan, pentoxifylline, taxotere, iritotecan, ciprofloxacin, dexamethasone, doxorubicin, vincristine, dacarbazine, Ara-C, vinorelbine, prednisone, cyclophosphamide, bortezomib, arsenic trioxide or a combination thereof.

42. (new) The method of claim 22, 23 or 24, which further comprises administering radiation therapy, hormonal therapy, biological therapy or immunotherapy.

43. (new) The method of claim 36, wherein the second active agent is taxotere.

44. (new) The method of claim 43, wherein the compound is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione.

45. (new) The method of claim 43, wherein the cancer is hormone refractory prostate cancer and the compound is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione.

46. (new) The method of claim 36, wherein the second active agent is GM-CSF.

47. (new) The method of claim 46, wherein the compound is 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione.

48. (new) The method of claim 38, wherein the compound is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, and the second active agent is melphalan or prednisone.

49. (new) The method of claim 38, wherein the compound is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, and the second active agent is cyclophosphamide.

50. (new) The method of claim 38, wherein the compound is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, and the second active agent is bortezomib.

51. (new) The method of claim 38, wherein the compound is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, and the second active agent is dexamethasone.

52. (new) The method of claim 38, wherein the compound is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, and the second active agent is arsenic trioxide.

## REMARKS

New claims 22-52 appear in the application for the Examiner's consideration. Claims 1-21 have been canceled without prejudice to Applicant's right to pursue them in one or more continuations, divisionals or continuations-in-part. The new claims are supported by canceled claims 1-21 and the originally filed specification. No new matter has been added.

If any fee is due for this Preliminary Amendment, please charge such fee to Jones Day Deposit Account No. 503013.

Respectfully submitted,

Date July 7, 2004

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8-25-04

16/4

Filed

**EXPRESS MAIL NO.: ED 300794913 US**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Application of: Jerome B. Zeldis

Group Art Unit: 1614

Serial No.: 10/438,213

Examiner: To be assigned

Filed: May 15, 2003

Attorney Docket No.: 501872-999073
(Formerly 9516-074-999)

For: METHODS AND COMPOSITIONS USING IMMUNOMODULATORY COMPOUNDS FOR TREATMENT AND MANAGEMENT OF CANCERS AND OTHER DISEASES

## INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. §1.56 AND §1.97

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the duty of disclosure imposed by 37 C.F.R. § 1.56 and § 1.97 to inform the Patent Office of all references coming to the attention of each individual associated with the filing or prosecution of the subject application, which are or may be material to the patentability of any claim of the application, Applicants hereby direct the Examiner's attention to the references **A01-A86, B01-B08 and C01 - C28** listed on the attached form PTO 1449 entitled "List of References Cited by Applicant."

Identification of the listed references is not to be construed an admission of Applicant or Attorneys for Applicant that such references are available as "prior art" against the subject application. Applicant respectfully requests that the Examiner review the foregoing references and that the references be made of record in the file history of the application.

This Information Disclosure Statement is filed under 37 C.F.R. §1.97(b) before the mailing of the first Office action on the merits. Therefore, no fee is believed to be due.

Should any fee be required, however, please charge such fee to Jones Day Deposit Account No. **503013**.

Respectfully submitted,

Date: August 23, 2004

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| ATTY DOCKET NO. | APPLICATION NO |
|---|---|
| 9516-074-999 | 10/438,213 |
| APPLICANT | |
| Zeldis | |
| FILING DATE | GROUP |
| May 15, 2003 | 1614 |

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(Use several sheets if necessary)

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| **EXAMINER** | **DATE CONSIDERED** |
|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with **MPEP 609**; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

10-15-04

1614
JPW

**EXPRESS MAIL NO.: EV475141229US**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Application of: Jerome B. Zeldis

Group Art Unit: 1614

Serial No.: 10/438,213

Examiner: To be assigned

Filed: May 15, 2003

Attorney Docket No.: 501872-999073
(Formerly 9516-074-999)

For: METHODS AND COMPOSITIONS USING IMMUNOMODULATORY COMPOUNDS FOR TREATMENT AND MANAGEMENT OF CANCERS AND OTHER DISEASES

## SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. §1.56 AND §1.97

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the duty of disclosure imposed by 37 C.F.R. § 1.56 and § 1.97 to inform the Patent Office of all references coming to the attention of each individual associated with the filing or prosecution of the subject application, which are or may be material to the patentability of any claim of the application, Applicants hereby direct the Examiner's attention to reference **C29** listed on the attached form PTO 1449 entitled "List of References Cited by Applicant."

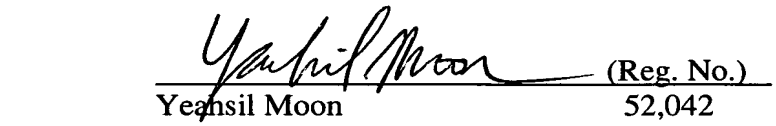
Identification of the listed references is not to be construed an admission of Applicant or Attorneys for Applicant that such references are available as "prior art" against the subject application. Applicant respectfully requests that the Examiner review the foregoing references and that the references be made of record in the file history of the application.

This Information Disclosure Statement is filed under 37 C.F.R. §1.97(b) before the mailing of the first Office action on the merits. Therefore, no fee is believed to be due.

Should any fee be required, however, please charge such fee to Jones Day Deposit Account No. **503013**.

Respectfully submitted,

Date: October 14, 2004

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Enclosures

# LIST OF REFERENCES CITED BY APPLICANT

(Use several sheets if necessary)

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|---|---|
| 9516-074-999 | 10/438,213 |
| APPLICANT | |
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| May 15, 2003 | 1614 |

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| *EXAMINER INITIAL | | DOCUMENT NUMBER | DATE | NAME | CLASS | SUBCLASS | FILING DATE IF APPROPRIATE |
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with **MPEP 609**; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

03-02-05 1614


Express Mail No.: EV452774510US

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Application of: | Zeldis | Confirmation No.: | 4802 |
| Serial No.: | 10/438,213 | Group Art Unit: | 1614 |
| Filed: | May 15, 2003 | Examiner: | To Be Assigned |
| For: | METHODS AND COMPOSITIONS USING IMMUNOMODULATORY COMPOUNDS FOR TREATMENT AND MANAGEMENT OF CANCERS AND OTHER DISEASES | Attorney Docket No.: | 9516-074-999 |

**SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. §1.97 & §1.56**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the duty of disclosure imposed by 37 C.F.R. §1.56 to inform the Patent and Trademark Office of all references coming to the attention of Applicant or his attorneys which are or may be related to patentability of the claimed invention, Applicant hereby directs the Examiner's attention to references **C30** to **C52,** which are listed on the accompanying revised PTO Form 1449.

Legible copies of listed references **C30** to **C52** are provided herewith. Applicants respectfully request that the Examiner review the foregoing references and that the references be made of record in the file history of the application. Identification of the listed references is not to be construed an admission by Applicant or his attorneys that such references are available as "prior art" against the subject application.



NYJD: 1535994.1

Pursuant to 37 C.F.R. § 1.97(b), it is estimated that no fee is due. However, if a fee is deemed to be due, please charge the required fee to Jones Day Deposit Account No. 50-3013. A duplicate of this sheet is enclosed for accounting purposes.

Respectfully submitted,

Date: March 1, 2005

Anthony M. Insogna 35,203
(Reg. No.)
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San Diego, California 92130
(858) 314-1200

By:

Yeah-Sil Moon 52,042
(Reg. No.)
**JONES DAY**
222 East 41st Street
New York, New York 10017-6702
(212) 326-3939

LIST OF REFERENCES CITED BY APPLICANT
(Use several sheets if necessary)

| ATTY DOCKET NO. | APPLICATION NO. |
|---|---|
| 9516-074-999 | 10/438,213 |
| APPLICANT | |
| Zeldis | |
| FILING DATE | GROUP |
| May 15, 2003 | 1614 |

## U.S. PATENT DOCUMENTS

| *EXAMINER INITIAL | | DOCUMENT NUMBER | DATE | NAME | CLASS | SUBCLASS | FILING DATE IF APPROPRIATE |
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## FOREIGN PATENT DOCUMENTS

| | | DOCUMENT NUMBER | DATE | COUNTRY | CLASS | SUBCLASS | TRANSLATION | |
|---|---|---|---|---|---|---|---|---|
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## OTHER REFERENCES *(Including Author, Title, Date, Pertinent Pages, Etc.)*

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| | C30 | Alexanian et al., 2004, "VTD (Velcade, thalidomide, dexamethasone) as primary therapy for newly-diagnosed multiple myeloma," Am. Soc. Hematol. 46th Ann. Meeting Dec. 4-7, 2004, San Diego, CA Abstract #210 |
| | C31 | Anderson, 2000, "Thalidomide: Therapeutic potential in hematologic malignancies," Seminars in Hematology 37(1 Supp 3): 1-4 |
| | C32 | Attal et al., 2004, "Maintenance treatment with thalidomide after autologous transplantation for myeloma: First analysis of a prospective randomized study of the Intergroupe Francophone du Myelome (IFM 99 02)," Am. Soc. Hematol. 46th Ann. Meeting Dec. 4-7, 2004, San Diego, CA Abstract #535 |
| | C33 | Bernardeschi et al., 2003, J. Exp. Clin. Cancer Res. 22(4):129-133 |
| | C34 | Corral et al., 1999, "Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha," J. Immunol. 163(1):380-386 |
| | C35 | Davies et al., 2001, "Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma," Blood 98(1):210-216 |
| | C36 | Dimopoulos et al., 2004, "Primary treatment with puilsed melphalan, dexamethasone, thalidomide (MDT) for symptomatic patients with multiple myeloma ≥75 years of age," Am. Soc. Hematol. 46th Ann. Meeting Dec. 4-7, 2004, San Diego, CA Abstract #1482 |
| | C37 | Eisen et al., 2000, "Continuous low dose Thalidomide: a phase II study in advanced melanoma, renal cell, ovarian and breast cancer," Br. J. Cancer 82(4):812-817 |
| | C38 | Fakhouri et al., 2004, "Thalidomide in patients with multiple myeloma and renal failure," Br. J. Haematol. 125:90-102 |
| | C39 | Fenk et al., 2005, "Single-agent thalidomide for treatment of first relapse following high-dose chemotherapy in patients with multiple myeloma," Leukemia 19(1):156-159 |
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| | C45 | Raje et al., 1999, "Thalidomide--a revival story," N. Engl. J. Med. 341(21):1606-1609 |
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| | C47 | Rajkumar et al., 2000, "Prognostic value of bone marrow angiogenesis in multiple myeloma," Clin. Cancer Res. 6(8):3111-3116 |
| | C48 | Ribatti et al., 1999, "Bone marrow angiogenesis and mast cell density increase simultaneously with progression of human multiple myeloma," Br. J. Cancer 79(3-4):451-455 |

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| | C49 | Singhal et al., 1999, Antitumor activity of thalidomide in refractory multiple myeloma," N. Engl. J. Med. 341(21):1565-1571 |
| | C50 | Steins et al., 2002, "Efficacy and safety of thalidomide in patients with acute myeloid leukemia," Blood 99(3):834-839 |
| | C51 | Vacca et al., 1999, "Bone marrow neovascularization, plasma cell angiogenic potential, and matrix metalloproteinase-2 secretion parallel progression of human multiple myeloma," Blood 93(9):3064-3073 |
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| EXAMINER | DATE CONSIDERED |
|---|---|

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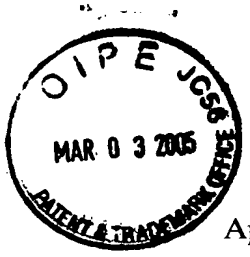
3-7-05 1614




**EXPRESS MAIL NO. EV452774452US**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Application of: Jerome B. Zeldis

Group Art Unit: 1614

Serial No.: 10/438,213

Examiner: To be assigned

Filed: May 15, 2003

Attorney Docket No.: 501872-999073
(Formerly 9516-074-999)

For: METHODS AND COMPOSITIONS USING IMMUNOMODULATORY COMPOUNDS FOR TREATMENT AND MANAGEMENT OF CANCERS AND OTHER DISEASES

**SUPPLEMENTAL PRELIMINARY AMENDMENT**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Prior to examination on the merits, please enter the following amendments and remarks into the file of the above-captioned application.

**Amendments to the Claims** are reflected in the listing of the claims that begins on page 2 of this paper.

**Remarks** begin on page 6 of this paper.



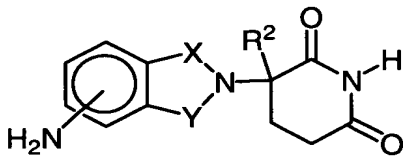
NYJD: 1532187.2

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of the Claims:**

Claims 1-21. (canceled without prejudice)

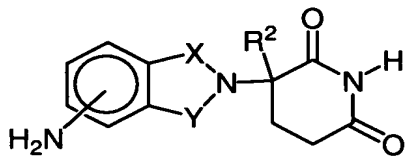
22. (previously presented) A method of treating prostate cancer, which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I):



(I)

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, wherein one of X and Y is C=O, the other of X and Y is C=O or $CH_2$, and $R^2$ is hydrogen or lower alkyl.

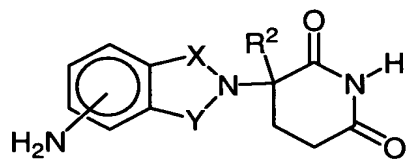
23. (previously presented) A method of treating metastatic melanoma, which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I):



(I)

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, wherein one of X and Y is C=O, the other of X and Y is C=O or $CH_2$, and $R^2$ is hydrogen or lower alkyl.

24. (previously presented) A method of treating multiple myeloma, which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I):



(I)

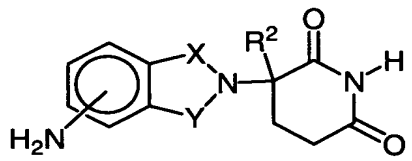
or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, wherein one of X and Y is C=O, the other of X and Y is C=O or $CH_2$, and $R^2$ is hydrogen or lower alkyl.

25. (previously presented) The method of claim 22, wherein the prostate cancer is hormone refractory prostate cancer, hormone-insensitive prostate cancer, androgen independent prostate cancer, androgen dependent stage IV non-metastatic prostate cancer, or chemotherapy-insensitive prostate cancer.

26. (previously presented) The method of claim 24, wherein the multiple myeloma is smoldering myeloma, indolent myeloma, chemotherapy responsive multiple myeloma, refractory myeloma, relapsed myeloma, or relapsed and refractory Dune-Salmon stage III multiple myeloma.

27. (previously presented) The method of claim 22, 23 or 24, wherein $R^2$ is hydrogen.

28. (previously presented) The method of claim 22, 23 or 24, wherein the compound has formula (I):




(I)

wherein one of X and Y is C=O, the other of X and Y is C=O or $CH_2$ , and $R^2$ is hydrogen or lower alkyl.

29. (previously presented) The method of claim 22, 23 or 24, wherein the compound is a pharmaceutically acceptable salt.

30. (previously presented) The method of claim 22, 23 or 24, wherein the compound is a pharmaceutically acceptable solvate.

31. (previously presented) The method of claim 22, 23 or 24, wherein the compound is a pharmaceutically acceptable stereoisomer.

32. (previously presented) The method of claim 31, wherein the stereoisomer is an enantiomerically pure R isomer.

33. (previously presented) The method of claim 31, wherein the stereoisomer is an enantiomerically pure S isomer.

34. (previously presented) The method of claim 22, 23 or 24, wherein the compound is 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione.

35. (previously presented) The method of claim 22, 23 or 24, wherein the compound is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione.

36. (previously presented) The method of claim 22, which further comprises administering a therapeutically effective amount of a second active agent.

37. (previously presented) The method of claim 23, which further comprises administering a therapeutically effective amount of a second active agent.

38. (previously presented) The method of claim 24, which further comprises administering a therapeutically effective amount of a second active agent.

39. (previously presented) The method of claim 36, 37 or 38, wherein the second active agent is hematopoietic growth factor, a cytokine, or an anti-cancer agent.

40. (previously presented) The method of claim 39, wherein the second active agent is G-CSF, GM-CSF, EPO, IL 2, IFN, or a pharmacologically active mutant or derivative thereof.

41. (previously presented) The method of claim 39, wherein the second active agent is oblimersen, melphalan, topotecan, pentoxifylline, taxotere, irinotecan, ciprofloxacin, dexamethasone, doxorubicin, vincristine, dacarbazine, Ara-C, vinorelbine, prednisone, cyclophosphamide, bortezomib, arsenic trioxide or a combination thereof.

42. (previously presented) The method of claim 22, 23 or 24, which further comprises administering radiation therapy, hormonal therapy, biological therapy or immunotherapy.

43. (previously presented) The method of claim 36, wherein the second active agent is taxotere.

44. (previously presented) The method of claim 43, wherein the compound is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione.

45. (previously presented) The method of claim 43, wherein the cancer is hormone refractory prostate cancer and the compound is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione.

46. (previously presented) The method of claim 36, wherein the second active agent is GM-CSF.

47. (previously presented) The method of claim 46, wherein the compound is 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione.

48. (previously presented) The method of claim 38, wherein the compound is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, and the second active agent is melphalan or prednisone.

49. (previously presented) The method of claim 38, wherein the compound is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, and the second active agent is cyclophosphamide.

50. (previously presented) The method of claim 38, wherein the compound is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, and the second active agent is bortezomib.

51. (previously presented) The method of claim 38, wherein the compound is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, and the second active agent is dexamethasone.

52. (previously presented) The method of claim 38, wherein the compound is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, and the second active agent is arsenic trioxide.

53. (new) The method of claim 38, wherein the compound is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione and the second active agent is irinotecan.

54. (new) The method of claim 53, wherein the irinotecan is a pharmaceutically acceptable salt.

55. (new) The method of claim 54, wherein the pharmaceutically acceptable salt is a hydrochloride salt.

56. (new) The method of claim 55, wherein the hydrochloride salt is CPT-11.

## REMARKS

Claims 22-56 are pending in this application. Claims 22-52 were previously presented on July 7, 2004 and claims 53-56 have been newly added. The new claims are supported by claim 41 and the originally filed specification, for example, page 17, line 16; page 20, line 22; page 23, line 29 to page 24, line 2; page 24, line 29; and page 46, line 12 to page 48, line 7. No new matter has been added.

If any fee is due for this Preliminary Amendment, please charge such fee to Jones Day Deposit Account No. 503013.

Respectfully submitted,

Date March 3, 2005

Yeahsil Moon (Reg. No. 52,042)
**Jones Day**
222 East 41st Street
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Tel: 212-326-3778

For: Anthony M. Insogna (Reg. No. 35,203)
**Jones Day**
12750 High Bluff Drive, Suite 300
San Diego, CA 92130

3-16-05

1614

JPW

**EXPRESS MAIL NO.: EV452774863US**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Application of: Jerome B. Zeldis

Group Art Unit: 1614

Serial No.: 10/438,213

Examiner: To be assigned

Filed: May 15, 2003

Attorney Docket No.: 501872-999073
(Formerly 9516-074-999)

For: METHODS AND COMPOSITIONS USING IMMUNOMODULATORY COMPOUNDS FOR TREATMENT AND MANAGEMENT OF CANCERS AND OTHER DISEASES

**SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. §1.56 AND §1.97**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the duty of disclosure imposed by 37 C.F.R. § 1.56 and § 1.97 to inform the Patent Office of all references coming to the attention of each individual associated with the filing or prosecution of the subject application, which are or may be material to the patentability of any claim of the application, Applicants hereby direct the Examiner's attention to reference **A87** listed on the attached form PTO 1449 entitled "List of References Cited by Applicant."

Identification of the listed references is not to be construed an admission of Applicant or Attorneys for Applicant that such references are available as "prior art" against the subject application. Applicant respectfully requests that the Examiner review the foregoing references and that the references be made of record in the file history of the application.

This Information Disclosure Statement is filed under 37 C.F.R. §1.97(b) before the mailing of the first Office action on the merits. Therefore, no fee is believed to be due.

Should any fee be required, however, please charge such fee to Jones Day Deposit Account No. **503013**.

Respectfully submitted,

Date: March 15, 2005


| | (Reg. No.) |
|---|---|
| Yeahsil Moon | 52,042 |
| For: Anthony M. Insogna | 35,203 |

**JONES DAY**
222 East 41st Street
New York, New York 10017
(212) 326-3939


Enclosures

# LIST OF REFERENCES CITED BY APPLICANT

(Use several sheets if necessary)

| ATTY. DOCKET NO. | APPLICATION NO. |
|---|---|
| 9516-074-999 | 10/438,213 |
| APPLICANT | |
| Zeldis | |
| FILING DATE | GROUP |
| May 15, 2003 | 1614 |

## U.S. PATENT DOCUMENTS

| *EXAMINER INITIAL | | DOCUMENT NUMBER | DATE | NAME | CLASS | SUBCLASS | FILING DATE IF APPROPRIATE |
|---|---|---|---|---|---|---|---|
| | A87 | 2004/0266809 | 12/30/04 | Emanuel et al. | | | |
| | A88 | | | | | | |
| | A89 | | | | | | |
| | A90 | | | | | | |
| | A91 | | | | | | |

## FOREIGN PATENT DOCUMENTS

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| | B01 | | | | | | | |
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## OTHER REFERENCES *(Including Author, Title, Date, Pertinent Pages, Etc.)*

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| | C01 | |
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| EXAMINER | DATE CONSIDERED |
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04-18-05 1614

**EXPRESS MAIL NO.: EV452775064US**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Application of: Jerome B. Zeldis

Group Art Unit: 1614

Serial No.: 10/438,213

Examiner: To be assigned

Filed: May 15, 2003

Attorney Docket No.: 501872-999073
(Formerly 9516-074-999)

For: METHODS AND COMPOSITIONS USING IMMUNOMODULATORY COMPOUNDS FOR TREATMENT AND MANAGEMENT OF CANCERS AND OTHER DISEASES

**SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. §1.56 AND §1.97**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the duty of disclosure imposed by 37 C.F.R. § 1.56 and § 1.97 to inform the Patent Office of all references coming to the attention of each individual associated with the filing or prosecution of the subject application, which are or may be material to the patentability of any claim of the application, Applicants hereby direct the Examiner's attention to references **C53** to **C60** listed on the attached form PTO 1449 entitled "List of References Cited by Applicant."

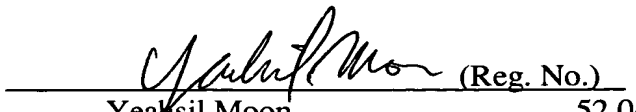
Identification of the listed references is not to be construed an admission of Applicant or Attorneys for Applicant that such references are available as "prior art" against the subject application. Applicant respectfully requests that the Examiner review the foregoing references and that the references be made of record in the file history of the application.

This Information Disclosure Statement is filed under 37 C.F.R. §1.97(b) before the mailing of the first Office action on the merits. Therefore, no fee is believed to be due.

Should any fee be required, however, please charge such fee to Jones Day Deposit Account No. **50-3013**.

Respectfully submitted,

Date: April 15, 2005



Yeahsil Moon (Reg. No.) 52,042
For: Anthony M. Insogna 35,203
**JONES DAY**
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New York, New York 10017
(212) 326-3939

Enclosures

# LIST OF REFERENCES CITED BY APPLICANT

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| 9516-074-999 | 10/438,213 |
| APPLICANT | |
| Zeldis | |
| FILING DATE | GROUP |
| May 15, 2003 | 1614 |

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| | | | | | | | ☐ | ☐ |

## OTHER REFERENCES *(Including Author, Title, Date, Pertinent Pages, Etc.)*

| | | |
|---|---|---|
| | C53 | Bach, 1963, "Thalidomide in Cancer Chemotherapy," *The Lancet*, No. 1271, pg. 71 |
| | C54 | Bach, 1963, "Studies on the Possible Anti-Neoplastic Effect of Thalidomide," *Acta Pathologica Et Microbiologica Scandinavica* 59:491-499 |
| | C55 | Chaundhry, 1966, *Cancer Research*, "Effect of Prednisolone and Thalidomide on Induced Submandibular Gland Tumors in Hamster," 26(part 1)1884-86 |
| | C56 | DiPaolo, 1963, "Effect of Thalidomide on a Variety of Transplantable Tumors," *Cancer Chemotherapy Reports* No. 29, p. 99-102 |
| | C57 | DiPaolo, 1963, "*In vitro* Test Systems for Cancer Chemotherapy, II. Correlation of *in vitro* Inhibition of Dehydrogenase and Growth with *in vivo* Inhibition of Ehrlich Asoites Tumor," *Proceedings of the Society for Experimental Biology & Medicine*, 114:384-387 |
| | C58 | DiPaolo, 1964, "Thalidomide: Effects on Ehrlich Ascites Tumor Cells *in vitro*" Science 144:1583 |
| | C59 | Mauad, 1963, "Clinical Improvements Obtained in Advanced Caner Patients with Treatment with Thalidomide Associated with Hormones," Anais *Paulistas de Medicina e Cirurgia* 86:13-40 |
| | C60 | Roe and Mitchley, 1963, "Thalidomide and Neoplasia" *Nature* 200:1016-1017 |

| EXAMINER | DATE CONSIDERED |
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|---|---|---|
| | APPLICANT Zeldis | |
| | FILING DATE May 15, 2003 | GROUP 1614 |



## U.S. PATENT DOCUMENTS

| *EXAMINER INITIAL | | DOCUMENT NUMBER | DATE | NAME | CLASS | SUBCLASS | FILING DATE IF APPROPRIATE |
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## FOREIGN PATENT DOCUMENTS

| | | DOCUMENT NUMBER | DATE | COUNTRY | CLASS | SUBCLASS | TRANSLATION YES | TRANSLATION NO |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| | | | | | | | ☐ | ☐ |

## OTHER REFERENCES *(Including Author, Title, Date, Pertinent Pages, Etc.)*

| | | |
|---|---|---|
| | C53 | Bach, 1963, "Thalidomide in Cancer Chemotherapy," *The Lancet*, No. 1271, pg. 71 |
| | C54 | Bach, 1963, "Studies on the Possible Anti-Neoplastic Effect of Thalidomide," *Acta Pathologica Et Microbiologica Scandinavica* 59:491-499 |
| | C55 | Chaundhry, 1966, *Cancer Research*, "Effect of Prednisolone and Thalidomide on Induced Submandibular Gland Tumors in Hamster," 26(part 1)1884-86 |
| | C56 | DiPaolo, 1963, "Effect of Thalidomide on a Variety of Transplantable Tumors," *Cancer Chemotherapy Reports* No. 29, p. 99-102 |
| | C57 | DiPaolo, 1963, "*In vitro* Test Systems for Cancer Chemotherapy, II. Correlation of *in vitro* Inhibition of Dehydrogenase and Growth with *in vivo* Inhibition of Ehrlich Asoites Tumor," *Proceedings of the Society for Experimental Biology & Medicine*, 114:384-387 |
| | C58 | DiPaolo, 1964, "Thalidomide: Effects on Ehrlich Ascites Tumor Cells *in vitro*" Science 144:1583 |
| | C59 | Mauad, 1963, "Clinical Improvements Obtained in Advanced Caner Patients with Treatment with Thalidomide Associated with Hormones," Anais *Paulistas de Medicina e Cirurgia* 86:13-40 |
| | C60 | Roe and Mitchley, 1963, "Thalidomide and Neoplasia" *Nature* 200:1016-1017 |

| EXAMINER | DATE CONSIDERED |
|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with **MPEP 609**; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/438,213 | 05/15/2003 | Jerome B. Zeldis | 9516-074-999 | 4802 |

20583 7590 06/30/2005

JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

| EXAMINER | |
|---|---|
| GRAFFEO, MICHELLE | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1614 | |

DATE MAILED: 06/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/438,213 | ZELDIS, JEROME B. | |
| | Examiner | Art Unit | |
| | Michelle Graffeo | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 22-56 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 22-56 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 8/23,4/15,3/1,3/15, 10/14
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Claims 1-21 have been cancelled by amendment (filed 7 July 2004) and claims 22-56 are pending and examined.

### *Claim Objections*

Claims 40, 46 and 56 are objected to because of the following informalities: abbreviations/acronyms such as IL-2 and INF should not be used. Instead the full name of the composition should be written out, such as interleukin-2 and interferon before any use of the abbreviation/acronym. Appropriate correction is required.

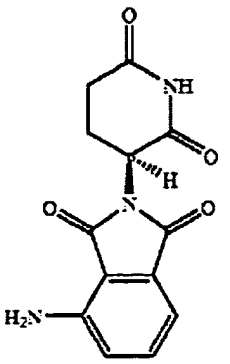
### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

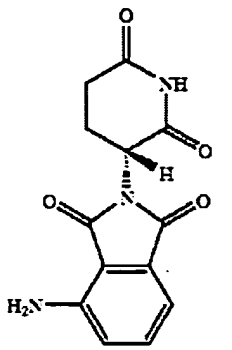
> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 22-25 and 27-34 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent Application Publication No. 2004/0147558 to Treston et al.

Treston et al. teach the use of substantially enantiomerically pure S(-)-3-amino-thalidomide and R(+)-3-amino-thalidomide having the structures below to treat prostate cancer, melanoma and multiple myeloma (paragraphs 47 and 48):




S(-)-3-amino-thalidomide




R(+)-3-amino-thalidomide

Although Treston et al. do not recite the treatment of various forms of prostate cancer, for example hormone-insensitive prostate cancer. Absent evidence to the contrary, an anti-angiogenesis compound would have a different mechanism of action than hormone therapy such that the hormone insensitive nature of the prostate cancer would not affect treatment of the prostate cancer with an anti-angiogenesis compound. Thus, hormone insensitive prostate cancer will necessarily be treated by an anti-angiogenesis compound.

Treston et al. do not specifically recite that a salt or solvate of the thalidomide analog (also known as Actimid™) can be administered. Methods of preparing and use of salts and solvates of pharmaceuticals is a standard practice in the industry. Thus one skilled in the art would understand that the present invention can be practiced with a salt or solvate of the enantiomeric compound.

Claims 22-28, 34-56 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent Application Publication NO. 2004/0067953 to Stein et al.

Stein et al. teach treating prostate cancer, melanoma (see paragraph 125) and myelomas such as smoldering myeloma (see paragraph 559) with a JNK inhibitor in combination with surgery, biological therapies, radiation therapies, standard and experimental chemotherapies (see Abstract) such as Actimid™ or Revimid™ (see paragraph 108). The additional therapies include the administering of cytokines such as interferon alpha and interleukin-2, melphalan (see paragraph 124), irinotecan (see paragraph 108), docetaxel (taxotere) and cyclophosphamide (see paragraph 565), prednisone (see paragraph 565) and dexamethasone (see paragraph 564). Absent any evidence of their criticality, other known chemotherapies such as bortezomib (Velcade), arsenic trioxide (Trisenox), specific cytokines such as GM-CSF and salts such as CPT-11 of chemotherapies would be readily foreseen by one skilled in the art.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

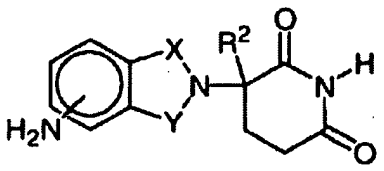
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 22-56 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-13 of copending Application No. 11/102742. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows:

The '742 application claims treating a variety of cancers such as prostate cancers, melanoma (claim 5) and multiple myeloma (claim 6) with the compound of formula (I), or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, below:




(I)

wherein one of X and Y is C=O, the other of X and Y is C=O or $CH_2$, and $R^2$ is hydrogen or lower alkyl.

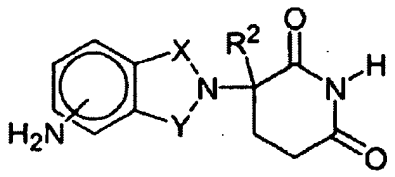
'742 also claims the method of treating cancer with the compound of formula (I) and an additional agent such as GM-CSF, irinotecan and salts thereof (claim 9), radiation therapy (claim 2), taxotere, melphalan and dexamethasone (claim 9). Although bortezomib, CPT-11 and arsenic trioxide are not specifically recited, one

skilled in the art would readily foresee the use of other common/standard chemotherapeutic agents.

Claims 22-56 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-6, 8-15, 18-19, 21-22 and 25-29 of copending Application No. 10/704237. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows:

The '237 application claims treating a variety of cancers such as prostate cancers which are hormone insensitive, smoldering melanoma and indolent melanoma (claim 5) and multiple myeloma (claim 6) with the compound of formula (I), or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, below:




(I)

wherein one of X and Y is C=O, the other of X and Y is C=O or $CH_2$, and $R^2$ is hydrogen or lower alkyl.

'237 also claims the method of treating cancer with the compound of formula (I) and an additional agent such as a cytokine (GM-CSF), irinotecan and salts thereof (claim 9), radiation therapy (claim 2), taxotere, melphalan and dexamethasone (claim 9). Although bortezomib, CPT-11 and arsenic trioxide are not specifically recited, one skilled in the art would readily foresee the use of other common/standard chemotherapeutic agents.

Claims 24, 26-56 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-13 of copending Application No. 10/534324. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows:

Claims 1-13 of the '324 application claim a method of treating a myeloproliferative disease such as smoldering myeloma comprising among other agents a cytokine inhibitory drug which is enantiomerically pure in some instances or a salt or solvate thereof. Actimid™ and Revimid™ for example are cytokine inhibitory drugs and the additional agents that can be used in the instant method are standard chemotherapy agents such as irinotecan and taxotere or standard techniques for treating cancer such as radiation and immunotherapy.

Claims 24, 27-56 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-7, 22-25 of copending Application No. 10/531552. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows:

Claims 1-7, 22-25 of the '552 application claim a method of treating a myelodysplastic syndrome comprising a second agent along a cytokine inhibitory drug which is an enantiomer in some instances or a salt or solvate thereof. Actimid™ and Revimid™ for example are cytokine inhibitory drugs and the additional agents that can be used in the instant method are standard chemotherapy agents such as irinotecan and taxotere or standard techniques for treating cancer such as radiation and immunotherapy.

Claims 22-56 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-9, 18-26 of copending Application No. 10/515270. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows:

Claims 1-7, 22-25 of the '270 application claim a method of treating cancer in general, wherein specific examples such hormone independent prostate cancer and smoldering myeloma are also claimed, comprising a second agent along with a cytokine inhibitory drug which is an enantiomer in some instances or a salt or solvate thereof. Actimid™ and Revimid™ for example are cytokine inhibitory drugs and the additional agents that can be used in the instant method are standard chemotherapy agents such as irinotecan and taxotere or standard techniques for treating cancer such as radiation and immunotherapy.

No claim is allowed.

US Patent Application No. 2005/0049265 to Adams is considered an equivalent to Stein et al.

Please note that documents A01 through A05 on the information discloseure statement of 23 Aug 2004 are not *per se* printed documents and have been lined through on the attached PTO 1449. They will not be printed on any patent that may

issue from this application, however, documents A01 through A05 have been considered insofar as they pertain to the current application.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Graffeo whose telephone number is 571-272-8505. The examiner can normally be reached on 9am to 5:30pm Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

June 22, 2005
MG

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CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

**Express Mail No.: EV654850660US**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Application of: Jerome B. Zeldis

Continuation No.: 4802
Group Art Unit: 1614

Serial No.: 10/438,213

Examiner: Graffeo, Michelle

Filed: May 15, 2003

Attorney Docket No.: 9516-074-999
(CAM: 501872-999073)

For: METHODS FOR TREATMENT OF A PROSTATE CANCER, METASTATIC MELANOMA OR MULTIPLE MYELOMA USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE (as amended)

**RESPONSE**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to Office Action dated June 30, 2005, please consider and enter the amendments and remarks provided below into the file of the above-captioned application. A Petition for Extension of Time is submitted herewith with authorization to charge any required fee to extend the time for a response for a month to and including October 30, 2005. Applicant submits concurrently herewith a Supplemental Information Disclosure Statement with authorization to charge any required fee. The Commissioner is hereby authorized to charge any other required fee(s) to Jones Day Deposit Account No. 50-3013. A copy of this sheet is enclosed for such purpose.

**Amendment to the Title** begins on page 2 of this response.

**Amendments to the Claims** are reflected in the listing of the claims that begins on page 3 of this paper.

**Remarks** begin on page 8 of this paper.

**Amendment to the Title:**

Please amend the title of the application as follows: METHODS ~~AND COMPOSITIONS USING IMMUNOMODULATORY COMPOUNDS~~ FOR TREATMENT ~~AND MANAGEMENT OF CANCERS AND OTHER DISEASES~~ OF A PROSTATE CANCER, METASTATIC MELANOMA OR MULTIPLE MYELOMA USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE

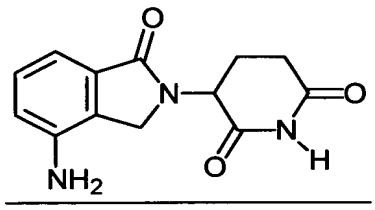
**Amendment to the Claims:**

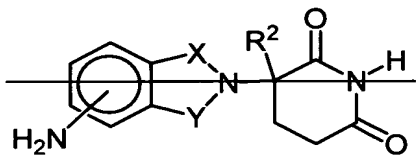
This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of the Claims:**

Claims 1-21. canceled.

22. (currently amended) A method of treating prostate cancer, which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of the formula ~~(I)~~:

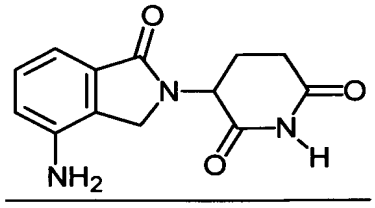


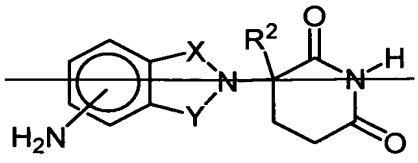


~~(I)~~

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof~~, wherein one of X and Y is C=O, the other of X and Y is C=O or $CH_2$, and $R^2$ is hydrogen or lower alkyl~~.

23. (currently amended) A method of treating metastatic melanoma, which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of the formula ~~(I)~~:

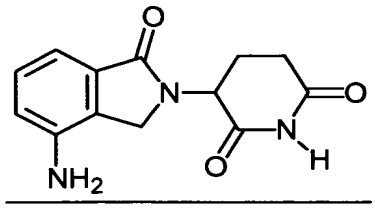


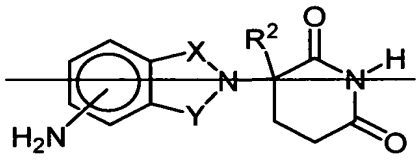


~~(I)~~

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof~~, wherein one of X and Y is C=O, the other of X and Y is C=O or $CH_2$, and $R^2$ is hydrogen or lower alkyl~~.

24. (currently amended) A method of treating multiple myeloma, which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of the formula ~~(I)~~:





~~(I)~~

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof~~, wherein one of X and Y is C=O, the other of X and Y is C=O or $CH_2$, and $R^2$ is hydrogen or lower alkyl~~.

25. (previously presented) The method of claim 22, wherein the prostate cancer is hormone refractory prostate cancer, hormone-insensitive prostate cancer, androgen independent prostate cancer, androgen dependent stage IV non-metastatic prostate cancer, or chemotherapy-insensitive prostate cancer.

26. (previously presented) The method of claim 24, wherein the multiple myeloma is smoldering myeloma, indolent myeloma, chemotherapy responsive multiple myeloma, refractory myeloma, relapsed myeloma, or relapsed and refractory Dune-Salmon stage III multiple myeloma.

27-28. canceled.

29. (previously presented) The method of claim 22, 23 or 24, wherein the compound is a pharmaceutically acceptable salt.

30. (previously presented) The method of claim 22, 23 or 24, wherein the compound is a pharmaceutically acceptable solvate.

31. (previously presented) The method of claim 22, 23 or 24, wherein the compound is a pharmaceutically acceptable stereoisomer.

32. (previously presented) The method of claim 31, wherein the stereoisomer is an enantiomerically pure R isomer.

33. (previously presented) The method of claim 31, wherein the stereoisomer is an enantiomerically pure S isomer.

34-35. canceled.

36. (previously presented) The method of claim 22, which further comprises administering a therapeutically effective amount of a second active agent.

37. (previously presented) The method of claim 23, which further comprises administering a therapeutically effective amount of a second active agent.

38. (previously presented) The method of claim 24, which further comprises administering a therapeutically effective amount of a second active agent.

39. (previously presented) The method of claim 36, 37 or 38, wherein the second active agent is hematopoietic growth factor, a cytokine, or an anti-cancer agent.

40. (currently amended) The method of claim 39, wherein the second active agent is ~~G-CSF, GM-CSF, EPO, IL2, IFN,~~ granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), erythropoietin (EPO), interleukin (IL), interferon (IFN), or a pharmacologically active mutant or derivative thereof.

41. (previously presented) The method of claim 39, wherein the second active agent is oblimersen, melphalan, topotecan, pentoxifylline, taxotere, irinotecan, ciprofloxacin, dexamethasone, doxorubicin, vincristine, dacarbazine, Ara-C, vinorelbine, prednisone, cyclophosphamide, bortezomib, arsenic trioxide or a combination thereof.

42. (previously presented) The method of claim 22, 23 or 24, which further comprises administering radiation therapy, hormonal therapy, biological therapy or immunotherapy.

43. (previously presented) The method of claim 36, wherein the second active agent is taxotere.

44-45. canceled

46. (currently amended) The method of claim 36, wherein the second active agent is granulocyte-macrophage colony-stimulating factor(GM-CSF).

47. canceled.

48. (currently amended) The method of claim 38, wherein ~~the compound is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, and~~ the second active agent is melphalan or prednisone.

49. (currently amended) The method of claim 38, wherein ~~the compound is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, and~~ the second active agent is cyclophosphamide.

50. (currently amended) The method of claim 38, wherein ~~the compound is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, and~~ the second active agent is bortezomib.

51. (currently amended) The method of claim 38, wherein ~~the compound is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, and~~ the second active agent is dexamethasone.

52. (currently amended) The method of claim 38, wherein ~~the compound is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, and~~ the second active agent is arsenic trioxide.

53. (currently amended) The method of claim 38, wherein ~~the compound is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione and~~ the second active agent is irinotecan.

54. (previously presented) The method of claim 53, wherein the irinotecan is a pharmaceutically acceptable salt.

55. (previously presented) The method of claim 54, wherein the pharmaceutically acceptable salt is a hydrochloride salt.

56. canceled.

57. (new) The method of claim 22, 23 or 24, wherein the cancer is relapsed, refractory or resistant to conventional therapy.

58. (new) The method of claim 22, 23 or 24, wherein the compound is administered orally.

59. (new) The method of claim 58, wherein the compound is administered in the form of a capsule or tablet.

60. (new) The method of claim 22, 23 or 24, wherein the compound is administered in an amount of from about 1 to about 50 mg per day.

61. (new) The method of claim 60, wherein the compound is administered in an amount of about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 mg per day.

62. (new) The method of claim 60, wherein the compound is administered in an amount of from about 5 mg per day to about 25 mg per day.

63. (new) The method of claim 60, wherein the compound is administered in an amount of about 25 mg per day.

64. (new) The method of claim 22, 23 or 24, wherein the compound is administered cyclically.

65. (new) The method of claim 64, wherein one cycle comprises four to six weeks.

66. (new) The method of claim 64, wherein one cycle comprises the administration of the compound for 21 days followed by seven days rest.

67. (new) The method of claim 64, wherein the compound is administered for four to twenty-four weeks with one to six weeks of rest.

68. (new) The method of claim 22, 23 or 24, wherein the compound is administered in an amount of from about 5 to about 25 mg per day for 21 days every 28 days for sixteen to twenty-four weeks.

69. (new) The method of claim 68, wherein the compound is administered in an amount of about 25 mg per day for 21 days followed by seven days rest in a 28 day cycle.

70. (new) The method of claim 24, wherein the compound is administered in an amount of about 25 mg per day and dexamethasone is administered in an amount of about 40 mg per day on days 1-4 every four to six weeks.

## REMARKS

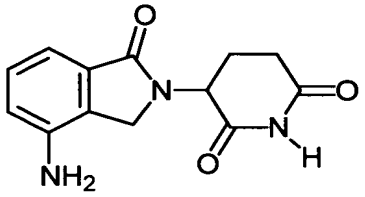
### Amendments to the Title and Claims

The title of the application has been amended to more accurately reflect the subject matter of the present claims. Claims 1-21 were previously canceled. Claims 27, 28, 34, 35, 44, 45, 47 and 56 have been canceled by this amendment without prejudice. Applicant reserves the right to prosecute the subject matter of any canceled claims in one or more continuation, continuation-in-part, or divisional applications.

Claims 22-24, 40, 46 and 48-53 have been amended to clearly define the subject matter of the invention. New claims 57-70 have been added for specific cancers, administration routes, doses and dosing regimens. The new claims are supported by the originally filed specification. For example, claim 57 is supported by page 4, lines 18-20 and page 25, lines 14-17. Claims 58-63 are supported by *e.g.*, page 29, lines 7-11, and page 36, lines 5-7. Claims 64-70 are supported by *e.g.*, page 32, lines 13-20 and page 50, line 24 to page 51, line 12. Claims 22-26, 29-33, 36-43, 46, 48-55 and 57-70 will be pending in this application after the entry of this amendment. No new matter has been added. Applicant respectfully submits that the pending claims are allowable for the following reasons.

### The Invention

Independent claim 22, 23 or 24 recites a method of treating prostate cancer, metastatic melanoma or multiple myeloma, comprising administering 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione having the formula:




or a pharmaceutically acceptable salt, solvate or stereoisomer thereof. In other words, the invention relates to the use of a specific compound to treat specific cancers. *See*, *e.g.*, claims 25, 26 and 57. The claims also relate to methods further employing specific combination therapies, claims 36-43, 46, 48-55 and 70; specific doses, claims 58-63; and specific dosing regimens, claims 64-70. As discussed below, *none* of the cited references are prior art against the claims, or disclose or suggest the specific methods claimed herein.

**The Claim Objection Should Be Withdrawn**

Claims 40, 46 and 56 are objected to because of the informalities on the ground that abbreviations such as IL-2 and INF should not be used. (Office Action, page 2). Applicant has amended the claims by adding the full names of the second active agents recited. Applicant respectfully requests that this objection be withdrawn.

**The Claimed Invention Is Not Anticipated Under 35 U.S.C. § 102(e)**

Claims 22-25 and 27-34 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Treston *et al.* (US2004/0147558, hereinafter Treston). (Office Action, pages 2-3). The Examiner alleges that Treston teaches the use of R- or S-3-amino-thalidomide to treat the cancer recited in the present claims at paragraphs 47 and 48. *Id.* Applicant respectfully traverses this rejection.

It is well settled that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 6319, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in ... [the] claim." Manual of Patent Examining Procedure (MPEP) § 2131 (8th ed., August 2004); and *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Without acquiescing to the rejection of the Examiner, and solely in order to promote the progress of the present application, the pending claims have been amended to recite methods of treating prostate cancer, metastatic melanoma or multiple myeloma, comprising administering a specific compound of the formula as depicted in the claim and which can be named 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, which compound was recited in canceled claim 35.

Treston allegedly relates to the use of different compounds, specifically different isomers that the Examiner refers to as R- or S-3-amino-thalidomide. The presently pending claims relate to methods of treating specific cancers employing 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, or a salt, isomer or solvate thereof. Treston does not disclose the use of the presently claimed compound to treat specific cancers, much less the claimed methods of using the compound. Therefore, Treston fails to disclose each and every element as set forth in the claims of the present invention. Accordingly, the present invention cannot be anticipated by Treston. It is respectfully submitted that the rejection under § 102(e) by Treston should be withdrawn.

Next, claims 22-28, and 34-56 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Stein *et al.* (US 2004/0067953, hereinafter Stein). (Office Action, pages 3-4). The Examiner alleges that Stein teaches methods of treating the claimed cancers with a JNK inhibitor in combination with other therapies such as Actimid™ and Revimid™ at paragraphs 108, 125 and 559, and Abstract. *Id.* The Examiner further alleges that the uses of certain second active agents are taught by Stein at paragraphs 108, 124, 564 and 565, and that the use of other claimed agents would be readily foreseen by one skilled in the art, absent any evidence of their criticality. *Id.* Applicant respectfully traverses the rejection.

Stein is not available as prior art under 35 U.S.C. § 102(e) for two reasons: (a) the invention claimed herein was conceived prior to a filing date of Stein (March 8, 2002) and was diligently reduced to practice from prior to the date in question to the filing date of the present application; and (b) the disclosure in question in fact relates to the invention of the inventor of the instant claims.[1] *See*, Manual of Patent Examining Procedure (MPEP) §2132.01 (8th ed., August 2001).

To the extent that the particular disclosure of Stein is available as prior art under § 102(e), it is entitled to a date of only March 8, 2002, which date is not before the date of the invention to which the instant claims are entitled. In this regard, the attention of the Examiner is respectfully directed to the DECLARATION BY JEROME B. ZELDIS, M.D., Ph.D. UNDER 37 C.F.R. § 1.131 ("Declaration") filed concurrently herewith. As evidenced by Dr. Zeldis' Declaration, Stein is not prior art to the instant claims. *See, e.g.*, MPEP §§ 706.02(b) and 715.

In addition, Applicant points out that Stein is an application filed by the colleagues of the assignee of the present application and that the disclosures of Stein which the Examiner relied upon was in fact derived from the invention by Applicant, Dr. Zeldis. *See, e.g.*, MPEP § 2132.01. Therefore, Stein is not prior art and the rejection under 35 U.S.C. § 102(e) in view of Stein should be withdrawn.[2]

**The Double Patenting Rejection Should Be Withdrawn**

Claims 22-56 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 of Application

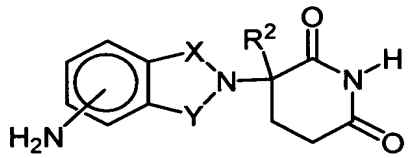
[1] Applicant reserves the right to present further arguments demonstrating the differences between the claimed invention and the disclosure of Stein. However, in view of the fact that Stein is not prior art, this rejection must be withdrawn.

No. 11/102,742 (hereinafter '742 application), on the ground that both applications claim methods of treating a variety of cancers using immunomodulatory compounds having same general formula. (Pages 4-6 of the Office Action). Applicant respectfully traverses the rejection.

Applicant respectfully submits that this rejection is improper because claims 1-13 of the '742 application have been canceled. Therefore, the obviousness-type double patenting rejection over claims 1-13 of the '742 application must be withdrawn.

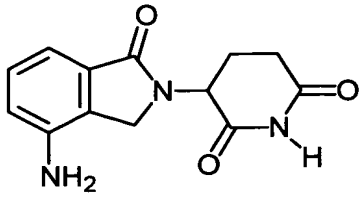
Further, claims 22-56 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 8-15, 18-19, 21-22 and 25-29 of Application No. 10/704,237 (hereinafter '237 application), on the ground that both applications claim methods of treating a variety of cancers using immunomodulatory compounds having same general formula, alone or in combination with second active agents. (Pages 6-7 of the Office Action). Applicant respectfully traverses the rejection.

The claims of '237 application recite, in part, methods of treating cancer, using immunomodulatory compounds of the formula:




or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, wherein one of X and Y is C=O, the other of X and Y is C=O or $CH_2$, and $R^2$ is hydrogen or lower alkyl. The genus of compounds recited by the claims of '237 application encompass a number of compounds. Similarly, the cancers claimed in '237 application are broad.

In contrast, the pending claims recite methods of treating a prostate cancer, metastatic melanoma or multiple myeloma, using a specific single compound, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione having the formula:




It is well-established that a specific chemical compound may be patentably distinct from a genus that encompasses such a compound. *See, e.g., In re Baird*, 16 F.3d 380, 383 (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a

disclosed generic formula does not by itself render that compound obvious."). For at least these reasons, the obviousness-type double patenting rejection over the claims of the '237 application must be withdrawn. In any event, Applicant requests that this rejection be held in abeyance until the claims of the present application are deemed otherwise allowable.

Claims 24 and 26-56 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 of Application No. 10/534,324 (hereinafter '324 application), on the ground that both applications claim common subject matter because '324 application claims methods of treating a myeloproliferative disease such as smoldering myeloma using a cytokine inhibitory drug such as Actimid™ and Revimid™ and additional agents can be used. (Page 7 of the Office Action). Applicant respectfully traverses this rejection.

The claims of '324 application recite methods of treating a myeloproliferative disease using a selective cytokine inhibitory drug. The claims, as amended herein, do not relate to the use of a selective cytokine inhibitory drug, but a specific immunomodulatory compound. The compound recited by the pending claims is totally different from, and is not encompassed by, the compounds of '324 application. The claims of '324 application recite a selective cytokine inhibitory drug, whose structure and characteristics are distinctive from the specific immunomodulatory compound recited by the pending claims. *See* the specification of '324 application, *e.g.*, page 10, line 21 to page 22.

Further, a myeloproliferative disease recited in '324 application is distinct from, and is not an obvious variant of prostate cancer, metastatic melanoma or multiple myeloma. In sum, the claims of '324 application do not disclose or suggest methods of treating cancers using the compound recited by the pending claims. The Examiner has made no *prima facie* case that the pending claims are obvious in light of the claims of '324 application.

Claims 24 and 27-56 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 and 22-25 of Application No. 10/531,552 (hereinafter '552 application), on the ground that both applications claim common subject matter because '552 application claims methods of treating a myelodysplastic syndrome using a cytokine inhibitory drug such as Actimid™ and Revimid™ and additional agents can be used. (Page 8 of the Office Action). Applicant respectfully traverses rejection.

The claims of '552 application recite methods of treating a myelodysplastic disease using a selective cytokine inhibitory drug. The claims of '552 application recite a

selective cytokine inhibitory drug, while the pending claims recites the specific immunomodulatory compound now known as Revlimid®. The compound of the pending claims is not disclosed or suggested by '552 application.

Further, a myelodysplastic disease recited in '552 application is distinct from, and is not an obvious variant of prostate cancer, metastatic melanoma or multiple myeloma. The claims of '552 application do not disclose or suggest methods of treating cancers using the specific compound of the pending claims. Therefore, the pending claims are patentably distinct from the claims of '552 application.

Claims 22-56 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 and 18-26 of Application No. 10/515,270 (hereinafter '270 application), on the ground that both applications claim common subject matter because '270 application claims methods of treating cancer using a cytokine inhibitory drug such as Actimid™ and Revimid™ and additional agents can be used. (Pages 8-9 of the Office Action). Applicant respectfully traverses rejection.

The claims of '270 application recite methods of treating cancer using a selective cytokine inhibitory drug. As explained above, the selective cytokine inhibitory drug is totally different from the specific immunomodulatory compound of the pending claims. The subject matters of the claims of both applications are not encompassed by each other. The specific immunomodulatory compound of the pending claims is not disclosed or suggested by '270 application. The Examiner has made no *prima facie* case that the pending claims are obvious in light of the claims of '270 application.

In sum, Applicant respectfully submits that the rejection of the pending claims under judicially created obviousness-type double patenting should be withdrawn because no *prima facie* case of obviousness has been established for the pending claims over any of the cited applications. Applicant further submits that no terminal disclaimer over the cited applications is necessary.

## Conclusion

In view of the foregoing, all the rejections of the claims should be withdrawn. Reconsideration, entry of the above amendment and remarks, and allowance of the pending claims are respectfully requested. Should the Examiner not agree that all claims are allowable, a personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application.

Respectfully submitted,

Date: October 28, 2005

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**EXPRESS MAIL NO.: EV654850660US**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Application of: Jerome B. Zeldis

Group Art Unit: 1614
Confirmation No.: 4802

Serial No.: 10/438,213

Examiner: Graffeo, Michelle

Filed: May 15, 2003

Attorney Docket No.: 9516-074-999
(CAM: 501872-999073)

For: METHODS AND COMPOSITIONS USING IMMUNOMODULATORY COMPOUNDS FOR TREATMENT AND MANAGEMENT OF CANCERS AND OTHER DISEASES

**SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. §1.56 AND §1.97**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the duty of disclosure imposed by 37 C.F.R. § 1.56 and § 1.97 to inform the Patent Office of all references coming to the attention of each individual associated with the filing or prosecution of the subject application, which are or may be material to the patentability of any claim of the application, Applicants hereby direct the Examiner's attention to references **C61** to **C63** listed on the attached form PTO 1449 entitled "List of References Cited by Applicant."

Identification of the listed references is not to be construed an admission of Applicant or Attorneys for Applicant that such references are available as "prior art" against the subject application. Applicant respectfully requests that the Examiner review the foregoing references and that the references be made of record in the file history of the application.

Applicant believes that the fee for filing this Information Disclosure Statement is $180.00. However, should the Patent Office determine otherwise, please charge any required fee to Jones Day Deposit Account No. **50-3013**. A duplicate of this sheet is enclosed for accounting purposes.

Respectfully submitted,

Date: October 28, 2005

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Enclosures

# LIST OF REFERENCES CITED BY APPLICANT

(Use several sheets if necessary)

| ATTY DOCKET NO. | APPLICATION NO |
|---|---|
| 9516-074-999 | 10/438,213 |
| APPLICANT | |
| Zeldis | |
| FILING DATE | GROUP |
| May 15, 2003 | 1614 |

## U.S. PATENT DOCUMENTS

| *EXAMINER INITIAL | | DOCUMENT NUMBER | DATE | NAME | CLASS | SUBCLASS | FILING DATE IF APPROPRIATE |
|---|---|---|---|---|---|---|---|
| | A01 | | | | | | |
| | A02 | | | | | | |
| | A03 | | | | | | |
| | A04 | | | | | | |

## FOREIGN PATENT DOCUMENTS

| | | DOCUMENT NUMBER | DATE | COUNTRY | CLASS | SUBCLASS | TRANSLATION | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | YES | NO |
| | B01 | | | | | | | |
| | B02 | | | | | | | |
| | B03 | | | | | | | |
| | B04 | | | | | | | |

## OTHER REFERENCES *(Including Author, Title, Date, Pertinent Pages, Etc.)*

| | | |
|---|---|---|
| | C61 | Liu *et al.*, "Phase I study of CC-5013 (Revimid), a thalidomide derivative, in patients with refractory metastatic cancer," *American Society of Clinical Oncology, Abstract #927*, 2003. |
| | C62 | Zangari *et al.*, "Results of phase I study of CC-5013 for the treatment of multiple myeloma (MM) patients who relapse after high dose chemotherapy (HDCT)," *American Society of Hematology, Abstract #3226*, 2001. |
| | C63 | Zeldis *et al.*, "Update on the evolution of the IMiD™," *International Society for Biological Therapy of Cancer, Oral Abstract*, 2003. |
| | C64 | |
| | C65 | |
| | C66 | |

| EXAMINER | DATE CONSIDERED |
|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with **MPEP 609**; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | | | |
|---|---|---|---|
| Application of: | Jerome B. Zeldis | Confirmation No.: | 4802 |
| Serial No.: | 10/438,213 | Art Unit: | 1614 |
| Filed: | May 15, 2003 | Examiner: | Graffeo, Michelle |
| For: | METHODS FOR TREATMENT OF A PROSTATE CANCER, METASTATIC MELANOMA OR MULTIPLE MYELOMA USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE (as amended) | Attorney Docket No.: | 9516-074-999 (CAM: 501872-999073) |

**DECLARATION BY JEROME B. ZELDIS, M.D., Ph.D. UNDER 37 C.F.R. § 1.131**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Jerome B. Zeldis, M.D., Ph.D. declare that:

1. I earned an M.D. and a Ph.D. in Molecular Biophysics and Biochemistry at Yale University School of Medicine (New Haven, CT). After completion of these degrees, I completed an internship in Internal Medicine at U.C.L.A. Medical Center (Los Angeles, CA). I then completed a residency in Internal Medicine at U.C.L.A. Medical Center (Los Angeles, CA). I also held a Research Fellowship in Medicine at Harvard Medical School (Boston, MA) and at Massachusetts General Hospital (Boston, MA). In addition, I have held academic appointments at Harvard Medical School (Boston, MA), University of California (Davis, CA), and Cornell University Medical College (New York, NY). I am licensed to practice medicine in the States of California, New York, and New Jersey and in the Commonwealth of Massachusetts. I am presently a Vice President and the Chief Medical Officer of Celgene Corporation (Summit, NJ).

2. I am the sole named inventor of the claims presently pending in the above-identified patent application ("the '213 application"), and I am familiar with its

disclosure and claims. A copy of the claims that I understand are currently pending is attached hereto as Exhibit A.

3. The '213 application discloses and presently claims, in part, methods of treating a prostate cancer, metastatic melanoma or multiple myeloma, which comprise administering to a patient in need thereof a therapeutically effective amount of an immunomodulatory compound that may be referred as 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione or REVLIMID®, previously known as REVIMID® or REVIMID™. (*See* claims 22 to 24).

4. I understand that an Office Action issued on June 30, 2005 in connection with the '213 application rejecting the claims as unpatentable for lack of novelty over a patent application by Stein *et al.*, United States Patent Application Publication No. 2004/0067953 ("Stein"), attached hereto as Exhibit B, which is an application that currently names my colleagues at Signal Pharmaceuticals, LLC ("Signal") as co-inventors.[1] I understand that the Examiner stated that Stein teaches methods for the treatment of prostate cancer, melanoma or myeloma using a JNK inhibitor in combination with ACTIMID™ or REVLIMID® at paragraphs 108, 125 and 559, and the use of additional agents recited in the pending claims of the '213 application at paragraphs 108, 124, 564 and 565, and that the other additional agents required by the pending claims would be readily foreseen by one skilled in the art, absent any evidence of their criticality. (Office Action, pages 3-4, attached hereto as Exhibit C).

5. I conceived of the presently claimed invention in the '213 application prior to March 8, 2002, the date of the first filed application to which Stein claims priority. This is evidenced by clinical trial protocols of the assignee (Celgene Corporation) of the present application for the claimed cancers. Redacted copies of the front pages of each protocol are attached hereto as Exhibit D to H. (PROTOCOL CDC-501-001 entitled "AN OPEN LABEL STUDY OF THE SAFETY AND EFFICACY OF CC-5013 TREATMENT FOR PATIENTS WITH RELAPSED MULTIPLE MYELOMA"; PROTOCOL CDC-501-002 entitled "UARK 2000-29, AN OPEN LABEL STUDY OF THE SAFETY AND EFFICACY OF CC-5013 TREATMENT FOR MULTIPLE MYELOMA PATIENTS WHO

[1] I understand that Signal is and was at the time of the '213 application a wholly owned subsidiary of Celgene Corporation.

RELAPSE AFTER HIGH DOSE CHEMOTHERAPY"; Clinical Study Protocol (HCR: 590/CE) (identified within Celgene Corporation as "PROTOCOL CDC-501-ST-001") entitled "Pilot Study to Determine the Safety and Tolerability of CC-5013 (an Analogue of Thalidomide) in Cancer Patients" for studying melanoma patients; PROTOCOL CDC-501-ST-003 entitled "A SINGLE-CENTER, OPEN-LABEL, BETWEEN-PATIENT, DOSE-ESCALATION PHASE I STUDY OF CDC-501 IN PATIENTS WITH SOLID TUMORS" for studying melanoma patients; and NCI # 02-C-0083 (identified within Celgene Corporation as "PROTOCOL CDC-501-ST-002") entitled "A Multidose Phase I Study of Oral CC-5013, a Thalidomide Derivative, in Patients with Refractory Metastatic Cancer" for studying prostate cancer patients.

6. Specifically, the protocols for treating multiple myeloma, metastatic melanoma or prostate cancer with REVLIMID® were designed based upon the earlier conception, and were performed under my supervision and direction, prior to March 8, 2002. Patients were enrolled and treated with REVLIMID® under the protocol from prior to March 8, 2002 to the filing date of the present application. This is evidenced, in part, by the abstracts reporting the results obtained under the protocols, as attached hereto as Exhibit I to K. (Zangari *et al.*, "Results of phase I study of CC-5013 for the treatment of multiple myeloma (MM) patients who relapse after high dose chemotherapy (HDCT)," *American Society of Hematology, Abstract #3226*, 2001; Zeldis *et al.*, "Update on the evolution of the IMiD™," *International Society for Biological Therapy of Cancer, Oral Abstract*, 2003; and Liu *et al.*, "Phase I study of CC-5013 (Revimid), a thalidomide derivative, in patients with refractory metastatic cancer," *American Society of Clinical Oncology, Abstract #927*, 2003). Portions of the studies are also referred to in the present application, Section 6.5.2 "Treatment of Relapsed Multiple Myeloma" on pages 46-48 of the specification, Section 6.5.3 "Treatment of Solid Tumors" on pages 48-49 of the specification, and Section 6.5.5 "Treatment of Metastatic Melanoma" on page 50 of the specification.

7. I offer this declaration to demonstrate only that Stein is not, to my knowledge, prior art to the invention claimed herein.

8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like may be punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent issuing from the '213 application.

Dated: 26 October 2005

Jerome B. Zeldis, M.D., Ph.D.

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United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/438,213 | 05/15/2003 | Jerome B. Zeldis | 9516-074-999 | 4802 |

20583 7590 12/19/2005

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| EXAMINER | |
|---|---|
| GRAFFEO, MICHEL | |
| **ART UNIT** | **PAPER NUMBER** |
| 1614 | |

DATE MAILED: 12/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/438,213 | ZELDIS, JEROME B. | |
| | Examiner | Art Unit | |
| | Michel Graffeo | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *22-26,29-43,46,48-55 and 57-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-26,29-43,46,48-55 and 57-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *28 Oct 05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Action*

Claims 22-26, 29-43, 46, 48-55 and 57-70 are pending and examined.

Applicant has amended claims 22-24, 40 and 46-53, canceled claims 27-28, 34-35, 44-45, 47 and 56 and provided arguments for the patentability of claims 22-26, 29-43, 46, 48-55 and 57-70 in the response filed 28 October 2005.

In light of Applicant's Amendment dated 28 October 2005, the objection to claims 40, 46 and 6 under 35 USC §112, the rejection to claims 22-28, 34-56 under 35 USC §102 over Stein et al., the Double Patenting rejection over Application Serial No. 11/102742 and the Double Patenting rejection over Application No. 10/531552 have been withdrawn. Per Applicant's request, the Double Patenting rejection over Application 10/704237, although recited below, will be kept in abeyance until allowable subject matter is indicated as allowable in the instant application. Any rejection not specifically stated in this Office Action has been withdrawn.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 60-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain new subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, page 29 as pointed out by the Applicant discloses a range of applicable dosages. Such range does not specifically point to or describe the incremental amounts of claim 61 nor the more narrow range of claim 60. New matter includes not only the addition of wholly unsupported subject matter, but may also include adding specific percentages or compounds after a broader original disclosure, or even the omission of a step from a method. In other words, a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species.

***Claim Rejections - 35 USC § 103***

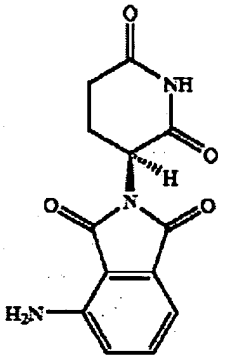
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

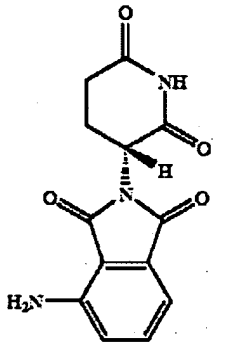
Claims 22-26, 29-43, 46, 48-55 and 57-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent Application Publication No. 2004/0147558 to

Treston et al. in view of Corral et al. Immunomodulation by thalidomide and thalidomide analoques.. Ann. Rheum. 1999; 58; 107-13.

Treston et al. teach the use of substantially enantiomerically pure S(-)-3-amino-thalidomide and R(+)-3-amino-thalidomide having the structures below to treat prostate cancer, melanoma and multiple myeloma (paragraphs 47 and 48):



S(-)-3-amino-thalidomide



R(+)-3-amino-thalidomide

Treston et al. teach a dosage of from 0.1 to 300mg/kg/day and that the dosages can be given in cycles (in current claims 59-70; see paragraph 51 and Example 8 of paragraph 84) with the caveat that the dosage will depend on the condition being treated, the particular compound and other clinical factors such as weight and condition of the patient (see paragraph 51). Although each of the dose/cycle combinations are not specifically recited in Treston et al., the teaching that the dose can vary and that a patient can be dosed in cycles lasting from 11-15 days for example, would have made the claimed combinations obvious over Treston et al.

Treston et al. do not teach the inclusion of an additionally anti cancer agent in the therapy or formulation. Nonetheless, combining agents which are known to be useful as anticancer agents individually into a singe composition useful for the very same

purpose is prima facie obvious. See In re Kerkhoven 205 USPQ 1069. Since it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose, the idea of combining Revimid™ with another anticancer agent flows logically from their having been individually taught in the prior art.

Although Treston et al. do not recite the treatment of various forms of prostate cancer, for example hormone-insensitive prostate cancer. Absent evidence to the contrary, an anti-angiogenesis compound would have a different mechanism of action than hormone therapy such that the hormone insensitive nature of the prostate cancer would not affect treatment of the prostate cancer with an anti-angiogenesis compound. Thus, hormone insensitive prostate cancer will necessarily be treated by an anti-angiogenesis compound.

Treston et al. do not specifically recite that a salt or solvate of the thalidomide analog (also known as Actimid™) can be administered. Methods of preparing and use of salts and solvates of pharmaceuticals is a standard practice in the industry. Thus one skilled in the art would understand that the present invention can be practiced with a salt or solvate of the enantiomeric compound.

Corral et al. teach that Actimid™ and Revimid™ have the same mechanisms of action relative LPS induced inflammation, T-cell activation etc. (in current claims 22-26, 29-43, 46, 48-55 and 57-70; see page 110 Table 1) and have potential as cancer therapies (in current claims 22-26, 29-43, 46, 48-55 and 57-70; see Conclusions page 111).

One of ordinary skill in the art would have been motivated to combine the above references and as combined would teach the invention as claimed. One of ordinary skill in the art would have been motivated to combine Treston et al. and Corral et al. because both are directed to Thalidomide derivatives and the mechanism of action and potential use as a cancer therapy for both as well. As combined, one of ordinary skill in the art would have appreciated the obviousness of using Revimid™ to treat the claimed cancers. Since Treston et al. teach that Actimid™ is efficacious in the treatment of prostate cancer and multiple myeloma for example, the similarities in function between Actimid™ and Revimid™ more than suggest the applicability of Revimid™ for the same indications. Moreover, Corral et al. teach that both derivatives, Actimid™ and Revimid™, are potential cancer therapies. Thus, the combined references teach and make prima facie obvious how to use the claimed invention at the time that it was made.

***Response to Arguments***

Applicant's arguments filed 28 October 2005 with respect to Stein et al. have been fully considered and are persuasive. The Declaration under 37 C.F.R. §1.131 demonstrated reduction to practice with the results of clinical trials with Revimid™.

Applicant's arguments filed 28 October 2005 with respect to Treston et al. have been fully considered but they are not persuasive. Although Applicant's amendment to claims removed Actimid™ as a claim element, the functional similarities between Actimid™ and Revimid™ provide for a proper basis for obviousness as explained above.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

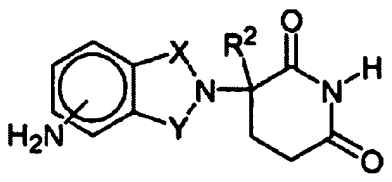
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 22-56 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-6, 8-15, 18-19, 21-22 and 25-29 of copending Application No. 10/704237. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully claimed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows:

The '237 application claims treating a variety of cancers such as prostate cancers which are hormone insensitive, smoldering melanoma and indolent melanoma (claim 5) and multiple myeloma (claim 6) with the compound of formula (I), or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, below:



(I)

wherein one of X and Y is C=O, the other of X and Y is C=O or $CH_2$, and $R^2$ is hydrogen or lower alkyl.

'237 also claims the method of treating cancer with the compound of formula (I) and an additional agent such as a cytokine (GM-CSF), irinotecan and salts thereof (claim 9), radiation therapy (claim 2), taxotere, melphalan and dexamethasone (claim 9). Although bortezomib, CPT-11 and arsenic trioxide are not specifically recited, one skilled in the art would readily foresee the use of other common/standard chemotherapeutic agents.

Claims 24, 26-56 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-13 of copending Application No. 10/534324. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows:

Claims 1-13 of the '324 application claim a method of treating a myeloproliferative disease such as smoldering myeloma comprising among other agents a cytokine inhibitory drug which is enantiomerically pure in some instances or a salt or solvate thereof. Actimid™ and Revimid™ for example are cytokine inhibitory drugs and the additional agents that can be used in the instant method are standard chemotherapy agents such as irinotecan and taxotere or standard techniques for treating cancer such as radiation and immunotherapy.

Claims 22-56 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-9, 18-26 of copending Application No. 10/515270. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows:

Claims 1-7, 22-25 of the '270 application claim a method of treating cancer in general, wherein specific examples such hormone independent prostate cancer and smoldering myeloma are also claimed, comprising a second agent along with a cytokine inhibitory drug which is an enantiomer in some instances or a salt or solvate thereof. Actimid™ and Revimid™ for example are cytokine inhibitory drugs and the additional agents that can be used in the instant method are standard chemotherapy agents such

as irinotecan and taxotere or standard techniques for treating cancer such as radiation and immunotherapy.

***Response to Arguments***

Applicant's arguments filed 28 October 2005 with respect to the Double Patenting rejection over Application No. 10/704237 have been fully considered but they are not persuasive. Examiner agrees that a method of treating a disease with a claimed species compound may be patentably distinct over a method of treating a disease with a genus compound. Since Applicant has not provided any evidence or reasons for why or how the specific method is differentiated over the '237 application, this rejection is maintained but held in abeyance until patentable subject matter is indicated.

Applicant's arguments over the rejection over Application No. 10/532324 has been fully considered but they are not persuasive. The rejection over Application No. 10/532324 is maintained because Revimid™ is a cytokine inhibiting drug (see Corral et al. page 110 in table 1).

Applicant's arguments over the rejection over Application No. 10/531552 have been fully considered and are persuasive. As Applicant points out, myelodysplastic disease is distinct from the claimed cancers.

Applicant's arguments over the rejection over Application No. 10/515270 has been fully considered but they are not persuasive because Revimid™ is a cytokine inhibiting drug (see Corral et al. page 110 in table 1). Moreover, since no drug is defined in claims 1-9 and 18-26 of the '270 application, the rejection is proper.

***Conclusion***

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Graffeo whose telephone number is 571-272-8505. The examiner can normally be reached on 9am to 5:30pm Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

7 December 2005
MG

Christopher S. F. Low

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

| Notice of References Cited | Application/Control No. 10/438,213 | Applicant(s)/Patent Under Reexamination ZELDIS, JEROME B. | |
|---|---|---|---|
| | Examiner Michel Graffeo | Art Unit 1614 | Page 1 of 1 |

**U.S. PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Name | Classification |
|---|---|---|---|---|---|
| | A | US- | | | |
| | B | US- | | | |
| | C | US- | | | |
| | D | US- | | | |
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| | J | US- | | | |
| | K | US- | | | |
| | L | US- | | | |
| | M | US- | | | |

**FOREIGN PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Country | Name | Classification |
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**NON-PATENT DOCUMENTS**

| * | | Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages) |
|---|---|---|
| | U | Corral et al. Immunomodulation by thalidomide and thalidomide analoques.. Ann. Rheum. 1999; 58; 107-13. |
| | V | |
| | W | |
| | X | |

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

# LIST OF REFERENCES CITED BY APPLICANT

(Use several sheets if necessary)

| ATTY DOCKET NO. | APPLICATION NO |
|---|---|
| 9516-074-999 | 10/438,213 |
| APPLICANT | |
| Zeldis | |
| FILING DATE | GROUP |
| May 15, 2003 | 1614 |

## U.S. PATENT DOCUMENTS

| *EXAMINER INITIAL | | DOCUMENT NUMBER | DATE | NAME | CLASS | SUBCLASS | FILING DATE IF APPROPRIATE |
|---|---|---|---|---|---|---|---|
| | A01 | | | | | | |
| | A02 | | | | | | |
| | A03 | | | | | | |
| | A04 | | | | | | |

## FOREIGN PATENT DOCUMENTS

| | | DOCUMENT NUMBER | DATE | COUNTRY | CLASS | SUBCLASS | TRANSLATION | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | YES | NO |
| | B01 | | | | | | | |
| | B02 | | | | | | | |
| | B03 | | | | | | | |
| | B04 | | | | | | | |

## OTHER REFERENCES *(Including Author, Title, Date, Pertinent Pages, Etc.)*

| | | |
|---|---|---|
| MG | C61 | Liu *et al.*, "Phase I study of CC-5013 (Revimid), a thalidomide derivative, in patients with refractory metastatic cancer," *American Society of Clinical Oncology, Abstract #927*, 2003. |
| | C62 | Zangari *et al.*, "Results of phase I study of CC-5013 for the treatment of multiple myeloma (MM) patients who relapse after high dose chemotherapy (HDCT)," *American Society of Hematology, Abstract #3226*, 2001. |
| | C63 | Zeldis *et al.*, "Update on the evolution of the IMiD™," *International Society for Biological Therapy of Cancer, Oral Abstract*, 2003. |
| | C64 | |
| | C65 | |
| | C66 | |

| EXAMINER | Michael Hafeo | DATE CONSIDERED | 12/7/05 |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Express Mail No.: EV452776467US

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Application of: Jerome B. Zeldis

Continuation No.: 4802
Group Art Unit: 1614

Serial No.: 10/438,213

Examiner: Graffeo, Michel

Filed: May 15, 2003

Attorney Docket No.: 9516-074-999
(CAM: 501872-999073)

For: METHODS FOR TREATMENT OF A MULTIPLE MYELOMA USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE (as amended)

**AMENDMENT, STATEMENT OF INTERVIEW SUMMARY AND RESPONSE WITH REQUEST FOR CONTINUED EXAMINATION**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
Mail Stop AF

Sir:

In response to Final Office Action dated December 19, 2005, please consider and enter the amendments and remarks provided below. Submitted herewith are a Request for Continued Examination, Petition for Extension of Time and Supplemental Information Disclosure Statement, each with the provision for the required fees.

**Amendment to the Title** begins on page 2 of this response.

**Amendments to the Claims** are reflected in the listing of the claims that begins on page 3 of this paper.

**Remarks** begin on page 8 of this paper.

**Amendment to the Title:**

Please amend the title of the application as follows:

METHODS FOR TREATMENT OF A ~~PROSTATE CANCER, METASTATIC MELANOMA OR~~ MULTIPLE MYELOMA USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE

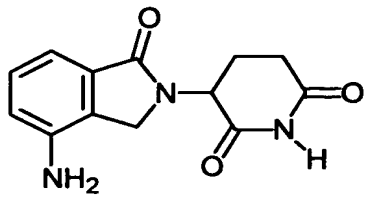
**Amendment to the Claims**:

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of the Claims:**

Claims 1-23. (canceled)

24. (currently amended) A method of treating multiple myeloma, which comprises administering to a patient having multiple myeloma ~~in need thereof a therapeutically effective amount~~ about 1 to about 150 mg per day of a compound of the formula:



or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

25. (canceled)

26. (previously presented) The method of claim 24, wherein the multiple myeloma is smoldering myeloma, indolent myeloma, chemotherapy responsive multiple myeloma, refractory myeloma, relapsed myeloma, or relapsed and refractory Dune-Salmon stage III multiple myeloma.

27-28. (canceled)

29. (currently amended) The method of claim ~~22, 23 or~~ 24, wherein the compound is a pharmaceutically acceptable salt.

30. (currently amended) The method of claim ~~22, 23 or~~ 24, wherein the compound is a pharmaceutically acceptable solvate.

31. (currently amended) The method of claim ~~22, 23 or~~ 24, wherein the compound is a pharmaceutically acceptable stereoisomer.

32. (previously presented) The method of claim 31, wherein the stereoisomer is an enantiomerically pure R isomer.

33. (previously presented) The method of claim 31, wherein the stereoisomer is an enantiomerically pure S isomer.

34-37. (canceled)

38. (previously presented) The method of claim 24, which further comprises administering a therapeutically effective amount of a second active agent.

39. (currently amended) The method of claim ~~36, 37 or~~ 38, wherein the second active agent is hematopoietic growth factor, a cytokine, or an anti-cancer agent.

40. (previously presented) The method of claim 39, wherein the second active agent is granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), erythropoietin (EPO), interleukin (IL), interferon (IFN), or a pharmacologically active mutant or derivative thereof.

41. (previously presented) The method of claim 39, wherein the second active agent is oblimersen, melphalan, topotecan, pentoxifylline, taxotere, irinotecan, ciprofloxacin, dexamethasone, doxorubicin, vincristine, dacarbazine, Ara-C, vinorelbine, prednisone, cyclophosphamide, bortezomib, arsenic trioxide or a combination thereof.

42. (currently amended) The method of claim ~~22, 23 or~~ 24, which further comprises administering radiation therapy, hormonal therapy, biological therapy or immunotherapy.

43- 47. (canceled)

48. (previously presented) The method of claim 38, wherein the second active agent is melphalan or prednisone.

49. (previously presented) The method of claim 38, wherein the second active agent is cyclophosphamide.

50. (previously presented) The method of claim 38, wherein the second active agent is bortezomib.

51. (previously presented) The method of claim 38, wherein the second active agent is dexamethasone.

52. (previously presented) The method of claim 38, wherein the second active agent is arsenic trioxide.

53. (previously presented) The method of claim 38, wherein the second active agent is irinotecan.

54. (previously presented) The method of claim 53, wherein the irinotecan is a pharmaceutically acceptable salt.

55. (previously presented) The method of claim 54, wherein the pharmaceutically acceptable salt is a hydrochloride salt.

56. canceled.

57. (currently amended) The method of claim ~~22, 23 or~~ 24, wherein the cancer is relapsed, refractory or resistant to conventional therapy.

58. (currently amended) The method of claim ~~22, 23 or~~ 24, wherein the compound is administered orally.

59. (previously presented) The method of claim 58, wherein the compound is administered in the form of a capsule or tablet.

60. (currently amended) The method of claim ~~22, 23 or~~ 24, wherein the compound is administered in an amount of from about 1 to about 50 mg per day.

61. (currently amended) The method of claim 60, wherein the compound is administered in an amount of about 5, 10, ~~15~~, 20, 25, 30, ~~35, 40, 45,~~ or 50 mg per day.

62. (previously presented) The method of claim 60, wherein the compound is administered in an amount of from about 5 mg per day to about 25 mg per day.

63. (previously presented) The method of claim 60, wherein the compound is administered in an amount of about 25 mg per day.

64. (currently amended) The method of claim ~~22, 23 or~~ 24, wherein the compound is administered cyclically.

65. (previously presented) The method of claim 64, wherein one cycle comprises four to six weeks.

66. (previously presented) The method of claim 64, wherein one cycle comprises the administration of the compound for 21 days followed by seven days rest.

67. (previously presented) The method of claim 64, wherein the compound is administered for four to twenty-four weeks with one to six weeks of rest.

68. (currently amended) The method of claim ~~22, 23 or~~ 24, wherein the compound is administered in an amount of from about 5 to about 25 mg per day for 21 days every 28 days for sixteen to twenty-four weeks.

69. (previously presented) The method of claim 68, wherein the compound is administered in an amount of about 25 mg per day for 21 days followed by seven days rest in a 28 day cycle.

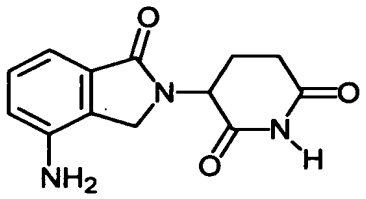
70. (previously presented) The method of claim 24, wherein the compound is administered in an amount of about 25 mg per day and dexamethasone is administered in an amount of about 40 mg per day on days 1-4 every four to six weeks.

71. (new) The method of claim 60, wherein the compound is administered in an amount of 5 mg per day.

72. (new) The method of claim 60, wherein the compound is administered in an amount of 10 mg per day.

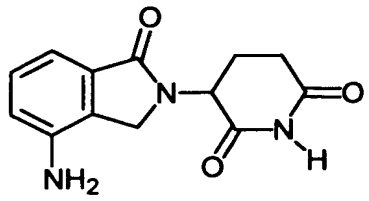
73. (new) The method of claim 60, wherein the compound is administered in an amount of 25 mg per day.

74. (new) A method of treating multiple myeloma, which comprises administering to a patient having multiple myeloma a therapeutically effective amount of a compound of the formula:



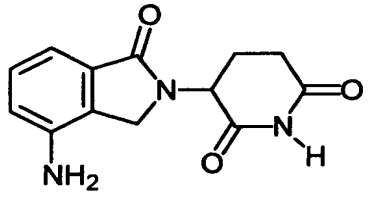

and a therapeutically effective amount of dexamethasone.

75. (new) A method of treating multiple myeloma, which comprises administering to a patient having multiple myeloma about 25 mg per day of a compound of the formula:



or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, and about 40 mg per day of dexamethasone.

76. (new) A method of treating multiple myeloma, which comprises administering to a patient having multiple myeloma about 1 to about 150 mg per day of a compound of the formula:



## REMARKS

### I. Amendments to the Claims

Claims 1-23, 25, 27, 28, 34-37, 43-47 and 56 have been canceled without prejudice. Applicant reserves the right to prosecute the subject matter of any canceled claims in one or more continuation, continuation-in-part, or divisional applications.

Claims 24 and 61 have been amended to clearly define the subject matter of the invention by the addition of a range of doses and to incorporate a patient having multiple myeloma as proposed by the Examiner at a personal interview held on June 7, 2006. Claims 71-76 have also been added. The claims are supported by the originally filed specification. For example, the claims are supported by page 23, lines 21-34; page 29, lines 7-11; page 46, line 12 to page 47, line 1; and page 51, lines 1-12. Claims 29-31, 39, 42, 57, 58, 60, 64 and 68 have been amended to correct claim dependencies. No new matter has been added.

Claims 24, 26, 29-33, 38-42, 48-55 and 57-76 are pending. Applicant respectfully submits that the pending claims are allowable for the following reasons.

### II. Applicant's Statement of the Substance of Interview and Response to the Examiner's Interview Summary of Record

A personal interview with Supervisory Patent Examiner Marschel and Patent Examiner Graffeo, as well as with Messrs. Insogna and Girards and Ms. Moon, attorneys for Applicant, was held on June 7, 2006. Applicant appreciates the Examiners' interview.

During the interview, the Examiners and attorneys for Applicant discussed the Applicant's proposed amendments to the pending claims, the § 103 rejection and obviousness-type double patenting rejection that have been pending in this application.

First, the Examiners and attorneys for Applicant discussed the pending § 103 rejection. Attorneys for Applicant pointed out that Treston is not available as prior art in view of Dr. Zeldis' Declaration, attached hereto, and that even if it were, the claims as amended are not obvious. The Examiners stated that even if Treston were not prior art, Corral could stand alone in a rejection under § 103, because Corral is alleged to teach thalidomide and analogues as inhibitors of TNF alpha and suggest their use against cancer. Attorneys for Applicant emphasized why Corral fails to suggest the use of the recited compound for treating a cancer, much less multiple myeloma as claimed, and why Corral fails to provide a reasonable expectation of success.

Attorneys for Applicant further explained that § 103 obviousness rejection can be overcome by unexpected results of the claimed invention which are found in the

specification of the present application and several articles published after the filing date of the application. The Examiners agreed that unexpected results of the claimed invention can overcome the § 103 obviousness rejection, and they agreed to consider such evidence carefully.

Next, Attorneys for Applicant addressed the issue of obviousness-type double patenting rejection. Attorneys for Applicant pointed out the differences of the compounds and diseases recited in the instant claims and cited applications. Attorneys for Applicant stressed that the Corral reference clearly distinguishes the compound recited in the present claims from the selective cytokine inhibitory drugs recited in the claims of the cited applications.

The Examiners stated that they would favorably consider arguments and evidence to overcome the § 103 rejection and obviousness-type double patenting rejection. Attorneys for Applicant noted that they would present additional evidence and submit an amendment to the claims as proposed by the Examiners. Applicant's arguments and evidence are discussed below and presented herewith.

## III. Arguments and Response to Rejections

### The Claimed Invention Satisfies Written Description Requirement

On pages 2-3 of the Office Action, claims 60-61 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with written description requirement, on the ground that the claims contain new subject matter because a range of doses recited in the claims are not supported by the specification. Applicant respectfully traverses this rejection.

Amended claim 60 recites a dose range of from about 1 to about 50 mg per day, and claim 61 recites a dose range of about 5, 10, 20, 25, 30, or 50 mg per day. The dose ranges recited in the claims are supported by the originally filed specification, *e.g.*, page 23, lines 21-34 (from about 0.10 to about 150 mg/day, and 5, 10, 20, 25, 30 and 50 mg/day); page 29, lines 7-11 (from about 1 to about 50 mg/day); page 46, line 12 to page 47, line 1 (5, 10, 25, 50 mg/day); and page 51, lines 1-12 (about 1 to 150 mg/day).

From the descriptions, it is clear that the specification disclosed the claimed dose ranges at the time the application was filed, and the claims do not contain any new subject matter. In addition, one skilled in the art would be able to recognize the claimed dose ranges according to the description of the specification. *See, e.g., See Manual of Patent Examining Procedure (MPEP)*, § 2163.06; *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Blaser*, 556 F.2d 534, 194 USPQ 122 (CCPA 1977); and 2002 WL

519791 (Bd. Pat. App & Interf., "a broader range (1-50 mM) recited in the specification shows possession of a narrower range (1-30 mM or 25-30 mM) recited in the claims"). *Wertheim* concerned a rejection, under § 112, written description requirement, of a claim reciting between 35% to 60% coffee solid, while the specification discloses a range of 25% to 60% solid. The court held that "the rejection of the claim was improper, since a person skilled in the art would consider process employing 35% to 60% content range to be part of the applicant's invention...and the PTO has done nothing more than argue lack of literal support, which is not enough." *In re Wertheim,* at 265, 191 USPQ at 98.

The same rationale applies here. In this case, from the disclosures of the specification (1 to 50 mg, or 5, 10, 20, 25, 30 or 50 mg), one of ordinary skill in the art would readily recognize that the inventor had possession of the present claimed invention (1 to 50 mg recited in claim 60, or 5, 10, 20, 25, 30 or 50 mg recited in claim 61). *See, e.g.*, 2002 WL 519791 (Bd. Pat. App & Interf.) (quoting *Vas-Cath Inc. v. Mahurkar,* 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991)). *See, also, In re Kaslow*, 707 F.2d 1366 (Fed. Cir. 1983) ("The test for determining compliance with the written description requirement is whether the disclosure of the application ... reasonably conveys to the artisan that the inventor had possession at that time ... rather than the presence or absence of literal support in the specification for the claim language."). Therefore, the disclosures of the present application satisfy the written description requirement and Applicant respectfully request that the rejection be withdrawn.

**Treston is Not Prior Art**

Claims 22-26, 29-43, 46, 48-55 and 57-70 are rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Treston *et al.* (US 2004/0147558, hereinafter "Treston") in view of Corral *et al.* (*Ann. Rheum.* 1999;58; 107-13, hereinafter "Corral"). (pages 3-6 of the Office Action). Applicant respectfully traverses this rejection.

Treston is not available as prior art under any provision of 35 U.S.C. § 102 or § 103, much less under 35 U.S.C. § 102(e), because the inventions claimed herein were conceived prior to a priority date of Treston (assuming *arguendo* actual support for the disclosures that the Examiner relied upon, the date would be November 30, 2000) and the inventions were reduced to practice from prior to the date in question to the filing date of the present application.[1] *See*, Manual of Patent Examining Procedure (MPEP) §2136.05 (8th ed., Volume 2, Incorporating Revision No. 4, August 2005).

[1] Applicant presents further arguments demonstrating the differences between the claimed invention and the disclosure of Treston as discussed below. However, in view of the fact that Treston is not

Further, the disclosures relied upon by the Examiner (paragraphs 47, 48, 51, 84 of Treston) are not presented in the priority application filed on November 30, 2000. To the extent that the particular disclosure of Treston is available as prior art under § 102(e), it is entitled to a date of only November 30, 2001, the international application filing date, which is after the date of the invention to which the instant claims are entitled. In this regard, the attention of the Examiner is respectfully directed to the DECLARATION BY JEROME B. ZELDIS, M.D., Ph.D. UNDER 37 C.F.R. § 1.131 ("Declaration") filed concurrently herewith. As evidenced by Dr. Zeldis' Declaration, Treston is not prior art to the instant claims. *See, e.g.*, MPEP §§ 706.02(b) and 715. Therefore, for this reason alone, the rejection under 35 U.S.C. § 103(a) over Treston should be withdrawn.

During the personal interview held on June 7, 2006, the Examiners maintained that even if Treston were not prior art, the claimed invention could be rejected as obvious over Corral. Such a rejection of obviousness over Corral will be discussed below.

**Even if Treston were Prior Art, the Claimed Invention is Not Obvious**

Applicant respectfully submits that the Examiner has not shown that the claimed invention is obvious, because prior to this invention, the cited references, alone or in combination, would not have provided any teaching or suggestion of the claimed invention, nor motivation to modify or combine the cited references, as discussed below. Further, the references fail to suggest each and every element of the pending claims, much less provide a reasonable expectation of success.

Under the current law, prior art references cannot render a claim obvious unless the PTO provides evidence that the references meet a three-part test for *prima facie* obvious. To begin with, the prior art reference or references must provide "motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant." *See In re Kotzab*, 217 F.3d 1365, 1370, 55 U.S.P.Q.2d 1313, 1316 (Fed. Cir. 2000); *Princeton Biochemicals, Inc. v. Beckman Coulter, Inc.*, 2005 WL 1355127, at *4, 75 U.S.P.Q.2d 1051, 1054 (Fed. Cir. 2005). Where one reference is relied upon by the PTO, there must be a suggestion or motivation to modify the teachings of that reference. *See In re Kotzab*, 217 F.3d at 1370, 55 U.S.P.Q.2d at 1316-17. Where an obviousness determination relies on the combination of two or more references, there must be some suggestion or motivation to combine the references. *See WMS Gaming Inc. v. International Game Technology*, 184 F.3d 1339, 1355, 51 U.S.P.Q.2d 1385, 1397 (Fed. Cir. 1999);

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prior art, this rejection must be withdrawn. Moreover, Applicant does not agree that Treston has support in the first filed application for the relevant subject matter as discussed below.

*Princeton Biochemicals, Inc.*, 2005 WL 1355127, at *4, 75 U.S.P.Q.2d at 1054; *Teleflex, Inc. v. Ficosa North America Corp.*, 299 F.3d 1313, 1334, 63 U.S.P.Q.2d 1374, 1387 (Fed. Cir. 2002). Second, the prior art references cited by the PTO must suggest to one of ordinary skill in the art that the invention would have a reasonable expectation of success. *See In re Dow Chemical*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988); *Boehringer Ingelheim Vetmedica, Inc.*, 320 F.3d 1339, 1354, 65 U.S.P.Q.2d 1961, 1971 (Fed. Cir. 2003); *Noelle v. Lederman*, 355 F.3d 1343, 1352, 69 U.S.P.Q.2d 1508, 1516 (Fed. Cir. 2004). Further, "[b]oth the suggestion and the reasonable expectation of success 'must be founded in the prior art, not in the applicant's disclosure.'" *Noelle*, 355 F.3d at 1352, 69 U.S.P.Q.2d at 1515-16 (quoting *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991)). Finally, the PTO must show that the prior art references, either alone or in combination, teach or suggest each and every limitation of the rejected claims. *See Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1473, 43 U.S.P.Q.2d 1481, 1490 (Fed. Cir. 1997); *Litton Systems, Inc. v. Honeywell, Inc.*, 87 F.3d 1559, 1569, 39 U.S.P.Q.2d 1321, 1327 (Fed. Cir. 1996).

The pending claims recite, *inter alia*, methods of treating multiple myeloma, comprising administering about 1 to 150 mg/day of a specific compound named 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione.

Treston and Corral, even viewed in combination, fail to establish a *prima facie* case of obviousness. Treston allegedly relates to the use of different compounds, specifically certain isomers that the Examiners refer to as R- and S-3-amino-thalidomide. Thus, even if Treston were prior art, it would not disclose or suggest the compound recited in the pending claims. The Examiner recognized that Treston does not disclose or suggest the use of the compound of the claimed methods, much less the claimed methods of using the compound in treating multiple myeloma.

Nevertheless, the Examiner alleged that Corral, either standing alone or in combination with Treston, renders the claimed invention obvious, because Corral allegedly teaches that Actimid™[2] and Revimid™[3] have the same mechanisms of actions such as LPS

[2] Applicant is assuming that, by referring to Actimid™, the Examiner is referring to 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione, a species referenced by the trademark Actimid™ which is pending in the United States Patent and Trademark Office.

[3] Applicant is assuming that, by referring to Revimid™, the Examiner is referring to 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, a species referenced by the registered trademark Revimid®. Celgene Corporation presently markets pharmaceutical compositions comprising 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione under the mark Revlimid®.

induced inflammation and T-cell activation (Table 1 at page 1110) and have potential as cancer therapies (Conclusion at page 1111). (Pages 5-6 of the Office Action). However, the Examiner has not demonstrated that Corral discloses or suggests essential elements of the claimed invention herein, *e.g.*, the claimed use of 3-(4-amino-1 oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione for treating multiple myeloma. That is, the Examiner has not shown that Corral cures the deficiencies of Treston. Moreover, the Examiner has not established any suggestion or motivation to combine or modify the disclosures so as to obtain the claimed methods.

Even when Treston and Corral are combined, there is no suggestion or motivation to use the compound in the claimed methods, because the references fail to teach or suggest that the claimed compound is useful for the treatment of multiple myeloma as recited in the instant claims. Corral purportedly reports different classes of thalidomide analogues and their characteristics. In Corral, Actimid™ and Revimid® are listed as IMiDs® immunodulatory drugs. *See*, Figure 1 of page 1109 (structures of IMiDs® immunomodulatory drugs and SelCiDs® drugs[4]. Table 1 at page 1110 describes different immunomodulatory activities of thalidomide and its analogues. Corral concludes at page 1111 that two classes of thalidomide analogues (referenced under the trademarks IMiDs® and SelCiDs®) have different properties and should be investigated in different disorders, without mentioning a specific cancer. The Examiner has identified no disclosure or suggestion that Actimid™ or Revimid® may be used in treating a cancer, much less multiple myeloma. The Examiner has not shown that Corral, alone or in combination with Treston, would have provided any teaching or suggestion of the claimed methods of using 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione against multiple myeloma.

Nevertheless, the Examiner alleges that Treston teaches that Actimid™ is effective in treating cancers, and that the similarities of function between Actimid™ and Revimid® disclosed in Corral more than suggest the applicability of Revimid® for the claimed cancers. (Page 6 of the Office Action). Treston discloses that enantiomers of 3-amino-thalidomide have angiogenesis inhibitory activities, that angiogenesis is associated with cancers, and that the method of treating diseases comprises administering a composition in a dosage sufficient to inhibit angiogenesis. (*See*, paragraphs [0028] and [0042]). However, Corral does not teach or suggest anything about angiogenesis inhibitory

[4] Applicant respectfully directs the attention of the Examiner to the fact that IMiDs® refers to Celgene Corporation's registered trademark for immunomodulatory drugs and SelCiDs® refers to Celgene Corporation's registered trademark for selective cytokine inhibitory drugs.

activities of thalidomide analogues, nor does Corral disclose or suggest any relationship between the properties of thalidomide analogues and clinical applications in cancers. Corral only teaches that thalidomide, IMiDs® immunomodulatory drugs and SelCiDs® drugs have distinct immunomodulatory profiles, and they are or should be investigated in different clinical settings. *See*, right column of page 1109 to left column of page 1110 (two distinct classes of molecules), Table 1 of page 1110 (immunomodulatory profiles of thalidomide, IMiDs® immunomodulatory drugs and SelCiDs® drugs), and right column of page 1111 (conclusion).

Further, Treston fails to teach or suggest that the enantiomers of "3-amino-thalidomide" may be substituted with the compound recited in the instant claims. That is, there is no motivation to use the compound of the instant methods in place of "3-amino-thalidomide." Accordingly, the combination of two references would not provide one of ordinary skill in the art with motivation for selecting the claimed compound in treating a cancer. The Examiner's unsupported allegation fails to provide the requisite legal suggestion, and is premised on unsound basis. The examiner's statement is nothing but conclusory opinion and it cannot form a basis for obviousness rejection. *In re Sang-Su Lee*, 277 F.3d 1338, 1343-4 (Fed. Cir. 2002).

Further, during the personal interview, the Examiners alleged that TNF alpha inhibition of thalidomide analogues suggests their potential uses against cancer. Corral does not disclose or suggest any application of thalidomide analogues against cancer, irrespective of the reported TNF alpha inhibitory activity. Indeed, Corral reports that the distinct activities of thalidomide and its analogues suggest the different applications in clinical settings. *See*, right column of page 1109 to left column of page 1110 (two distinct classes of molecules), Table 1 of page 1110, and right column of page 1111 (conclusion). Further, art relating to cancer is highly unpredictable and there are many complex mechanisms involved in treatment of cancer. Therefore, based upon *in vitro* or *in vivo* TNF alpha inhibition activity alone, one cannot establish a *prima facie* case of obviousness against the pending claims.

In sum, Corral does not disclose or suggest the use of Revimid® or Actimid™ as an agent to treat a cancer, much less the claimed methods of treating multiple myeloma using the recited compound. Therefore, Corral alone or in combination with Treston does not render the claims obvious.

Further, Treson and Corral combined do not provide a reasonable expectation of success. The Examiner has not established that the prior art provided one of ordinary skill in the art with a reasonable expectation of success for methods for treating

specific cancers using the claimed compound alone (*e.g.*, claims 24, 26, 29-33 and 71-73) or in combination with particular agents (*e.g.*, claims 38-42, 48-55 and 74), much less methods using specific administration routes and doses (*e.g.*, claims 57-70). *See In re Fine*, 837 F.2d at 1075. Indeed, Corral cautions that thalidomide analogues to be used in patients must be non-toxic and non-teratogenic and such properties may have been yet-to-be determined. (Corral, page 1109, from last sentence of left column to first paragraph of right column). In other words, although there was interest in further studying these compounds, Corral does not provide the legally required expectation of the successful use of the compounds in treatment of patients. Treston does not cure this deficiency of Corral, because it relates to the compounds different from those claimed in the present application. Finally, the Examiner has not shown that the references, either alone or in combination, teach or suggest each and every limitation of the instant claims. *See Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461. The combination of the references cited by the Examiner does not teach or suggest all of the limitations of the pending claims for methods of treating multiple myeloma using 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione.

In view of the foregoing, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

**There Are Sufficient Unexpected Results To Rebut Even a *Prima Facie* Case**

Further, even assuming, *arguendo*, a *prima facie* case of obviousness is established by the cited references alone or in combination, there is ample evidence of unexpected or superior results in the present specification and publications to rebut a *prima facie* case of obviousness. As the Examiner is well aware, such unexpected results can rebut even a *prima facie* case of obviousness. *In re May*, 574 F.2d 1082, 1094 (C.C.P.A. 1978); *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987); *Ortho-Mcneil Pharmaceutical v. Mylan Laboratories*, 348 F.Supp.2d 713, 755 (N.D.W.Va. 2004); and *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991). In fact, the Examiners at the personal interview held on June 7, 2006 stated that arguments and evidence on the unexpected results would overcome the obviousness rejection.

The specification of the present application discloses nonobvious or unexpected results of the claimed methods in clinical studies with multiple myeloma patients. For example, Applicant invites the Examiner's attention to the studies using the recited compound at the doses recited in the pending claims, which are disclosed in the specification, *e.g.*, Section 6.5.2. "Treatment of Relapsed Multiple Myeloma" on pages 46-47, and Section 6.5.6. "Treatment of Relapsed Or Refractory Multiple Myeloma" on page 51 of the specification.

The unexpected results of the claimed invention are also evidenced by several references in the record of this application. Applicant submitted publications with the previous response and with Dr. Zeldis' Declaration, as Exhibit J, *i.e.*, Zeldis *et al.*, "Update on the evolution of the IMiD™," *International Society for Biological Therapy of Cancer, Oral Abstract*, 2003. For example, Zeldis *et al.* reported that a phase I study, administering the recited dose of the recited compound to patients with relapsed and refractory multiple myeloma, resulted in at least 25% reduction in paraprotein levels in 17 of 24 (71%) patients, with no significant toxicities.

Further, Applicant respectfully submits herewith additional publications published after the earliest filing date of the application, to show such unexpected or superior results of the claimed invention with Supplemental Information Disclosure Statement and List of References Cited.[5] For example, the safety, tolerability, and clinical benefits of the recited compound, administered to multiple myeloma patients recited in *e.g.*, claim 24, are corroborated by Richardson *et al.*, "Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma, " *Blood*, 100:3063-3067, 2002; Barlogie *et al.*, "Thalidomide and CC-5013 in Multiple Myeloma: The University of Arkansas Experience," *Seminars in Hematology,* Vol. 40, No. 4, Suppl 4, 2003: pp 33-38; Anderson, "The Role of Immunomodulatory Drugs in Multiple Myeloma," *Seminars in Hematology,* Vol. 40, No. 4, Suppl 4, 2003: pp 23-32; Weber, "Thalidomide and Its Derivatives: New Promise for Multiple Myeloma," *Cancer Control*, Vol. 10, No. 5, 375-383, 2003; and Sorbera *et al.*, "CC-5013. Treatment of multiple myeloma. Treatment of Melanoma. Treatment of myelodysplastic syndrome. Angiogenesis inhibitor. TNF-α production inhibitor," *Drugs of the Future*, 2003, 28(5):425-431. The authors reported that the compound recited in the pending claims demonstrated good efficacy, tolerability and safety in phase I and II studies with multiple myeloma patients. It was also reported that the studies corroborated the ability of the recited compound to overcome resistance to prior thalidomide therapy. *See*, Richardson *et al.*, at pages 3065-3067; Barlogie *et al.*, at pages 36-38; Anderson at pages 30-31; Weber at page 381; and Sorbera *et al.*, at pages 429-430.

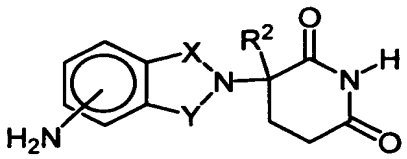
[5] Applicant notes that some of references cited in IDS are not discussed herein. Applicant requests that all the references be made of record in the file history of the application and that the Examiner execute the 1449 Form enclosed.

The evidence in the specification and publications rebuts even a *prima facie* case of obviousness.[6] In view of the unexpected or superior results of the present invention, the presently claimed invention is not obvious. *In re May*, at 1094; *In re Chupp*, at 646; and *Ortho-Mcneil Pharmaceutical v. Mylan Laboratories*, at 755. Therefore, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) over Treston in view of Corral be withdrawn.

**The Double Patenting Rejection Should Be Withdrawn**

Claims 22-56 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 8-15, 18-19, 21-22 and 25-29 of Application No. 10/704,237 (hereinafter '237 application), on the ground that both applications claim methods of treating a variety of cancers using immunomodulatory compounds having same compound of formula (I), alone or in combination with second active agents. (Pages 7-8 of the Office Action). Applicant respectfully traverses the rejection.

The Examiner alleges that the '237 application claims a method of treating prostate cancer, melanomas (claim 5) and multiple myeloma (claim 6) using the compound of the formula:




or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, wherein one of X and Y is C=O, the other of X and Y is C=O or $CH_2$, and $R^2$ is hydrogen or lower alkyl.

Applicant note that claims 1-32 of the '237 application were canceled on November 16, 2005 and that the pending claims do not recite the genus compound for use in prostate cancer, melanomas or multiple myeloma. Instead, the pending claims 33-63 of the '237 application recite methods of treating brain cancer which comprises administering 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-methylisoindoline. In contrast, the present claims recite methods of treating a multiple myeloma, using a different compound, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione. Therefore, both applications recite different methods using structurally distinct compounds for different diseases.

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6 These unexpected results should also be considered in the arguments for double patenting rejection below.

Accordingly, the claimed invention cannot be an obvious variation of the invention of the '237 application.

Claims 24 and 26-56 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 of Application No. 10/534,324 (hereinafter '324 application), on the ground that both applications claim common subject matter, because '324 application claims methods of treating a myeloproliferative disease such as smoldering myeloma using a cytokine inhibitory drug such as Actimid™ and Revimid™ and additional agents can be used. (Pages 8-9 of the Office Action). Applicant respectfully traverses this rejection.

The claims of '324 application recite methods of treating a myeloproliferative disease using a selective cytokine inhibitory drug, whose structure and characteristics are distinctive from those of the specific immunomodulatory compound recited by the pending claims of the present application. (*See* the specification of '324 application, *e.g.*, page 10, line 21 to page 22.) The claims, as amended herein, do not relate to the use of a selective cytokine inhibitory drug, but a specific immunomodulatory compound. Corral cited by the Examiner clearly distinguishes a selective cytokine inhibitory drug and an immunomodulatory compound. Thus, the compound recited by the pending claims is totally different from, and is not encompassed by, the compounds of '324 application.

Nonetheless, the Examiner alleges that Actimid™ and Revimid™ are cytokine inhibitory drugs, apparently referring to Corral, Table 1 at page 1110. Applicant respectfully asserts that the Examiner erroneously interpreted the reference as teaching that the claimed compound is a cytokine inhibitory drug. Applicant respectfully request the Examiner's attention that Table 1 of Corral does not indicate that Actimid™ or Revimid™ is a cytokine inhibitory drug. Table 1 summarizes different properties of thalidomide, IMiDs® immunomodulatory drugs and SelCiDs® drugs. Indeed, Figure 1 at page 1109 explicitly shows that the structures of Actimid™ and Revimid® belong to the category of IMiDs® immunomodulatory drugs but not SelCiDs® drugs. Corral *et al.* clearly distinguishes immunomodulatory compounds such as Actimid™ and Revimid® from selective cytokine inhibitory drugs. Corral *et al.* reports that thalidomide analogues comprise two distinct classes of molecules, first class being IMiDs® (Celgene's brand of Immunomodulatory Imide Drugs) and second class being SelCiDs® (Celgene's brand of Selective Cytokine Inhibitory Drugs), and that two classes of drugs possess distinct properties in inhibitions of PDE4, IL1ß, IL 12, IL6 and IL10 and distinct effects on T cell activation. For example, certain IMiDs® immunomodulatory drugs are potent inhibitors of

monocyte inflammatory cytokine production and also are strong co-stimulators of T cell activity. SelCiDs® drugs on the other hand, are generally potent PDE4 inhibitors and thus more selective inhibitors of TNF alpha. Unlike many IMiDs® immunomodulatory drugs SelCiDs® drugs do not ordinarily co-stimulate T cells but generally inhibit T cell activity. *See*, Figure 1 at page 1109 (structures of IMiDs® immunomodulatory drugs and SelCiDs® drugs), right column of page 1109 to left column at page 1110 (two distinct classes of molecules), Table 1 of page 1110 (immunomodulatory profiles of thalidomide, IMiDs® immunomodulatory drugs and SelCiDs® drugs, and right column at page 1111(conclusion).

Accordingly, Corral *et al.* concludes that the two classes of thalidomide analogues have different properties and their distinct activities suggest different applications in different disorders. *See*, right column of page 1110 to right column of page 1111 (potential clinical applications and conclusion).

In view of the foregoing, it is clear that the structure and characteristics of the specific immunomodulatory compound recited by the pending claims of the present application are distinct from those of selective cytokine inhibitory drugs in the claims of '324 application.

Further, a myeloproliferative disease recited in '324 application is distinct from, and is not an obvious variant of multiple myeloma. In sum, the claims of '324 application do not disclose or suggest methods of treating a specific cancer using the compound recited by the pending claims. The Examiner has made no *prima facie* case that the pending claims are obvious in light of the claims of '324 application.

Claims 22-56 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 and 18-26 of Application No. 10/515,270 (hereinafter '270 application), on the ground that both applications claim common subject matter because '270 application claims methods of treating cancer using a cytokine inhibitory drug such as Actimid™ and Revimid™ and additional agents can be used. (Pages 9-10 of the Office Action). Applicant respectfully traverses this rejection.

The claims of '270 application recite methods of treating cancer using selective cytokine inhibitory drugs. As explained above, the selective cytokine inhibitory drugs are significantly different from the specific immunomodulatory compound of the pending claims in their structures and properties. The subject matters of the claims of both applications are not encompassed by each other. The specific immunomodulatory compound of the pending claims is not disclosed or suggested by '270 application. The

Examiner has made no *prima facie* case that the pending claims are obvious in light of the claims of '270 application.

In sum, Applicant respectfully submits that the rejection of the pending claims under judicially created obviousness-type double patenting should be withdrawn because no *prima facie* case of obviousness has been established for the pending claims over any of the cited applications. Applicant further submits that no terminal disclaimer over the cited applications is necessary.

## Conclusion

In view of the foregoing, all the rejections of the claims should be withdrawn. Reconsideration, entry of the above amendment and remarks, and allowance of the pending claims are respectfully requested. Should the Examiner not agree that all claims are allowable, a personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application.

Respectfully submitted,

Date: June 16, 2006

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Application of: | Jerome B. Zeldis | Confirmation No.: | 4802 |
| Serial No.: | 10/438,213 | Art Unit: | 1614 |
| Filed: | May 15, 2003 | Examiner: | Graffeo, Michelle |
| For: | METHODS FOR TREATMENT OF A MULTIPLE MYELOMA USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE (as amended) | Attorney Docket No.: | 9516-074-999 (CAM: 501872-999073) |

**DECLARATION BY JEROME B. ZELDIS, M.D., Ph.D. UNDER 37 C.F.R. § 1.131**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Jerome B. Zeldis, M.D., Ph.D. declare that:

1. I earned an M.D. and a Ph.D. in Molecular Biophysics and Biochemistry at Yale University School of Medicine (New Haven, CT). After completion of these degrees, I completed an internship in Internal Medicine at U.C.L.A. Medical Center (Los Angeles, CA). I then completed a residency in Internal Medicine at U.C.L.A. Medical Center (Los Angeles, CA). I also held a Research Fellowship in Medicine at Harvard Medical School (Boston, MA) and at Massachusetts General Hospital (Boston, MA). In addition, I have held academic appointments at Harvard Medical School (Boston, MA), University of California (Davis, CA), and Cornell University Medical College (New York, NY). I am licensed to practice medicine in the States of California, New York, and New Jersey and in the Commonwealth of Massachusetts. I am presently a Vice President and the Chief Medical Officer of Celgene Corporation (Summit, NJ).

2. I am the named inventor of the claims presently pending in the above-identified patent application ("the '213 application"). I am familiar with its disclosure and claims. A copy of the claims that I understand are currently pending is attached hereto as Exhibit A.

3. The '213 application discloses and presently claims, in part, methods of treating a multiple myeloma, which comprise administering to a patient about 1 to about 150 mg per day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione or REVLIMID®, also known as REVIMID®. (*See* claim 24).

4. I understand that an Office Action issued on December 19, 2005 in connection with the '213 application rejecting the claims as being allegedly obvious over Treston *et al.*, United States Patent Application Publication No. 2004/0147558 ("Treston"), attached hereto as Exhibit B. I understand that the Examiner stated that Treston teaches methods for the treatment of prostate cancer, melanoma or myeloma using R or S enantiomer of 3-amino-thalidomide at paragraphs 47, 48, 51, 84. (Office Action, pages 3-5, attached hereto as Exhibit C).

5. I conceived of the presently claimed invention in the '213 application prior to November 30, 2000, the date of the first filed application to which Treston claims priority. This is evidenced by clinical trial protocols of the assignee (Celgene Corporation) of the present application for the claimed cancers. Redacted copies of the front pages of each protocol are attached hereto as Exhibit D to E. (PROTOCOL CDC-501-001 entitled "AN OPEN LABEL STUDY OF THE SAFETY AND EFFICACY OF CC-5013 TREATMENT FOR PATIENTS WITH RELAPSED MULTIPLE MYELOMA"; and PROTOCOL CDC-501-002 entitled "UARK 2000-29, AN OPEN LABEL STUDY OF THE SAFETY AND EFFICACY OF CC-5013 TREATMENT FOR MULTIPLE MYELOMA PATIENTS WHO RELAPSE AFTER HIGH DOSE CHEMOTHERAPY").

6. Specifically, the protocols for treating multiple myeloma with REVLIMID® were designed based upon the earlier conception, and were performed under my supervision and direction, prior to November 30, 2000. Patients were enrolled and treated with REVLIMID® under the protocol from prior to November 30, 2000 to the filing date of the present application. This is evidenced, in part, by the abstracts reporting the results obtained under the protocols, as attached hereto as Exhibit F to G. (Zangari *et al.*, "Results of phase I study of CC-5013 for the treatment of multiple myeloma (MM) patients who relapse after high dose chemotherapy (HDCT)," *American Society of Hematology, Abstract #3226*, 2001; and Zeldis *et al.*, "Update on the evolution of the IMiD™," *International Society for Biological Therapy of Cancer, Oral Abstract*, 2003. Portions of the

studies are also referred to in the present application, Section 6.5.2 "Treatment of Relapsed Multiple Myeloma" on pages 46-48 of the specification.

7. I offer this declaration to demonstrate that the November 30, 2000 filing date of Treston is not, to my knowledge, prior to my conception of the claimed invention.

8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like may be punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent issuing from the '213 application.

Dated: 30 May 2006

Jerome B. Zeldis, M.D., Ph.D.

**Express Mail No.: EV452776467US**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Application of: | Zeldis | Confirmation No.: | 4802 |
| Serial No.: | 10/438,213 | Group Art Unit: | 1614 |
| Filed: | May 15, 2003 | Examiner: | Michel Graffeo |
| For: | METHODS FOR TREATMENT OF MULTIPLE MYELOMA USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE | Attorney Docket No.: | 9516-074-999 |

**SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. §1.97 & §1.56**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the duty of disclosure imposed by 37 C.F.R. §1.56 to inform the Patent and Trademark Office of all references coming to the attention of Applicant or his attorneys which are or may be related to patentability of the claimed invention, Applicant hereby directs the Examiner's attention to references **C64** to **C185,** which are listed on the accompanying revised PTO Form 1449.

Legible copies of listed references **C64** to **C185** are provided herewith. Applicant respectfully requests that the Examiner review the foregoing references and that the references be made of record in the file history of the application. Identification of the listed references is not to be construed an admission by Applicant or his attorneys that such references are available as "prior art" against the subject application.

Pursuant to 37 C.F.R. § 1.97(b), Applicant estimates that no fee is due in connection with the filing of this Information Disclosure Statement. However, should the Patent Office determine otherwise, please charge the necessary fee to Jones Day Deposit Account No. 50-3013. A duplicate of this sheet is enclosed for accounting purposes.

Respectfully submitted,

Date: June 16, 2006


Yeahsil Moon (Reg. No.) 52,042
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Enclosures

| Substitute for Form 1449/PTO<br>INFORMATION DISCLOSURE STATEMENT BY APPLICANT<br>(Use several sheets if necessary) | ATTY DOCKET NO.<br>9516-074-999 | APPLICATION NO.<br>10/438,213 |
|---|---|---|
| | APPLICANT:<br>Zeldis | |
| | FILING DATE:<br>May 15, 2003 | ART UNIT: 1614 CONF. NO.: 4802 |

## U.S. PATENT DOCUMENTS

| EXAMINER'S INITIALS* | | DOCUMENT NUMBER | DATE MM/DD/YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
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## FOREIGN PATENT DOCUMENTS

| EXAMINER'S INITIALS* | | Country Code, Number, Kind of Code (if known) | DATE MM/DD/YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear | TRANSLATION YES | TRANSLATION NO |
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**NON PATENT LITERATURE DOCUMENTS** *(include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book ,magazine, journal, etc.,), date, page(s)s, volume, publisher, city and/or country where published., etc.)*

| EXAMINER'S INITIALS* | | |
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| | C67 | BARLOGIE et al., "Introduction: Thalidomide and the IMiDs in multiple myeloma," *Seminars in Hematology*, 2003, 40 (4):1-2 |
| | C68 | BARLOGIE, "Thalidomide and CC-5013 in Multiple Myeloma: The University of Arkansas experience," *Seminars in Hematology*, 2003, 40 (4):33-38 |
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| | C70 | BARTLETT et al., "Phase I study to determine the safety, tolerability and immunostimulatory activity of thalidomide analogue CC-5013 in patients with metastatic malignant melanoma and other advanced cancers," *British Journal of Cancer*, 2004, 90:955-961 |
| | C71 | BATTEGAY, "Angiogenesis: mechanistic insights, neovascular diseases, and therapeutic prospects," *J. Mol. Med.*, 1995, 73:333-346 |
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| EXAMINER | DATE CONSIDERED |
|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with **MPEP 609**; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

| Substitute for Form 1449/PTO<br><br>INFORMATION DISCLOSURE STATEMENT BY APPLICANT<br>(Use several sheets if necessary) | ATTY DOCKET NO.<br>9516-074-999 | APPLICATION NO.<br>10/438,213 |
|---|---|---|
| | APPLICANT:<br>Zeldis | |
| | FILING DATE:<br>May 15, 2003 | ART UNIT: 1614 CONF. NO.: 4802 |

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| EXAMINER'S INITIALS* | | |
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| | C76 | CELGENE CORPORATION, "Celgene Corporation receives orphan drug designation for Revimid™ for multiple myeloma," Press Release, October 2001 |
| | C77 | CELGENE CORPORATION, "Celgene Corporation announces third quarter results. Thalomid® (thalidomide) sales increase 24%. Prescriptions up 50%. Enhanced S.T.E.P.S.® launched. Pilot d-MPH data presented," Press Release, October 2001 |
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| | C84 | CELGENE CORPORATION, "Celgene receives fast track status from FDA for Revimid™ in myelodysplastic sydromes," Press Release, April 2003 |
| | C85 | CELGENE CORPORATION, "New Revimid™ clinical data shows potential as novel approach to treating myelodysplastic syndromes (MDS)," Press Release, May 2003 |
| | C86 | CELGENE CORPORATION, "Celgene corporation reports strong operating performance in second quarter as total sales increase 100 percent and profits rise," Press Release, July 2003 |
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| | C88 | CELGENE CORPORATION, "Celgene corporation advances ACTIMID™ (CC-4047) into phase II trial for prostate cancer," Press Release, October 2003 |
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|---|---|---|
| | APPLICANT:<br>Zeldis | |
| | FILING DATE:<br>May 15, 2003 | ART UNIT: 1614 CONF. NO.: 4802 |

**NON PATENT LITERATURE DOCUMENTS** *(include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book ,magazine, journal, etc.,), date, page(s)s, volume, publisher, city and/or country where published., etc.)*

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| | C96 | DALGLEISH et al., "Thalidomide analogues CC-5013 and CC-4047 induce T cell activation and IL-12 production in patients with both solid tumours and relapsed and refractory multiple myeloma," *British Journal of Cancer*, 2003, 88(Suppl I), S25-S54 |
| | C97 | DATABASE PHARMAML XP002369094 retrieved from STN. Database accession no. 1659300, & MARKETLETTER, October 9, 2001. |
| | C98 | DATABASE NLDB XP002369095 retrieved from STN. Database accession no. 2002:35280, & MARKETLETTER, June 18, 2001. |
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| | C101 | DIBBS et al., "Thalidomide and thalidomide analogs suppress TNFα secretion by myocytes," *Abstract # 1284, Circulation*, 1998 |
| | C102 | DIMOPOULOS et al., "Results of thalidomide and IMIDs in multiple myeloma,", *Abstract # P12.1.4, International Multiple Myeloma Workshop*, May 23-27, 2003 |
| | C103 | DIMOPOULOS et al., "Treatment of plasma cell dyscrasias with thalidomide and its derivatives," *Journal of Clinical Oncology*, Dec. 1, 2003, 21 (23)4444-4454 |
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| | C105 | DREDGE et al., "A costimulatory thalidomide analog enhances the partial anti-tumor immunity of an autologous vaccination in a model of colorectal cancer, *Abstract # 491, American Association for Cancer Research*, April 6-10, 2002 |
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| | C111 | DREDGE et al., "Thalidomide analogs as emerging anti-cancer drugs," *Anti-Cancer Drugs*, 2003, 14:331-335 |
| | C112 | FICKENTSCHER et al., "Stereochemical properties and teratogenic activity of some tetrahydrophthalimides," *Molecular Pharmacology*, 1976, 13:133-141 |
| | C113 | FIGG et al., "Inhibition of angiogenesis: treatment options for patients with metastatic prostate cancer," *Investigational New Drugs*, 2002, 20(2):183-194 |
| | C114 | GALUSTIAN et al., "Thalidomide-derived immunomodulatory drugs as therapeutic agents," *Expert Opin. Biol.* |

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|---|---|

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| Substitute for Form 1449/PTO<br><br>INFORMATION DISCLOSURE STATEMENT BY APPLICANT<br>(Use several sheets if necessary) | ATTY DOCKET NO.<br>9516-074-999 | APPLICATION NO.<br>10/438,213 |
|---|---|---|
| | APPLICANT:<br>Zeldis | |
| | FILING DATE:<br>May 15, 2003 | ART UNIT: 1614 CONF. NO.: 4802 |

**NON PATENT LITERATURE DOCUMENTS** *(include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book ,magazine, journal, etc.,), date, page(s)s, volume, publisher, city and/or country where published., etc.)*

| EXAMINER'S INITIALS* | | |
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| | C118 | He, W., et al., 1993, Abstract of papers, 206th American Chemical Society, Chicago, IL; Med. Chem., paper 216 |
| | C119 | HELM et al., "Comparative teratological investigation of compounds of structurally and pharmacologically related to thalidomide," *Arzneimittel Forschung/Drug Research*, 1981, 31 (I)941-949 |
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| | C124 | HUSSEIN et al., "Doxil (D), vincristine (V), reduced frequency dexamethasone (d) and Revlimid (DVd-R) a phase I/II trial in advanced relapsed/refractory multiple myeloma (Rmm) patients," *Blood, Abstract #208, American Society of Hematology*, Dec. 4-7, 2004 |
| | C125 | HWU et al., "Thalidomide and its analogues in the treatment of metastatic melanoma," *Chemotherapy Foundation Symposium, Abstract #44*, 2002 |
| | C126 | KYLE, "Current therapy of multiple myeloma," *Internal Medicine*, 2002, 41 (3)175-180 |
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|---|---|---|
| | APPLICANT:<br>Zeldis | |
| | FILING DATE:<br>May 15, 2003 | ART UNIT: 1614 CONF. NO.: 4802 |

**NON PATENT LITERATURE DOCUMENTS** *(include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book ,magazine, journal, etc.,), date, page(s)s, volume, publisher, city and/or country where published., etc.)*

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| | FILING DATE:<br>May 15, 2003 | ART UNIT: 1614 CONF. NO.: 4802 |

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| EXAMINER'S INITIALS* | | |
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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/438,213 | 05/15/2003 | Jerome B. Zeldis | 9516-074-999 | 4802 |

20583 7590 10/24/2006

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| EXAMINER | |
|---|---|
| GRAFFEO, MICHEL | |
| **ART UNIT** | **PAPER NUMBER** |
| 1614 | |

DATE MAILED: 10/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/438,213 | ZELDIS, JEROME B. | |
| | Examiner | Art Unit | |
| | Michel Graffeo | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *24,26,29-33,38-42,48-55 and 57-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24,26,29-33,38-42,48-55 and 57-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *16 June 06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Action*

Claims 24, 26, 29-33, 38-42, 48-55 and 57-76 are examined.

Applicant has amended claims 24 and 61, canceled claims 1-23, 25, 27-28, 34-37, 43-47 and 56 and provided arguments for the patentability of claims 24, 26, 29-33, 38-42, 48-55 and 57-76 in the response filed 16 June 2006.

Applicant's arguments, see response, filed 16 June 2006, have been fully considered and are persuasive to the extent that the rejections under 35 USC §112, §103 and §101 regarding copending Application No. 10/704237 have been withdrawn. However, upon further consideration, a new ground(s) of rejection is made. Any rejection not specifically stated in this Office Action has been withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action

has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 16 June 2006 has been entered.

***Claim Rejections - 35 USC § 103***

Claims 24, 26, 29-33, 38-42, 48-55 and 57-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Corral et al. Immunomodulation by thalidomide and thalidomide analoques. Ann. Rheum. 1999; 58; 107-13.

Corral et al. teach that Revimid™ and salts thereof such as Actimid™ (see Fig. 1) has the same mechanisms of action relative LPS induced inflammation, T-cell activation etc. (see page 1110 Table 1) and provide one of skill in the art with a reasonable expectation of success in treating cancer with Revimid™ because of Revimid's™ effect on TNF-alpha (see Conclusions page 1111). Although the Corral et al. reference does not teach the specific treatment for multiple myeloma with the claimed active, the reference teaches that the active is efficacious in treating cancer. To that extent, the treatment of multiple myeloma is included in and obvious over the treatment of cancer in general.

Although each of the dose/cycle combinations are not specifically recited in Corral et al., cyclical cancer treatments are common practice due to the toxicity of many therapies which would have made the claimed combinations obvious over Corral et al.Furthermore, one of skill in the art would routinely optimize patient dosages based on patient sensitivities and needs especially within the range of marketed dosages of Revimid™ (i.e. 5-25mg dosages).

Corral et al. do not teach the inclusion of an additional anti cancer agent in the therapy or formulation. Nonetheless, combining agents which are known to be useful as anticancer agents individually into a singe composition useful for the very same purpose is prima facie obvious. See In re Kerkhoven 205 USPQ 1069. Since it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose, the idea of combining Revimid™ with another anticancer agent flows logically from their having been individually taught in the prior art.

Although Corral et al. do not recite the treatment of various forms of prostate cancer, for example hormone-insensitive prostate cancer. Absent evidence to the contrary, an anti-angiogenesis compound would have a different mechanism of action than hormone therapy such that the hormone insensitive nature of the prostate cancer would not affect treatment of the prostate cancer with an anti-angiogenesis compound. Thus, hormone insensitive prostate cancer will necessarily be treated by an anti-angiogenesis compound.

***Response to Arguments - 35 USC § 103***

Applicant's arguments filed 16 June 2006 have been fully considered but they are not persuasive. Applicant argues that Corral et al. alone does not obviate the present invention. As noted above, Corral et al. teach that Revimid™ (see Fig. 1) is efficacious in treating cancer since it inhibits TNF-alpha production, which in turn can ameliorate toxicities of cancers caused by overproduction of TNF-alpha. To that extent, the Corral

et al. reference suggests the same "unexpected results" purported by Applicants in the 16 June 2006 response, that Revimid™ has low toxicities and is well tolerated by patients (see page 16 of the response).

Applicants additionally argue that multiple myeloma is not taught as an indication of the Corral et al. reference. That notwithstanding, the reference mimics the proposed anti-cancer mechanism of action as in the instant Specification (see pages 41-42 of the instant Specification) which is the reduced production of TNF-alpha caused by Revimid™. Therefore, the Corral et al. reference suggests the treatment of cancers via a reduction of TNF-alpha and tolerability of Revimid™.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 24, 26, 29-33, 38-42, 48-55 and 57-76 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-11 and 22-40 of copending Application No. 10/534324 in view of Corral et al. Immunomodulation by

thalidomide and thalidomide analoques. Ann. Rheum. 1999; 58; 107-13. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows:

Claims of the '324 application claim a method of treating a myeloproliferative disease such as smoldering myeloma comprising among other agents a cytokine inhibitory drug which is enantiomerically pure in some instances or a salt or solvate thereof. Actimid™ and Revimid™ for example are cytokine inhibitory drugs (see Corral et al. page 110 in table 1) and the additional agents that can be used in the instant method are standard chemotherapy agents such as irinotecan and taxotere or standard techniques for treating cancer such as radiation and immunotherapy. Moreover, since no drug is defined in the noted claims of the above copending applications, the rejection is proper.

Claims 24, 26, 29-33, 38-42, 48-55 and 57-76 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-9, 18-32 of copending Application No. 10/515270 in view of Corral et al. Immunomodulation by thalidomide and thalidomide analoques. Ann. Rheum. 1999; 58; 107-13. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows:

Claims of the '270 application claim a method of treating cancer in general, wherein specific examples such hormone independent prostate cancer and smoldering myeloma are also claimed, comprising a second agent along with a cytokine inhibitory drug which is an enantiomer in some instances or a salt or solvate thereof. Actimid™ and Revimid™ for example are cytokine inhibitory drugs (see Corral et al. page 110 in table 1) and the additional agents that can be used in the instant method are standard chemotherapy agents such as irinotecan and taxotere or standard techniques for treating cancer such as radiation and immunotherapy. Moreover, since no drug is defined in the noted claims of the above copending applications, the rejection is proper.

Claims 24, 26, 29-33, 38-42, 48-55 and 57-76 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-10 and 21-37 of copending Application No. 10531552 in view of Corral et al. Immunomodulation by thalidomide and thalidomide analoques. Ann. Rheum. 1999; 58; 107-13. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that

copending application since the referenced copending application and the instant application are claiming common subject matter, as follows:

Claims of the '552 application claims a method of treating a myelodysplastic syndrome in general, comprising a second agent along with a cytokine inhibitory drug which is an enantiomer in some instances or a salt or solvate thereof. Actimid™ and Revimid™ for example are cytokine inhibitory drugs (see Corral et al. page 110 in table 1) and the additional agents that can be used in the instant method are standard chemotherapy agents such as irinotecan and taxotere or standard techniques for treating cancer such as radiation and immunotherapy. Moreover, since no drug is defined in the noted claims of the above copending applications, the rejection is proper.

***Response to Arguments - Double Patenting***

Applicant's arguments filed 16 June 2006 with respect to the Double Patenting rejection over Application No. 10/534324, 10/515270 and 10/531552 have been fully considered but they are not persuasive.

Applicant's arguments over the rejections have been fully considered but they are not persuasive because Revimid™ is a cytokine inhibiting drug (see Corral et al. page 110 in table 1). Moreover, since no drug is defined in the noted claims of the above copending applications, the rejection is proper.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michel Graffeo whose telephone number is 571-272-8505. The examiner can normally be reached on 9am to 5:30pm Monday to Friday.

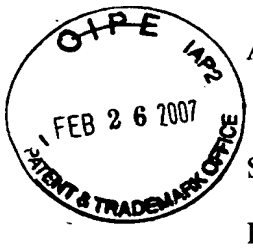
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

10 October 2006
MG

Ardin H. Marschel 10/14/06
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE




Application of: Jerome B. Zeldis

Continuation No.: 4802
Group Art Unit: 1614

Serial No.: 10/438,213

Examiner: Graffeo, Michel

Filed: May 15, 2003

Attorney Docket No.: 9516-074-999
(CAM: 501872-999073)

For: METHODS FOR THE TREATMENT OF MULTIPLE MYELOMA USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE (as amended)

## AMENDMENT AND RESPONSE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
Mail Stop Amendment

Sir:

In response to non-final Office Action dated October 24, 2006, please consider and enter the amendments and remarks provided below. Submitted herewith are Supplemental Information Disclosure Statement and Petition for Extension of Time and, each with the provision for the required fees.

**Amendments to the Claims** are reflected in the listing of the claims that begins on page 2 of this paper.

**Remarks** begin on page 7 of this paper.

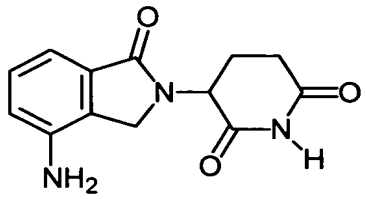
**Amendment to the Claims**:

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of the Claims:**

Claims 1-23. (canceled)

24. (currently amended) A method of treating multiple myeloma, which comprises administering to a patient having multiple myeloma about 1 to about 150 mg per day of a compound of the formula:



or a pharmaceutically acceptable salt, solvate or stereoisomer thereof,

and a therapeutically effective amount of dexamethasone.

25. (canceled)

26. (previously presented) The method of claim 24, wherein the multiple myeloma is smoldering myeloma, indolent myeloma, chemotherapy responsive multiple myeloma, refractory myeloma, relapsed myeloma, or relapsed and refractory Dune-Salmon stage III multiple myeloma.

27-28. (canceled)

29. (previously presented) The method of claim 24, wherein the compound is a pharmaceutically acceptable salt.

30. (previously presented) The method of claim 24, wherein the compound is a pharmaceutically acceptable solvate.

31. (previously presented) The method of claim 24, wherein the compound is a pharmaceutically acceptable stereoisomer.

32. (previously presented) The method of claim 31, wherein the stereoisomer is an enantiomerically pure R isomer.

33. (previously presented) The method of claim 31, wherein the stereoisomer is an enantiomerically pure S isomer.

34-37. (canceled)

38. (currently amended) The method of claim 24, which further comprises administering a therapeutically effective amount of ~~a second~~ an additional active agent.

39. (currently amended) The method of claim 38, wherein the ~~second~~ additional active agent is hematopoietic growth factor, a cytokine, or an anti-cancer agent.

40. (currently amended) The method of claim 39, wherein the ~~second~~ additional active agent is granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), erythropoietin (EPO), interleukin (IL), interferon (IFN), or a pharmacologically active mutant or derivative thereof.

41. (currently amended) The method of claim 39, wherein the ~~second~~ additional active agent is oblimersen, melphalan, topotecan, pentoxifylline, taxotere, irinotecan, ciprofloxacin, ~~dexamethasone,~~ doxorubicin, vincristine, dacarbazine, Ara-C, vinorelbine, prednisone, cyclophosphamide, bortezomib, arsenic trioxide or a combination thereof.

42. (previously presented) The method of claim 24, which further comprises administering radiation therapy, hormonal therapy, biological therapy or immunotherapy.

43-56. (canceled)

57. (previously presented) The method of claim 24, wherein the cancer is relapsed, refractory or resistant to conventional therapy.

58. (currently amended) The method of claim 24, wherein the compound and dexamethasone are ~~is~~ administered orally.

59. (previously presented) The method of claim 58, wherein the compound is administered in the form of a capsule or tablet.

60. (previously presented) The method of claim 24, wherein the compound is administered in an amount of from about 1 to about 50 mg per day.

61. (previously presented) The method of claim 60, wherein the compound is administered in an amount of about 5, 10, 20, 25, 30, or 50 mg per day.

62. (previously presented) The method of claim 60, wherein the compound is administered in an amount of from about 5 mg per day to about 25 mg per day.

63. (previously presented) The method of claim 60, wherein the compound is administered in an amount of about 25 mg per day.

64. (currently amended) The method of claim 24, wherein the compound and dexamethasone are ~~is~~ administered cyclically.

65. (previously presented) The method of claim 64, wherein one cycle comprises four to six weeks.

66. (previously presented) The method of claim 64, wherein one cycle comprises the administration of the compound for 21 days followed by seven days rest.

67. (previously presented) The method of claim 64, wherein the compound is administered for four to twenty-four weeks with one to six weeks of rest.

68. (previously presented) The method of claim 24, wherein the compound is administered in an amount of from about 5 to about 25 mg per day for 21 days every 28 days for sixteen to twenty-four weeks.

69. (currently amended) The method of claim ~~68~~ 64, wherein the compound is administered in an amount of about 25 mg per day for 21 days followed by seven days rest in a 28 day cycle; and dexamethasone is administered in an amount of about 40 mg once daily on Days 1 to 4, 9 to 12, and 17 to 20 of each cycle for first 4 cycles, and after the first 4 cycles dexamethasone is administered in an amount of about 40 mg once daily on Days 1 to 4 of each cycle.

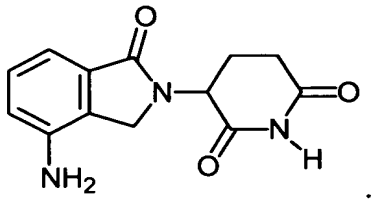
70. (previously presented) The method of claim 24, wherein the compound is administered in an amount of about 25 mg per day and dexamethasone is administered in an amount of about 40 mg per day on days 1-4 every four to six weeks.

71. (previously presented) The method of claim 60, wherein the compound is administered in an amount of 5 mg per day.

72. (previously presented) The method of claim 60, wherein the compound is administered in an amount of 10 mg per day.

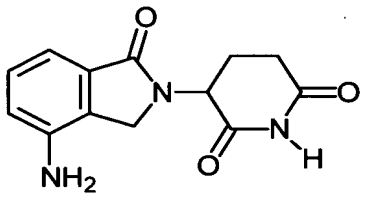
73. (currently amended) The method of claim 60, wherein the compound is administered in ~~an amount of 25 mg per day~~ a capsule of 5 mg, 10 mg, 15 mg or 25 mg.

74. (currently amended) ~~A method of treating multiple myeloma, which comprises administering to a patient having multiple myeloma a therapeutically effective amount of a compound of the formula:~~ The method of claim 24, wherein the compound is



~~and a therapeutically effective amount of dexamethasone.~~

75. (previously presented) A method of treating multiple myeloma, which comprises administering to a patient having multiple myeloma about 25 mg per day of a compound of the formula:



or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, and about 40 mg per day of dexamethasone.

76. (canceled).

77. (new) The method of claim 24, wherein the compound is administered in an amount of about 15 mg/day twice or about 30 mg/day four times a day.

78. (new) The method of claim 24, which further comprises administering a therapeutically effective amount of doxorubicin and vincristine.

79. (new) The method of claim 24, which further comprises administering a therapeutically effective amount of melphalan.

80. (new) The method of claim 73, wherein the capsule comprises the compound, lactose anhydrous, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

## REMARKS

### I. Amendments to the Claims

Claims 1-23, 25, 27, 28, 34-37, 43-56 and 76 have been canceled without prejudice. Applicant reserves the right to prosecute the subject matter of any canceled claims in one or more continuation, continuation-in-part, or divisional applications.

Claim 24 has been amended to clearly define the subject matter of the invention by the addition of "and a therapeutically effective amount of dexamethasone." Claims 58, 64 and 69 have been amended to incorporate the administration of dexamethasone. The claims are supported by the originally filed specification, for example, page 20, line 19; page 24, line 30; page 25, lines 15-17; page 27, line 33 to page 28, line 6; page 31, lines 11-13 and 26-29; page 31, line 30 to page 33, line 2 and page 51, lines 1-12.

Claims 38-41 have been amended by changing "second" to "additional" and by deleting "dexamethasone" to avoid duplication of claim 24. Claim 73 has been amended for a capsule form. Claim 74 has been amended for dependency. The claims are supported by claim 24, 59 or 60.

Claims 77-80 have been added. Claim 77 is supported by page 25, lines 15-17 of the originally filed specification. Claim 78 is supported by page 27, line 33 to page 28, line 6 of the originally filed specification. Claim 79 is supported by page 51, lines 1-12 of the originally filed specification. Claim 80 is supported by page 36, line 5 to page 38, line 15 of the originally filed specification. No new matter has been added.

Claims 24, 26, 29-33, 38-42, 57-75 and 77-80 are pending. Applicant respectfully submits that the pending claims are allowable for the following reasons.

### II. The Claimed Invention is Not Obvious

Claims 24, 26, 29-33, 38-42, 48-55 and 57-76 are rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Corral *et al.* (*Ann. Rheum.* 1999;58; 107-13, hereinafter "Corral"). (pages 3-5 of the Office Action). Applicant respectfully traverses this rejection.

Under the current law, prior art references cannot render a claim obvious unless the PTO provides evidence that the references meet a three-part test for *prima facie* obvious. To begin with, the prior art reference or references must provide "motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant." *See In re Kotzab*, 217 F.3d 1365, 1370, 55 U.S.P.Q.2d 1313, 1316 (Fed. Cir. 2000); *Princeton Biochemicals, Inc. v. Beckman Coulter, Inc.*, 2005 WL 1355127, at *4, 75 U.S.P.Q.2d 1051, 1054 (Fed. Cir. 2005). Where one reference is relied upon by the

PTO, there must be a suggestion or motivation to modify the teachings of that reference. *See In re Kotzab*, 217 F.3d at 1370, 55 U.S.P.Q.2d at 1316-17. Second, the prior art references cited by the PTO must suggest to one of ordinary skill in the art that the invention would have a reasonable expectation of success. *See In re Dow Chemical*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988); *Boehringer Ingelheim Vetmedica, Inc.*, 320 F.3d 1339, 1354, 65 U.S.P.Q.2d 1961, 1971 (Fed. Cir. 2003); *Noelle v. Lederman*, 355 F.3d 1343, 1352, 69 U.S.P.Q.2d 1508, 1516 (Fed. Cir. 2004). Further, "[b]oth the suggestion and the reasonable expectation of success 'must be founded in the prior art, not in the applicant's disclosure.'" *Noelle*, 355 F.3d at 1352, 69 U.S.P.Q.2d at 1515-16 (quoting *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991)). Finally, the PTO must show that the prior art references, either alone or in combination, teach or suggest each and every limitation of the rejected claims. *See Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1473, 43 U.S.P.Q.2d 1481, 1490 (Fed. Cir. 1997); *Litton Systems, Inc. v. Honeywell, Inc.*, 87 F.3d 1559, 1569, 39 U.S.P.Q.2d 1321, 1327 (Fed. Cir. 1996).

The pending claims recite, *inter alia*, methods of treating multiple myeloma, comprising administering about 1 to 150 mg/day of a specific compound named 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, in combination with dexamethasone.

It is alleged that Corral renders the claimed invention obvious, because Corral allegedly teaches that Revimid®[1] and Actimid™[2] have the same mechanisms of actions such as LPS induced inflammation and T-cell activation (Table 1 at page 1110), and provides a reasonable expectation of success in treating cancer with Revimid® because of its effect on TNF-alpha (Conclusion at page 1111). (Page 3 of the Office Action).

However, Corral does not suggest using a specific compound--3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione--with dexamethasone, much less a specific amount of the specific compound, *i.e.*, about 1 to 150 mg/day of the recited compound. Moreover, Corral does not even suggest any methods of treating multiple

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[1] Applicant is assuming that, by referring to Revimid™, the Examiner is referring to 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, a species referenced by the registered trademark Revimid®. Celgene Corporation presently markets pharmaceutical compositions comprising 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione under the mark Revlimid®.

[2] Applicant is assuming that, by referring to Actimid™, the Examiner is referring to 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione, a species referenced by the trademark Actimid™ which is pending in the United States Patent and Trademark Office.

myeloma, much less the specifically claimed combination therapy with dexamethasone. In sum, it has not been established that Corral suggests the essential elements of the claimed invention herein, *e.g.*, the claimed methods using 3-(4-amino-1 oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione in specific amounts with dexamethasone for treating multiple myeloma. That is, Corral is missing any teaching or suggestion of essential elements of the claimed invention and thus the rejection should be withdrawn.

Corral purportedly reports thalidomide, two classes of thalidomide analogues and their immunomodulatory profiles. However, Corral fails to teach or suggest that the specific amounts of the recited compound and dexamethasone are useful for the treatment of the specific disorders as recited in the instant claims. Corral does not discuss or suggest any uses of specific amounts of the recited compound with any other agents as claimed. Thus, Corral provides a skilled in the art with no suggestion nor motivation to use the compound and dexamethasone against multiple myeloma, as recited in the claimed methods.

The Examiner has identified no teaching or suggestion that the recited compound in a specific amount may be used in treating a cancer, less multiple myeloma, much less the combination therapy with dexamethasone. In Corral, Actimid™ and Revimid® are listed as IMiDs® immunomodulatory compounds. *See*, Figure 1 of page 1109, structures of IMiDs® compounds and SelCIDs®[3] compounds Table 1 at page 1110 describes the immunomodulatory activities of thalidomide and its analogues. Corral concludes at page 1111 that two classes of thalidomide analogues have different properties and should be investigated in different disorders, without mentioning a specific cancer. Nowhere does Corral suggest or motivate the use of the recited compound for treating a cancer, let alone multiple myeloma. The Examiner has not shown that Corral would have provided any teaching or suggestion of the claimed methods of using about 1 to 150 mg/day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione in combination with dexamethasone against multiple myeloma.

Further, Corral concludes that "thalidomide analogues are being used as investigational tools in animal disease models to define mechanisms of pathogenesis and to continue to elucidate the mechanisms of drug action." *See*, page 1111, right column, last sentence. Thus, Corral reports that the mechanisms of diseases and actions of thalidomide analogues are yet to be determined. Even if one were to choose the recited compound as a drug for a cancer, in Corral there is no teaching to suggest that it is effective to treat a

[3] Applicant respectfully directs the attention of the Examiner to the fact that IMiDs® refers to Celgene Corporation's registered trademark for immunomodulatory compounds and SelCIDs® refers to Celgene Corporation's registered trademark for selective cytokine inhibitory drugs.

cancer, less multiple myeloma, much less the combination therapy with dexamethasone as recited in the present claims. Corral, at best, suggests that the recited compound can be tried in cancer generally. This merely provides an invitation to experiment. As the Examiner knows, "obvious to try" is not the proper legal standard for 35 U.S.C. § 103(a) rejection. *In re O'Farrel* 853 F.2d 894, 57 USLW 2147, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988).

Nevertheless, it is alleged that TNF alpha activity of Revimid® renders its use against multiple myeloma obvious. (Page 3 of the Office Action). However, the premise based on TNF alpha mechanism cannot be used for establishing a *prima facie* case of obviousness, because mechanisms of pathogenesis and actions of thalidomide analogues are yet to be elucidated, as Corral reports (page 1111, right Column, last sentence). Further, as the Examiner has recognized, given the complexity of "cancer," one needs more specific information than that of Corral, in order to conclude that the treatment of a specific cancer would be obvious. *See, e.g.*, BARTLETT *et al.*, "The evolution of thalidomide and its IMiD derivatives as anticancer agents," *Nature Reviews Cancer*, 2004, 4 (4):1-9; RICHARDSON *et al.*, "Novel biological therapies for the treatment of multiple myeloma," *Best Practice & Research Clinical Haematology,* 2005, 18 (4):619-634, submitted herewith again.

Further, the specification and Figure 1 indicate that the recited compound inhibited growth of multiple myeloma cells. (*See e.g.*, page 42, line 31 to page 43, line 8 of the specification). Corral does not teach or suggest anything about the inhibition of multiple myeloma cell growth using the specific immunommodulatory compound of the claims in conjunction with dexamethasone. Nor does Corral disclose or suggest any application of thalidomide analogues against any cancer, or any relationship between these properties of thalidomide analogues and clinical application in cancer. Corral merely states that the thalidomide analogues may prove to be useful in different clinical settings according to their immunomodulatory properties. *See*, right column of page 1111 (conclusion).

Therefore, based upon *in vitro* or *in vivo* TNF alpha inhibition activity alone, one cannot establish a *prima facie* case of obviousness against the pending claims. The Examiner's unsupported allegation fails to provide the requisite legal suggestion. The examiner's statement is nothing but conclusory opinion and it cannot form a basis for obviousness rejection. *In re Sang-Su Lee*, 277 F.3d 1338, 1343-4 (Fed. Cir. 2002).

In view of the foregoing, Corral does not suggest or motivate using a specific compound--3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione--with

dexamethasone, nor about 1 to 150 mg/day of the recited compound, much less the claimed methods of treating multiple myeloma using the combination therapy. Therefore, Corral does not render the claims obvious.

Further, it is alleged that Corral provides a reasonable expectation of success in treating cancer using Revlimid® because of an effect on TNF-alpha (Conclusion at page 1111). (Page 3 of the Office Action). Applicant disagrees. Indeed, Corral cautions that thalidomide analogues to be used in patients must be non-toxic and non-teratogenic, and such properties may have been yet to be determined (page 1109, from last sentence of left column to first paragraph of right column). Further, Corral concludes that the mechanisms of diseases and actions of thalidomide analogues need to be elucidated (page 1111, right column, last sentence). Thus, although there was interest in further studying thalidomide analogues, Corral does not provide the legally required expectation of the successful use of the recited compound with dexamethasone in treating patients with multiple myeloma.

In sum, the Examiner has not cited any references suggesting the claimed methods of treating multiple myeloma with the specific amounts of the recited compound and dexamethasone. The Examiner has not shown by Corral that those of ordinary skill in the art would have been motivated to modify the cited reference to arrive at the claimed invention. Further, Corral fails to provide the legally required expectation of the success of the claimed methods, and to teach or suggest each and every limitation of the rejected claims. Thus, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

## III. <u>There Are Sufficient Unexpected Results To Rebut Even a *Prima Facie* Case</u>

Further, even assuming, *arguendo*, a *prima facie* case of obviousness is established by the cited reference, there is ample evidence of unexpected or superior results in the present specification and publications to rebut a *prima facie* case of obviousness. As the Examiner is well aware, such unexpected results can rebut even a *prima facie* case of obviousness. *In re May*, 574 F.2d 1082, 1094 (C.C.P.A. 1978); *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987); *Ortho-Mcneil Pharmaceutical v. Mylan Laboratories*, 348 F.Supp.2d 713, 755 (N.D.W.Va. 2004); and *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991). In fact, the Examiners at the personal interview held on June 7, 2006 stated that arguments and evidence on the unexpected results would overcome the obviousness rejection.

The specification of the present application discloses nonobvious or unexpected results of the claimed methods in clinical studies with multiple myeloma

patients. For example, Applicant invites the Examiner's attention to the methods using the recited compound and dexamethasone, which are disclosed in the specification, *e.g.*, page 20, line 19; page 24, line 30; page 25, lines 15-17; page 27, line 33 to page 28, line 6; page 31, lines 11-13 and 26-29; and page 51, lines 1-12, Section 6.5.6. "Treatment of Relapsed or Refractory Multiple Myeloma."

The unexpected results of the claimed invention are also evidenced by several references in the record of this application. For the convenience of the Examiner's review, Applicant respectfully submits such publications herewith again. Also, Applicant submits additional publications published after the earliest filing date of the application, to show such unexpected or superior results of the claimed invention, with Supplemental Information Disclosure Statement and List of References Cited.[4]

For example, the safety, tolerability, and clinical benefits of the recited compound and dexamethasone administered to multiple myeloma patients are corroborated by *e.g.*, RAJKUMAR *et al.*, "Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma," *Blood*, Dec. 15, 2005, 106 (13)4050-4053; WEBER *et al.*, "A multicenter, randomized, parallel-group, double-blind, placebo-controlled study of lenalidomide plus dexamethasone versus dexamethasone alone in previously treated subjects with multiple myeloma," *Abstract # PO.738, International Multiple Myeloma Workshop*, April 10-14, 2005; RICHARDSON *et al.*, "A multi-center, randomized, phase 2 study to evaluate the efficacy and safety of 2 CDC-5013 dose regimens when used alone or in combination with dexamethasone (Dex) for the treatment of relapsed or refractory multiple myeloma (MM)," *Blood, Abstract # 825, American Society of Hematology*, Dec. 6-9, 2003; WEBER, "Lenalidomide (CC-5013, Revlimid™) and other ImiDs," *Abstract # PL5.02, International Multiple Myeloma Workshop*, April 10-14, 2005; CELGENE CORPORATION, "Celgene receives fast track status from FDA for Revimid™ in multiple myloma," Press Release, February 2003; RICHARDSON *et al.*, "Novel biological therapies for the treatment of multiple myeloma," *Best Practice & Research Clinical Haematology,* 2005, 18 (4):619-634; HUSSEIN *et al.*, "Doxil (D), vincristine (V), reduced frequency dexamethasone (d) and Revlimid (DVd-R) a phase I/II trial in advanced relapsed/refractory multiple myeloma (Rmm) patients," *Blood, Abstract #208, American Society of Hematology*, Dec. 4-7, 2004; and BAZ *et al.*, "Doxil (D), vincristine (V), reduced frequency dexamethasone (d) and revlimid (R) (DVd-R) results in a high response rate in

[4] Applicant notes that some of references cited in IDS are not discussed herein. Applicant requests that all the references be made of record in the file history of the application and that the Examiner execute the 1449 Form enclosed.

patients with refractory multiple myeloma (RMM)," *Blood, Abstract # 2559, American Society of Hematology*, December 10-13, 2005.

As in the publications, the authors reported that the use of dexamethasone and the compound recited in the pending claims demonstrated good efficacy, tolerability and safety in phase I, II and III studies with multiple myeloma patients.

Finally, it is respectfully submitted that the use of the recited compound in combination with dexamethasone to treat multiple myeloma was approved by the U.S. Food and Drug Administration (FDA) in June 2006.

All the evidence rebuts even a *prima facie* case of obviousness.[5] In view of the unexpected or superior results of the present invention, the presently claimed invention is not obvious. *In re May*, at 1094; *In re Chupp*, at 646; and *Ortho-Mcneil Pharmaceutical v. Mylan Laboratories*, at 755. Therefore, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) over Corral be withdrawn.

## IV. The Double Patenting Rejections Should Be Withdrawn

Claims 24, 26, 29-33, 38-42, 48-55 and 57-76 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 and 22-40 of Application No. 10/534,324 (hereinafter '324 application) in view of Corral, on the allegation that both applications claim common subject matter, because '324 application claims methods of treating a myeloproliferative disease such as smoldering myeloma using a cytokine inhibitory drug such as Actimid™ and Revimid® and additional agents can be used. (Pages 5-6 of the Office Action). Applicant respectfully traverses this rejection.

Because the claims of the present application have been amended to recite combination therapies with dexamethasone and the specific compound 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, which do not relate to the use of a selective cytokine inhibitory drug of the applications cited by the Examiner, all the rejections are moot.

The claims of '324 application recite methods of treating a myeloproliferative disease using a selective cytokine inhibitory drug. The '324 application discloses selective cytokine inhibitory drugs, whose structure and characteristics are distinctive from 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione recited by the pending claims of the present application. (*See* the specification of '324 application,

5 These unexpected results should also be considered in the arguments for double patenting rejection below.

*e.g.*, page 10, line 21 to page 22.) The '324 application does not disclose or suggest the specific compound 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione or its use, as recited by the pending claims of the present application. The claims, as amended herein, do not relate to the use of a selective cytokine inhibitory drug, but a specific immunomodulatory compound and dexamethasone as combination therapy. Indeed, Corral cited by the Examiner clearly distinguishes two classes of IMiDs® (referring to Celgene's brand of immunomodulatory compounds) and SelCIDs® (referring to Celgene's brand of selective cytokine inhibitory drugs), which generally speaking have distinct properties. Thus, the compound recited by the pending claims is totally different from, and is not encompassed by, the compounds of '324 application.

Nonetheless, the Examiner maintained to allege that Actimid™ and Revimid® are cytokine inhibitory drugs, apparently referring to Corral, Table 1 at page 1110. Applicant respectfully asserts that the Examiner erroneously interpreted the reference as teaching that the claimed compound is a cytokine inhibitory drug. Applicant respectfully request the Examiner's attention that Table 1 of Corral does not indicate that Actimid™ or Revimid® is a cytokine inhibitory drug. Table 1 summarizes different properties of thalidomide, IMiDs® immunomodulatory compounds and SelCIDs® selective cytokine inhibitory drugs. Indeed, Figure 1 at page 1109 explicitly shows that the structures of Actimid™ and Revimid® belong to the category of IMiDs® immunomodulatory compounds, but not SelCIDs® drugs. Corral clearly distinguishes certain IMiDs® immunomodulatory compounds such as Actimid™ and Revimid® from certain SelCIDs® selective cytokine inhibitory drugs. Corral reports that thalidomide analogues comprise two structurally distinct classes of molecules, the first class being IMiDs® immunomodulatory compounds and the second class being SelCIDs® selective cytokine inhibitory drugs and that two classes of drugs, very generally speaking, possess distinct properties in inhibitions of PDE4, IL1ß, IL 12, IL6 and IL10 and distinct effects on T cell activation. For example, certain IMiDs® immunomodulatory compounds are potent inhibitors of monocyte inflammatory cytokine production and also are strong co-stimulators of T cell activity. Certain SelCIDs® drugs on the other hand, are generally potent PDE4 inhibitors and thus more selective inhibitors of TNF alpha. Unlike certain IMiDs® immunomodulatory compounds, SelCIDs® drugs do not ordinarily co-stimulate T cells but generally inhibit T cell activity. *See*, Figure 1 at page 1109 (structures of IMiDs® compounds and SelCIDs® compounds), right column of page 1109 to left column at page 1110 (two distinct classes of molecules), Table 1 of page 1110 (immunomodulatory profiles of thalidomide, IMiDs® compounds and SelCIDs® compounds, and right column at page 1111(conclusion).

Accordingly, Corral concludes that the two classes of thalidomide analogues, generally speaking, have different properties and their distinct activities suggest different applications in different disorders. *See*, right column of page 1110 to right column of page 1111 (potential clinical applications and conclusion).

Applicant respectfully submit the publications to support that IMiDs® drugs and SelCIDs® drugs, generally speaking, are two different classes of thalidomide analogues having distinct properties.

In view of the foregoing, it is clear that the structure and characteristics of the specific immunomodulatory compound recited by the pending claims of the present application are distinct from those of selective cytokine inhibitory drugs in the claims of '324 application.

Further, a myeloproliferative disease recited in '324 application is distinct from, and is not an obvious variant of multiple myeloma. The claims of '324 application do not disclose or suggest methods of treating multiple myeloma using about 1 to 150 mg/day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione and dexamethasone. In sum, the subject matters of the claims of both applications are not encompassed by each other. The Examiner has made no *prima facie* case that the pending claims are obvious in light of the claims of '324 application.

Next, claims 24, 26, 29-33, 38-42, 48-55 and 57-76 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 and 18-32 of Application No. 10/515,270 (hereinafter '270 application) in view of Corral, on the ground that both applications claim common subject matter because '270 application claims methods of treating cancer using a cytokine inhibitory drug such as Actimid™ and Revimid® and additional agents can be used. (Pages 6-7 of the Office Action). Applicant respectfully traverses this rejection.

The claims of '270 application recite methods of treating cancer using selective cytokine inhibitory drugs. The '270 application discloses selective cytokine inhibitory drugs, whose structure and characteristics are distinctive from 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione recited by the pending claims of the present application. (*See* the specification of '270 application, *e.g.*, pages 6-19).

As explained above, the selective cytokine inhibitory drugs are significantly different from the specific immunomodulatory compound of the pending claims in their structures and properties. The '270 application does not disclose or suggest the use of about 1 to 150 mg/day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione and dexamethasone in multiple myeloma, as recited in the pending claims. The subject matters

of the claims of both applications are not encompassed by each other. The Examiner has made no *prima facie* case that the pending claims are obvious in light of the claims of '270 application.

Lastly, claims 24, 26, 29-33, 38-42, 48-55 and 57-76 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 and 21-37 of Application No. 10/531,552 (hereinafter '552 application) in view of Corral, on the ground that both applications claim common subject matter because '552 application claims methods of treating myelodysplastic syndrome using a cytokine inhibitory drug such as Actimid™ and Revimid® and additional agents can be used. (Pages 7-8 of the Office Action). Applicant respectfully traverses this rejection.

The claims of '552 application recite methods of treating myelodysplastic syndrome using selective cytokine inhibitory drugs. As explained above, the selective cytokine inhibitory drugs are significantly different from 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione of the pending claims in their structures and properties. The '552 application discloses selective cytokine inhibitory drugs, whose structure and characteristics are distinctive from 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione recited by the pending claims of the present application. (*See* the specification of '270 application, *e.g.*, pages 9-21). The '552 application does not disclose or suggest the use of about 1 to 150 mg/day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione and dexamethasone in multiple myeloma, as recited in the pending claims. The subject matters of the claims of both applications are not encompassed by each other. The Examiner has made no *prima facie* case that the pending claims are obvious in light of the claims of '552 application.

In sum, Applicant respectfully submits that the rejection of the pending claims under judicially created obviousness-type double patenting should be withdrawn because no *prima facie* case of obviousness has been established for the pending claims over any of the cited applications. Applicant further submits that no terminal disclaimer over the cited applications is necessary.

## V. Conclusion

In view of the foregoing, all the rejections of the claims should be withdrawn. Reconsideration, entry of the above amendment and remarks, and allowance of the pending claims are respectfully requested. Should the Examiner not agree that all claims are allowable, a personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application.

Respectfully submitted,

Date: February 26, 2007

Yean-Sil Moon (Reg. No. 52,042)
For Anthony M. Insogna (Reg. No. 35,203)
**JONES DAY**
222 East 41st Street
New York, NY 10017
Tel. (212) 326-3778

**Express Mail No.: EV473971197US**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Application of: | Zeldis | Confirmation No.: | 4802 |
| Serial No.: | 10/438,213 | Group Art Unit: | 1614 |
| Filed: | May 15, 2003 | Examiner: | Michel Graffeo |
| For: | METHODS FOR TREATMENT OF MULTIPLE MYELOMA USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE (AS AMENDED) | Attorney Docket No.: | 9516-074-999 |

**SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. §1.97 & §1.56**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

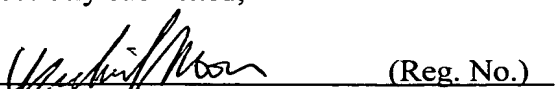
In accordance with the duty of disclosure imposed by 37 C.F.R. §1.56 to inform the Patent and Trademark Office of all references coming to the attention of Applicant or his attorneys which are or may be related to patentability of the claimed invention, Applicant hereby directs the Examiner's attention to references **C185** to **C204,** which are listed on the accompanying revised PTO Form 1449.

Legible copies of listed references **C185** to **C204** are provided herewith. Applicant respectfully requests that the Examiner review the foregoing references and that the references be made of record in the file history of the application. Identification of the listed references is not to be construed an admission by Applicant or his attorneys that such references are available as "prior art" against the subject application.

Please charge any necessary fee to Jones Day Deposit Account No. 50-3013. A duplicate of this sheet is enclosed for accounting purposes.

Respectfully submitted,

Date: February 26, 2007



| | (Reg. No.) |
|---|---|
| Yeahsil Moon | 52,042 |
| For: Anthony M. Insogna | 35,203 |

**JONES DAY**
222 East 41st Street
New York, New York 10017
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Enclosures

| Substitute for Form 1449/PTO<br>INFORMATION DISCLOSURE STATEMENT BY APPLICANT<br>(Use several sheets if necessary) | ATTY DOCKET NO.<br>9516-074-999 | APPLICATION NO.<br>10/438,213 |
|---|---|---|
| | APPLICANT:<br>Zeldis | |
| | FILING DATE:<br>May 15, 2003 | ART UNIT: 1614 CONF. NO.: 4802 |

## U.S. PATENT DOCUMENTS

| EXAMINER'S INITIALS* | | DOCUMENT NUMBER | DATE MM/DD/YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | | | | | |

## FOREIGN PATENT DOCUMENTS

| EXAMINER'S INITIALS* | | Country Code, Number, Kind of Code (if known) | DATE MM/DD/YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear | TRANSLATION YES | TRANSLATION NO |
|---|---|---|---|---|---|---|---|
| | | | | | | | |

**NON PATENT LITERATURE DOCUMENTS** *(include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, etc.,), date, page(s)s, volume, publisher, city and/or country where published., etc.)*

| EXAMINER'S INITIALS* | | |
|---|---|---|
| | C186 | PATT, Yehuda A.; HASSAN, Manal M.; LOZANO, Richard D.; ELLIS, Lee M.; PETERSON, J. Andrew; WAUGH, Kimberly A.; *Durable Clinical Response of Refractory Hepatocellular Carcinoma to Orally Administered Thalidomide*. American Journal of Clinical Oncology, 2000. |
| | C187 | RICHARDSON, Paul; HIDESHIMA, Teru; ANDERSON, Kenneth; *Thalidomide: The Revival of a Drug with Therapeutic Promise in the Treatment of Cancer*; Principles & Practice of Oncology, Vol. 15, No. 2, 2001. |
| | C188 | THOMAS, Melodie; DOSS, Deborah, *Thalidomide Nursing Roundtable Update*, Monograph, September, 2002 |
| | C189 | RICHARDSON, Paul; HIDESHIMA, Teru; ANDERSON, Kenneth; *Thalidomide: Emerging Role in Cancer Medicine*; Annual Review of Medicine, 2002. |
| | C190 | BERENSON, J.R.; BERGSAGEL, P. L.; MUNSHI, N.; *Initiation and Maintenance of Multiple Myeloma*; Seminars in Hematology, Vol. 36, No. 1, Supp. 3, January, 1999, pp.9-13. |
| | C191 | GOLLOB, J.A.; SCHINPPER, C.P.; ORSINI, E.; MURPHY, E.; DALEY, J.F.; LAZO, S.B.; FRANK. D.A.; *Characterization of a Novel Subset of CD8 T Cells That Expands in patients Receiving Interleukin-12,* 02, Am. Soc. For Clin. Investigation, Inc., Vol. 102, No. 3, August 1998, pp.561-575. |
| | C192 | CAVANAGH, L.L.; BARNETSON, R.S.; BASTEN, A.; HALLIDAY, G.M.; *Dendritic Epidermal T-Cell Involvement in Induction of CD8+ T-Cell-Mediated Immunity Against an Ultraviolet Radiation-Induced Skin Tumor* Int. J. Cancer: 70, 98-105, 1997. |
| | C193 | THOMAS, D.A., AGUAYO, A., ESTEY, E., ALBITAR, M., O'BRIEN, S., GILES, F.J., BERAN, M., CORTES, J., ZELDIS, J., KEATING, M.J., BARLOGIE, B., KANTARJIAN, H.M., Thalidomide as anti-angiogenesis therapy (rx) in refractory or relapsed leukemia. Abstract #2269, American Society of Hematology, December 3-7, 1999. |
| | C194 | BARLOGIE, B., DESIKAN, R., MUNSHI, N., SIEGEL, D., MEHTA, J., SINGHAL, S., ANAISSIE, E., Single Course D.T. Pace Anti-Angiochemotherapy Effects CR in Plasma Cell Leukemia and Fulminant Multiple Myeloma (MM). Abstract #4180. American Society of Hematology, December 4-9, 1998. |
| | C195 | HIDESHIMA, T., CHAUHAN, D., SHIMA, Y., NOOPUR, R., DAVIES, F.E., TAI, Y., TREON, S.P., LIN, B.K., SCHLOSSMAN, R.L., RICHARDSON, P.G., GUPTA, D., MULLER, G.W., STIRLING, D.I., ANDERSON, K.C., Thalidome (THAL) and its Analogs Overcome Drug Resistance of Human Multiple Myeloma (MM) Cells to Conventional Therapy. Abstract #1313. American Society of Hematology, December 1-5, 2000. |
| | C196 | PAYVANDI, F., WU, L., GUPTA, D., HIDESHIMA, T., HALEY, M., MULLER, G., CHEN, R., ANDERSON, K.C., STIRLING, D., Effects of a Thalidomide Analog on Binding Activity of Transcription Factors and Cell Cycle |

| EXAMINER | DATE CONSIDERED |
|---|---|
| | |

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with **MPEP 609**; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

| Substitute for Form 1449/PTO<br>INFORMATION DISCLOSURE STATEMENT BY APPLICANT<br>(Use several sheets if necessary) | ATTY DOCKET NO.<br>9516-074-999 | APPLICATION NO.<br>10/438,213 |
|---|---|---|
| | APPLICANT:<br>Zeldis | |
| | FILING DATE:<br>May 15, 2003 | ART UNIT: 1614 CONF. NO.: 4802 |

**NON PATENT LITERATURE DOCUMENTS** *(include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book ,magazine, journal, etc.,), date, page(s)s, volume, publisher, city and/or country where published., etc.)*

| EXAMINER'S INITIALS* | | |
|---|---|---|
| | | Progression of Multiple Myeloma Cell Lines. Abstract #2487. American Society of Hematology, December 1-5, 2000. |
| | C197 | DAVIES, F.E., RAJE, N., HIDESHIMA, T., LENTZSCH, S., YOUNG, G., TAI, Y., LIN, B.K., PODAR, K., CHAUHAN, D., TREON, S.P., GUPTA, D., MITSIADES, C., MITSIADES, N., HAYASHI, T., RICHARDSON, P.G., SCHLOSSMAN, R.L., MULLER, G.W., STIRLING, D. I., ANDERSON, K.C., Thalidomide (THAL) and Immunomodulatory Derivatives (IMiDS) Augment Natural Killer (NK) Cell Cytotocixity in Multiple Myeloma (MM). Abstract #3617. American Society of Hematology, December 1-5, 2000. |
| | C198 | HIDESHIMA, T., CHAUHAN, D., CASTRO, A., HAYASHI, T., MITSIADES, C., MITSIADES, N., AKIYAMA, M., RICHARDSON, P.G., SCHLOSSMAN, R.L., ADAMS, J., ANDERSON, K.C., NF-KB as a Therapeutic Target in Multiple Myeloma (MM). Abstract #1581. American Society of Hematology, December 7-11, 2001. |
| | C199 | LENTSCH, S., ROGERS, M., LEBLANC, R., BIRSNER, A., SHAH, J., ANDERSON K., D'Amato R., 3-Amino-Phthalimido-Glutarimide (S-3APG) Inhibits Angiogenesis and Growth in Drug Resistant Multiple Myeloma (MM) *in vivo*. Abstract #1976, American Society of Hematology, December 7-11, 2001. |
| | C200 | PARK, Y., KIM, S.A., KIM, C.J., CHUNG, J.H., Mechanism of the Effect of Thalidomide on Human Multiple Myeloma Cells. Abstract #2685. American Society of Clinical Oncology, May 12-17, 2001. |
| | C201 | PAYVANDI, F., WU, L., HALEY M., GUPTA, D., ZHANG, L., SCHAFER, P., MULLER, G.W., CHEN, R., ANDERSON, K.C., STIRLING, D., Thalidomide Analogs IMiDS Inhibit Expression of Cyclooxygenase-2 in Multiple Myeloma Cell Line and LPS Stimulated PBMCs. Abstract #2689. American Society of Hematology, December 7-11, 2001. |
| | C202 | MITSIADES, N., MITSIADES, C., POULAKI, V., AKIYAMA, M., TAI, Y., LIN, B., HAYASHI, T., CATLEY, L., HIDESHIMA, T., CHAUHAN, D., TREON, S.P., ANDERSON, K.C., Apoptotic Signaling Induced By Immunomodulatory Thalidomide Analogs (Imids) in Human Multiple Myeloma Cells; Therapeutic Implications. Abstract #3224. American Society of Hematology, December 7-11, 2001. |
| | C203 | RICHARDSON, P.G., SCHLOSSMAN, R.L., HIDESHIMA, T., DAVIES, F., LEBLANC, R., CATLEY, L., DOSS, D., KELLY, K.A., MCKENNEY, M., MECHLOWICZ, J., FREEMAN, A,. DEOCAMPO, R., RICH, R., RYOO, J., CHAUHAN, D., MUNSHI, N., WELLER, E., ZELDIS, J., ANDERSON, K.C., A Phase 1 Study of Oral CC5013, an Immunomodulatory Thalidomide (Thal) Derivative, in Patients With Relapsed and Refractory Multiple Myeloma (MM). Abstract #3225. American Society of Hematology, December 7-11, 2001. |
| | C204 | ZANGARI, M. TRICOT, G., ZELDIS, J., EDDLEMON, P., SAGHAFIFAR, F., BARLOGIE, B., Results of Phase 1 Study of CC5013, for the Treatment of Multiple Myeloma (MM) Patients Who Replase After High Dose Chemotherapy (HDCT). Abstract #3226. American Society of Hematology, December 7-11, 2001. |

NYI-3952061v1

| EXAMINER | DATE CONSIDERED |
|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with **MPEP 609**; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

| Interview Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/438,213 | ZELDIS, JEROME B. | |
| | Examiner | Art Unit | |
| | Michel Graffeo | 1614 | |

All participants (applicant, applicant's representative, PTO personnel):

(1) *Michel Graffeo*.

(2) *Ardin Marschel*.

(3) *Yeah-Sil Moon*.

(4) *Richard Girards*.

Date of Interview: *10 April 2007*.

Type: a)☐ Telephonic b)☐ Video Conference
c)☒ Personal [copy given to: 1)☐ applicant 2)☒ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: _____.

Claim(s) discussed: *Pending*.

Identification of prior art discussed: *Corral et al. Ann. Rheum. 1999; 58;107-13*.

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☒ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *The above reference was discussed along with unexpected results*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Examiner's signature, if required

# Summary of Record of Interview Requirements

**Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record**
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

**Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews**
Paragraph (b)
In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

---

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

**Examiner to Check for Accuracy**

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/438,213 | 05/15/2003 | Jerome B. Zeldis | 9516-074-999 | 4802 |

20583 7590 12/31/2007

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| EXAMINER | |
|---|---|
| SIMMONS, CHRIS E | |
| ART UNIT | PAPER NUMBER |
| 1614 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 12/31/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/438,213 | ZELDIS, JEROME B. | |
| | Examiner | Art Unit | |
| | Chris E. Simmons | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *24,26,29-33,38-42,57-75 and 77-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24,26,29-33,38-42,57-75 and 77-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/26/2007 and 07/27/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Status of the claims: Receipt of the amendment filed on 02/26/2007 is acknowledged. Claims 24, 38-41, 58, 69, 73-74 are amended. Claims 1-23, 25, 27-28, 34-37, 43-56, and 76 are canceled. Claims 77-80 are newly added. Claims 24, 26, 29-33, 38-42, 57-75, and 77-80 are pending.

Applicants' arguments, filed 10/26/2007, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 24, 26, 29-33, 38-42, 57-75, and 77-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kyle et al. ("The Application of Thalidomide in Multiple Myeloma", Semin Oncol. 2001 Dec; 28(6):583-7) in view of Davies et al. ("Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma", Blood. 2001 Jul 1;98(1):210-6).

The primary reference discloses, in the abstract, the treatment of multiple myeloma (MM) with thalidomide and dexamethasone. Thalidomide was administered in an initial dosage of 200 mg/d for 2 weeks and then increased as tolerated (in 200-mg increments at 2-week intervals) to a maximum daily dose of 800 mg. Dexamethasone was given orally in a dosage of 40 mg/d on days 1 through 4, 9 through 12, and 17 through 20 in odd cycles and 40 mg/d on days 1 through 4 in even cycles at monthly intervals. Patients with smoldering, indolent and relapsed myeloma showed results for thalidomide treatment. Signs of toxicity showed in some patients receiving 400 mg/day of thalidomide and the dosage had to be decreased, suggesting that the dosages must be altered depending on the side effects (see first paragraph on page 587). Table 2 at page 586 provides for potential strategies using thalidomide in MM treatment: Thalidomide may be used to treat MM in combination therapy with prednisone, vincristine, doxorubicin, melphalan, biological agents such as alpha2-interferon.

The primary reference does not expressly disclose Revimid® or its amounts.

The secondary reference discloses that thalidomide derivatives, including Revimid® - also known as IMID3, are useful in treating MM and more potent in causing

the lysis of MM cells (See Abstract, the section bridging the columns on page 213 *'Increased MM cell lysis induced by treatment of PBMCs with Thal and IMIDs is NK-cell mediated*, Fig 2, and Fig. 5).

Although the amount for Thalidomide begins at 200 mg per day in the primary reference, Revimid® is taught to be more potent than thalidomide and therefore would need a lesser amount for similar effect.

At the time of the invention it would have been obvious to a person of ordinary skill in the art to substitute Revimid® for thalidomide taught in the primary reference.

The suggestion/motivation for doing so would have been because Revimid® has a higher potency than thalidomide, therefore, lower doses can be used to decrease the potential toxicity of the chemotherapy.

Claims 29-33 of the instant application recite the salt, solvate, stereoisomer, pure R isomer and pure S isomer. One of ordinary skill in the art would have a reasonable expectation that the salt, solvate, stereoisomer, pure R isomer and pure S isomer would also share similar anticancer effects of Revimid®.

As for claims 38-42, Applicant claims a composition with both Lenalidomide and dexamethasone and an additional active agent selected from agents or methods known to be used for cancer therapy. However, as outlined above, Table 2 suggests treatment of MM using thalidomide in combination with several agents, including dexamethasone. Generally, it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose; the idea of combining them flows logically from their

having been individually taught in the prior art. In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980): In re Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960). Conversely, there is no evidence in the record establishing the Applicant's combination of agents is any more effective or in any way different than any single member of that combination. See In re Dial, 140 USPQ 244 (C.C.P.A. 1964).

2. Claims 59-63, 68-75, and 77 are rejected under 35 USC 103(a) as being unpatentable over U.S. 2001/0022973 in view of the combination of Kyle et al. and Davies et al.

The primary and secondary references, and the rationale for combining their teachings are discussed above.

The combination does not expressly disclose a capsule comprising croscarmellose sodium, microcrystalline cellulose, lactose, and magnesium stearate.

The secondary reference discloses a capsule comprising inert ingredients of which the most preferred inert ingredients comprise a combination of, *inter alia*, croscarmellose sodium, microcrystalline cellulose, lactose, and magnesium stearate.

It would be obvious to one skilled in the art to make a capsule containing the drug and well known excipients, to the composition of the capsule.

Generally, it is prima facie obvious to select a known material for incorporation into a composition, based on its recognized suitability for its intended purpose. See Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). See

also In re Leshin, 227 F.2d 197, 125 USPQ 416 (CCPA 1960). Accordingly, it would have been obvious to have used croscomellose sodium, microcrystalline cellulose, lactose and/or magnesium stearate in the primary reference's capsules, since same are well known excipients as taught by the secondary reference.

3. Claims 66-67 are rejected under 35 USC 103(a) as being unpatentable over the combination of Kyle et al and Davies et al. in view of Broder et al. ("Dideoxycytidine: current clinical experience and future prospects. A summary.", Am J Med. 1990 May 21;88(5B):31S-33S).

The primary and secondary references, and the rationale for combining their teachings are discussed above.

The combination does not expressly disclose the exact amount of days of drug administration and days of rest.

Concurrent chemotherapy with more than one drug may allow the use of decreased drug doses and thus reduce dose-dependent toxicities, whereas alternating schedules would provide rest periods from each drug without interrupting therapy (See abstract for Broder et al.).

The secondary reference discloses that phase I/II studies of CDC-501, the compound in claim 24, in multiple myeloma were in progress. CDC-501 has been selected for clinical development; it had been safely administered to volunteers in single doses of 50 to 400 mg and in multiple doses of 100 mg for 7 days.

As for claims 62-63, generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical; where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 24, 26, 29-33, 38-42, 57-75, and 77-80 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 and 22-40 of copending Application No. 10/534324 in view of the combination of Kyle et al. and Davies et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because of overlapping subject matter.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows:

Claims of the '324 application claim a method of treating a myeloproliferative disease such as smoldering myeloma comprising among other agents a cytokine inhibitory drug which is enantiomerically pure in some instances or a salt or solvate thereof. IMID3 (Revimid®) is an example of a cytokine inhibitory drug (see page 215, col. 2, first paragraph of Davies) and, therefore, is encompassed by the limitation "cytokine inhibitory compounds" in '324. Examples of anti-cancer drugs that can be used in the various embodiments of the invention are disclosed in the copending application (see, e.g., ¶ [0232]).

Applicant argues that the addition of the limitation, "a therapeutically effective amount of dexamethasone", in independent claim 24 distinctly differentiates the instant claims from the copending application's claims. Applicant's arguments have been fully

considered but not found persuasive because the copending application's claims also encompass dexamethasone as outlined above.

Applicant also argues that Corral (a reference used in a previous rejection) does not teach that Actimid® or Revimid® is a cytokine inhibitory compound. This argument is rendered moot because the reference is not used in the current rejection.

Applicant argues that the phrase "myeloproliferative disease" (MPD) does not encompass multiple myeloma. Applicant's argument has been fully considered but not found persuasive because the copending application defines MPD in ¶ [0031] as a hematopoietic stem cell disorder characterized by one or more of the following: clonal expansion of a multipotent hematopoietic progenitor cell with the overproduction of one or more of the formed elements of the blood (e.g., elevated red blood cell count, elevated white blood cell count, and/or elevated platelet count). MM results in the elevated level of the white blood cell count.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

5. Claims 24, 26, 29-33, 38-42, 57-75, and 77-80 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 and 18-32 of copending Application No. 10/515270 in view of the combination of Kyle et al. and Davies et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because of overlapping subject matter.

Applicant argues that the copending application recite cytokine inhibitory drugs whose structures are distinct from the instant claims. Applicant's arguments have been fully considered but not found persuasive because although the structures, *in arguendo*, may be distinct, they share the same function, Cytokine inhibition as disclosed in Davies.

6. Claims 24, 26, 29-33, 38-42, 57-75, and 77-80 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 and 21-37 of copending Application No. 10/531552 in view of the combination of Kyle et al. and Davies et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because of overlapping subject matter.

Applicant argues that the copending application recite cytokine inhibitory drugs whose structures are distinct from the instant claims. Applicant's argument has been fully considered but not found persuasive because although the structures, *in arguendo*, may be distinct, they share the same function, Cytokine inhibition as disclosed in Davies.

***Conclusion***

No claims are allowed.

***Correspondence***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chris E. Simmons whose telephone number is (571) 272-9065. The examiner can normally be reached on Monday - Friday from 7:30 - 5:00 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Chris Simmons
Patent Examiner
AU 1614

December 19, 2007

Frederick Krass
Primary Patent Examiner
AU 1614

2-21-08

Express Mail No.: EV654846254US

# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Jerome B. Zeldis

Continuation No.: 4802

Serial No.: 10/438,213

Group Art Unit: 1614

Filed: May 15, 2003

Examiner: Simmons, Chris E.

For: METHODS FOR THE TREATMENT OF MULTIPLE MYELOMA USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE (as amended)

Attorney Docket No.: 9516-074-999
(CAM: 501872-999073)

## AMENDMENT AND RESPONSE

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to non-final Office Action dated December 31, 2007, please consider and enter the amendments and remarks provided below.

**Amendments to the Claims** are reflected in the listing of the claims that begins on page 2 of this paper.

**Remarks** begin on page 7 of this paper.

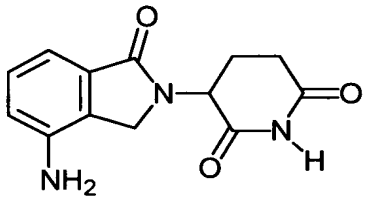
**Amendment to the Claims**:

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of the Claims:**

Claims 1-23. (canceled)

24. (currently amended) A method of treating multiple myeloma, which comprises administering to a patient having multiple myeloma about ~~1~~ 5 to about ~~150~~ 50 mg per day of a compound of the formula:



or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, and a therapeutically effective amount of dexamethasone.

25. (canceled)

26. (previously presented) The method of claim 24, wherein the multiple myeloma is smoldering myeloma, indolent myeloma, chemotherapy responsive multiple myeloma, refractory myeloma, relapsed myeloma, or relapsed and refractory Dune-Salmon stage III multiple myeloma.

27-28. (canceled)

29. (previously presented) The method of claim 24, wherein the compound is a pharmaceutically acceptable salt.

30. (previously presented) The method of claim 24, wherein the compound is a pharmaceutically acceptable solvate.

31. (previously presented) The method of claim 24, wherein the compound is a pharmaceutically acceptable stereoisomer.

32. (previously presented) The method of claim 31, wherein the stereoisomer is an enantiomerically pure R isomer.

33. (previously presented) The method of claim 31, wherein the stereoisomer is an enantiomerically pure S isomer.

34-37. (canceled)

38. (previously presented) The method of claim 24, which further comprises administering a therapeutically effective amount of an additional active agent.

39. (previously presented) The method of claim 38, wherein the additional active agent is hematopoietic growth factor, a cytokine, or an anti-cancer agent.

40. (previously presented) The method of claim 39, wherein the additional active agent is granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), erythropoietin (EPO), interleukin (IL), interferon (IFN), or a pharmacologically active mutant or derivative thereof.

41. (previously presented) The method of claim 39, wherein the additional active agent is oblimersen, melphalan, topotecan, pentoxifylline, taxotere, irinotecan, ciprofloxacin, doxorubicin, vincristine, dacarbazine, Ara-C, vinorelbine, prednisone, cyclophosphamide, bortezomib, arsenic trioxide or a combination thereof.

42. (previously presented) The method of claim 24, which further comprises administering radiation therapy, hormonal therapy, biological therapy or immunotherapy.

43-56. (canceled)

57. (previously presented) The method of claim 24, wherein the cancer is relapsed, refractory or resistant to conventional therapy.

58. (previously presented) The method of claim 24, wherein the compound and dexamethasone are administered orally.

59. (previously presented) The method of claim 58, wherein the compound is administered in the form of a capsule or tablet.

60. (currently amended) The method of claim 24, wherein the compound is administered in an amount of from about ~~1~~ 10 to about ~~50~~ 25 mg per day.

61. (currently amended) The method of claim ~~60~~ 24, wherein the compound is administered in an amount of about 5, 10, 20, 25, 30, or 50 mg per day.

62. (currently amended) The method of claim ~~60~~ 24, wherein the compound is administered in an amount of from about 5 mg per day to about 25 mg per day.

63. (previously presented) The method of claim 60, wherein the compound is administered in an amount of about 25 mg per day.

64. (previously presented) The method of claim 24, wherein the compound and dexamethasone are administered cyclically.

65. (previously presented) The method of claim 64, wherein one cycle comprises four to six weeks.

66. (previously presented) The method of claim 64, wherein one cycle comprises the administration of the compound for 21 days followed by seven days rest.

67. (previously presented) The method of claim 64, wherein the compound is administered for four to twenty-four weeks with one to six weeks of rest.

68. (previously presented) The method of claim 24, wherein the compound is administered in an amount of from about 5 to about 25 mg per day for 21 days every 28 days for sixteen to twenty-four weeks.

69. (previously presented) The method of claim 64, wherein the compound is administered in an amount of about 25 mg per day for 21 days followed by seven days rest in a 28 day cycle; and dexamethasone is administered in an amount of about 40 mg once daily on Days 1 to 4, 9 to 12, and 17 to 20 of each cycle for first 4 cycles, and after the first 4 cycles dexamethasone is administered in an amount of about 40 mg once daily on Days 1 to 4 of each cycle.

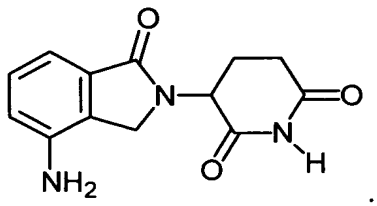
70. (previously presented) The method of claim 24, wherein the compound is administered in an amount of about 25 mg per day and dexamethasone is administered in an amount of about 40 mg per day on days 1-4 every four to six weeks.

71. (currently amended) The method of claim ~~60~~ 24, wherein the compound is administered in an amount of 5 mg per day.

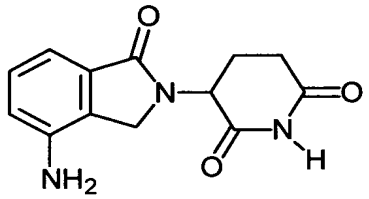
72. (previously presented) The method of claim 60, wherein the compound is administered in an amount of 10 mg per day.

73. (currently amended) The method of claim ~~60~~ 24, wherein the compound is administered in a capsule of 5 mg, 10 mg, 15 mg or 25 mg.

74. (previously presented) The method of claim 24, wherein the compound is



75. (previously presented) A method of treating multiple myeloma, which comprises administering to a patient having multiple myeloma about 25 mg per day of a compound of the formula:



or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, and about 40 mg per day of dexamethasone.

76. (canceled).

77. (previously presented) The method of claim 24, wherein the compound is administered in an amount of about 15 mg/day twice or about 30 mg/day four times a day.

78. (previously presented) The method of claim 24, which further comprises administering a therapeutically effective amount of doxorubicin and vincristine.

79. (previously presented) The method of claim 24, which further comprises administering a therapeutically effective amount of melphalan.

80. (previously presented) The method of claim 73, wherein the capsule comprises the compound, lactose anhydrous, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

## REMARKS

### I. Amendments to the Claims

Claims 1-23, 25, 27, 28, 34-37, 43-56 and 76 were previously canceled without prejudice. Applicant reserves the right to prosecute the subject matter of any canceled claims in one or more continuation, continuation-in-part, or divisional applications.

Claim 24 has been amended to clearly define the subject matter of the invention by the addition of the doses of the compound administered. Accordingly, claims 60, 61, 62, 71 and 73 have been amended for dependency. No new matter has been added.

Claims 24, 26, 29-33, 38-42, 57-75 and 77-80 are pending. Applicant respectfully submits that the pending claims are allowable for the following reasons.

### II. The Claimed Invention is Not Obvious

Claims 24, 26, 29-33, 38-42, 57-75, and 77-80 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kyle et al. (*Semin. Oncol.*, 2001, "Kyle") in view of Davies et al. (*Blood*, 2001, "Davies"). (pages 3-5 of the Office Action). Applicant respectfully traverses this rejection.

In *KSR International Co. v. Teleflex Inc.*, the U.S. Supreme Court rejected the Federal Circuit's *rigid application* of the "teaching, suggestion, motivation" test ("the TSM test") in determining obviousness in the particular case in question. 127 S.Ct. 1727, 82 U.S.P.Q.2d 1385, 1395 (2007) (emphasis added). According to the Supreme Court, the correct analysis is set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966). *Id.* However, the *KSR* decision indicated that while the TSM test is not the sole method for determining obviousness, it may still be used and in some cases is helpful. *Id.* at 1396. ("When it first established [the TSM test], the Court...captured a helpful insight."). Indeed, the guidelines for the examination of patents in the wake of the *KSR* decision make clear that an Examiner may still apply the TSM test, after resolution of the *Graham* analysis. *See* Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, 72 Fed. Reg. 57526, 57528 (Oct. 10, 2007) ("USPTO Guidelines").

**1. The PTO has failed to make a *prima facie* case of obviousness.**

The *Graham* factual inquiries are: (1) determine the scope and contents of the prior art; (2) ascertain the differences between the prior art and the claims at issue; (3) resolve the level of ordinary skill in the pertinent art; and (4) evaluate any evidence of secondary considerations. *KSR,* 82 U.S.P.Q.2d at 1395 (*citing Graham,* 383 U.S. at 15-17). Once the

*Graham* factors have been addressed, the Examiner may apply the TSM test, asking whether (1) a teaching, suggestion or motivation exists in the prior art to combine the references cited, and (2) one skilled in the art would have a reasonable expectation of success. *See* USPTO Guidelines at 57534.

The Office Action cited Kyle as a primary reference and Davies as a secondary reference. The Office Action states that Kyle teaches the treatment of multiple myeloma with thalidomide and dexamethasone; that Davies teaches that thalidomide derivatives, including Revimid®[1]-also known as IMID3[2], are useful in treating multiple myeloma; and that it would have been obvious to one of ordinary skilled in the art to substitute Revimid® for thalidomide (pages 3-4 of Office Action). Applicant respectfully traverses this rejection.

The amended claims recite, *inter alia*, methods of treating multiple myeloma, comprising administering about 5 to 50 mg/day of a specific compound named 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, and a therapeutically effective amount of dexamethasone. Kyle discloses the use of thalidomide and dexamethasone. However, Kyle does not disclose or suggest the use of the specific compound, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione for treating multiple myeloma as recited in the instant claims.

In fact, Kyle teaches away from the selection of the recited compound by focusing on the use of compounds different from that recited by the present claims. Indeed, Kyle concludes that thalidomide and dexamethasone can be effective (page 586). Thus, Kyle does not provide any suggestion, incentive or motivation for modification of thalidomide or its use with dexamethasone in multiple myeloma, to arrive at the selection of the instant compound.

Further, the current law of obviousness in cases concerning structurally similar compounds "requires a showing of 'adequate support in the prior art' for the change in

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[1] Applicant is assuming that, by referring to Revimid®, the Examiner is referring to 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, a species referenced by the registered trademark Revlimid®. Celgene Corporation presently markets pharmaceutical compositions comprising 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione under the mark Revlimid®.

[2] In contrast to the PTO's allegation, IMID3 was not known to beto Revimid®. Indeed, Celgene Corporation used that designation for different compounds. Thus, Davies is improperly cited for the 103 rejection.

structure." *Takeda Chemical Ind., Ltd. v. Alphapharm Pty., Ltd.*, 429 F.3d 1350, 1356 (Fed. Cir. 2007) (*quoting In re Grabiak*, 769 F.2d at 729, 731 (Fed. Cir. 1985)). As was the case in *Takeda* and *Grabiak*, there is no showing of support for the change in structure from the compounds of the cited art (in this case, *e.g.*, thalidomide), to the compound of the instant claims. Applicant respectfully points out that the structural changes for making the instant compound from thalidomide require the complete removal of one of four different carbonyl groups, and the addition of an amino group at one of four positions on the aromatic ring. Kyle provides no guidance for these changes. *Takeda* at 1359. *See also In re Jones,* 958 F.2d 347 (Fed. Cir. 1992); *Grabiak,* 769 F.2d 729, 731-32 (Fed. Cir. 1985) ("There must be adequate support in the prior art for the prior art ester/thioester change in structure, in order to complete the PTO's *prima facie* case and shift the burden of going forward to the applicant."); *In re Lalu,* 747 F.2d 703, 705 (Fed. Cir. 1984) ("The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound."). Therefore, in view of the current law of obviousness, the Examiner has not provided adequate support in the prior art for the instant change in structure.

Further, Kyle does not disclose or suggest the use of the specific doses (5 to 50 mg/day) of the specific compound, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione for treating multiple myeloma as recited in the instant claims. Kyle discloses that thalidomide was given at a dose of 200 mg/d for two weeks and then increased as tolerated by 200 mg/d every two weeks to a maximum dose of 800 mg/d (page 585). In fact, the doses used in Kyle are much higher than those recited in the instant claims (5 to 50 mg/day). Thus, Kyle teaches away from the selection of the instant doses of the recited compound by focusing on the doses different from those of the present claims. Kyle does not provide any suggestion or motivation for modification of the doses of the instant compound as claimed.

Davies does not cure the deficiency of Kyle. Davies provides no teaching or suggestion of the specific compound 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione of the instant claims. Davies allegedly teaches the potential immunomodulatory effects of thalidomide and unidentified thalidomide analogues for *in vitro* or *in vivo* study using multiple myeloma cells. Davies purportedly discloses that multiple myeloma cells were incubated or cultured with thalidomide, or 3 IMiDs®

immunomodulatory compounds (IMiD1, IMiD2 and IMiD3)[3]. *See*, page 212. Without identifying thalidomide analogs specifically by their chemical structures or names, Davies used the general terms, IMiD1, IMiD2, and IMiD3 to identify the compounds. From the disclosure of general terms without any specific chemical structures or names of the compounds tested, one skilled in the art would not have recognized which compounds were used in the study. As the Court held in *Takeda*, Davies does not provide a "finite number of identified, predictable solutions," but a "broad selection of compounds any of which could have been selected as the lead compound for further investigation." *Id.* at 1359.

Even assuming that the examiner disagrees, Applicant respectfully points out that the PTO bears the burden of establishing a case of *prima facie* obviousness against the claims as a whole. That is, all the claim elements must be considered in a 103 rejection. Here, Davies fails to teach or suggest the method of treating multiple myeloma using the specific amount (5 to 50 mg/day) of the instant compound and dexamethasone as in the amended claims. Davies does not teach or suggest about 5 to about 50 mg per day of the compound recited in the present claims. Davies discloses the use of 0.1μg/ML, 1μg/ML and 5μg/ML of thalidomide, IMiD1, IMiD2 and IMiD3. *See* pages 212-215. The concentrations disclosed in Davies are not predictive of any doses (5 to 50 mg/day) used in the instant claims. Thus, the doses of the recited compound as claimed are not taught or suggested. Davies fails to suggest or motivate the methods using the specific amounts of the recited compound, and does not render obvious the instant claims reciting the specific amounts of a particular compound.

Furthermore, in Davies there is no teaching or suggestion as to the treatment of multiple myeloma using the specific compound in specific amounts with dexamethasone of the instant claims. Davies examined the mechanisms of actions of thalidomide and immunomodulatory derivatives in multiple myeloma (MM). Davies reports that thalidomide and immunomodulatory derivatives augment natural killer (NK) cell cytotoxicity in MM, although the in vivo relevance of NK-cell-mediated MM cell killing is unknown. (Pages 210 (Abstract), 212 and 216). Davies concludes that the study accessing the mechanisms of potential new drugs in MM lead to a better understanding of MM pathogenesis and may help to define a therapy at different stages of disease. *See*, page 216, right column. In Davies, there is no teaching or suggestion that the instant compound is

[3] Applicant respectfully directs the attention of the Examiner to the fact that IMiDs® refers to Celgene Corporation's registered trademark for immunomodulatory compounds.

effective to treat multiple myeloma, much less the combination therapy with dexamethasone as recited in the present claims. Thus, Davies does not provide one skilled in the art with any suggestion or motivation for the claimed methods.

In view of the foregoing, Kyle and Davies in combination does not teach, suggest or motivate using a specific compound--3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione--with dexamethasone, nor about 5 to 50 mg/day of the recited compound, much less the claimed methods of treating multiple myeloma using the combination therapy. As in *Takeda* and *Grabiak,* one of ordinary skill would not be motivated to use the recited compound, the specific doses of the compound, or the specific combination with dexamethasone, much less the combination of all these elements for treating multiple myeloma. Indeed, the court noted that "we have cautioned 'that generalization should be avoided insofar as specific chemical structures are alleged to be prima facie obvious one from the other.'" *Id.* at 1361 (*quoting In re Grabiak*, 769 F.2d 729, 731 (Fed. Cir. 1985)). Accordingly, withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

**2. One skilled in the art would have no reasonable expectation of success to arrive at the instant claims in view of the teachings of the cited references.**

Further, the references cited by the Examiner do not suggest to one of ordinary skill in the art that the present invention would have a reasonable expectation of success. To have a reasonable expectation of success, "one must be motivated to do more than merely 'vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave...no direction as to which of many possible choices is likely to be successful.'" *Medichem, S.A. v. Robaldo*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (*quoting In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988). Furthermore, the courts have long recognized the unpredictability of biological properties of chemical compounds. *See In re Eli Lilly & Co.*, 902 F.2d. 943, 948 (Fed. Cir. 1990) ("we recognize and give weight to the unpredictability of biological properties..."); *see also Takeda*, 429 F.3d at 1361.

Kyle directs one skilled in the art to use thalidomide itself as does Davies. To the extent Davies directs one to experiment with IMiDs, it provides no teaching or suggestion for using the recited compound. As in *Takeda*, the claimed compound is not *prima facie* obvious over those of the cited references (*e.g.*, thalidomide, IMiD1, IMiD2 and IMiD3), and there was no reasonable expectation that the modifications or changes from the cited compounds to the instant compound would provide the desired pharmacological properties.

*Id.* at 1360. Further, there is no teaching or suggestion that such a modified compound could be used in a method at the dose claimed. The Examiner has identified no teaching or suggestion that the recited compound in the specific amounts may be used in treating a cancer, in particular multiple myeloma, much less the combination therapy with dexamethasone. As a result, the PTO has not established that the combination of the two references suggests the claimed methods and has not provided the legally required reasonable expectation of success.

Simply put, to arrive at the methods of the instant claims, one skilled in the art must "vary all parameters or try each of numerous possible choices" of the cited references without "direction as to which of many possible choices is likely to be successful." *Medichem*, 437 F.3d at 1165. This is precisely what the courts have held not to be a reasonable expectation of success. *Id.*; *O'Farrell*, 853 F.2d at 903-04. Because the PTO has not demonstrated that one skilled in the art would have had a reasonable expectation of success in practicing the methods of the instant claims by combining the teachings of the references, the instant claims are not obvious.

**3. Claims are not obvious by U.S. 2001/0022973 in view of Kyle and Davies.**

Next, claims 59-63, 68-75, and 77 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. 2001/0022973 ("'973 publication") in view of the combination of Kyle and Davies (pages 5-6 of the Office Action). It is alleged that it would have been obvious to have used a capsule comprising croscarmellose sodium, microcrystalline cellulose, lactose and magnesium stearate in the primary reference's capsule, since the same are well known excipients as taught by the secondary reference. *Id.* Applicant respectfully traverses this rejection.

Pending claims 59, 73 and 80 recite, *inter alia*, methods of treating multiple myeloma administering a therapeutically effective amount of dexamethasone and a capsule comprising the specific compound 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione in specific amounts of about 5 to 50 mg per day.

The '973 publication teaches a pharmaceutical composition for certain piperidinoalkanol compounds having antihistaminic, antiallergic, bronchodilatory, or urticaria-reduction effects (column 5). However, the '973 publication is silent as to the instant compound, the specific amounts, and the use of the instant capsule for treating multiple myeloma. Thus, the '973 publication is completely irrelevant to the instant claims. The '973 publication suggests nothing about the combination therapy administering a capsule comprising the recited compound and dexamethasone in treating multiple myeloma

as claimed. Kyle or Davies does not teach or suggest a method for treating multiple myeloma using a capsule comprising the specific doses of the specific compound with dexamethasone, as recited in the present claims. Accordingly, the '973 publication in view of the combination of Kyle and Davies does not provide any suggestion or motivation for the claimed methods administering the capsule comprising the recited compound in specific amounts and dexamethasone in treating multiple myeloma. Accordingly, withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

**4. Kyle and Davies in view of Broder fail to render claims obvious.**

Claims 66-67 are rejected under 35 U.S.C. § 103(a) as being unpatentable over the combination of Kyle and Davies, in view of Broder et al. (*Am. J. Med.*, 1990, "Broder"). (page 6 of the Office Action). It is alleged that although the combination does not expressly disclose the exact amount of days of drug administration and days of rest, alternating schedules would provide rest periods from each drug without interrupting therapy. *Id.* Applicant respectfully traverses this rejection.

Pending claims 66-67 recite, *inter alia*, methods of treating multiple myeloma cyclically administering a therapeutically effective amount of dexamethasone, and about 5 to 50 mg per day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione for 21 days followed by seven days rest, for four to twenty-four weeks with one to six weeks of rest.

Broder teaches studies using dideoxycytidine in treating HIV, AIDS or tuberculosis patients. Broder is directed to an alternating therapy with a different compound in HIV or AIDS patients. Thus, Broder is not relevant to the use of the instant compound in multiple myeloma patients as claimed. Broder is silent as to the instant compound, let alone the administration of the specific amounts of the compound, much less the cycling therapy for treating multiple myeloma. Thus, Broder suggests nothing about the cycling therapy administering the recited compound and dexamethasone in treating multiple myeloma as claimed. Kyle or Davies does not teach or suggest the cyclic administration of dexamethasone and the recited compound in the specific amounts. Accordingly, the combination of Kyle and Davies in view of Broder does not provide any suggestion or motivation for the claimed cycling methods.

The Office Action also alleges that the secondary reference discloses phase I/II studies in multiple myeloma administering CDC-501, the compound of claim 24, in single doses of 50-400 mg and multiple doses of 100 mg for 7 days, and that the differences in

concentration (5-25 mg) of claims 62-63 would not support the patentability. (Page 7 of the Office Action). Applicant respectfully disagree.

Indeed, in Kyle or Davies, there is no teaching or suggestion for the specific amounts of the recited compound as claimed. If the PTO's allegations were true, the cited art would not render the instant methods using the lower doses obvious. To the contrary to the PTO's contention, the recited compound, much less any doses of the recited compound are not taught or suggested in any references cited (Davies, Kyle or Broder). Furthermore, in any of the references there is no teaching or suggestion as to the treatment of multiple myeloma using the specific compound in specific amounts of the instant claims. The references are simply devoid of any teachings or suggestion on the use of the specific doses of the specific compound in combination with dexamethasone. Thus, the references fail to suggest or motivate the methods of treating multiple myeloma by administering the specific amounts of the recited compound and dexamethasone, and does not render obvious the instant claims reciting the specific amounts of a particular compound.

Accordingly, withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

**III. <u>There Are Sufficient Unexpected Results To Rebut Even a *Prima Facie* Case</u>**

Further, even assuming, *arguendo*, a *prima facie* case of obviousness is established by the cited references in combination, there is evidence of unexpected or superior results for the activity of the recited compound to rebut a *prima facie* case of obviousness. As the Examiner is well aware, such unexpected results can rebut even a *prima facie* case of obviousness. *In re May*, 574 F.2d 1082, 1094 (C.C.P.A. 1978); *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987); *Ortho-Mcneil Pharmaceutical v. Mylan Laboratories*, 348 F.Supp.2d 713, 755 (N.D.W.Va. 2004); and *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991).

The specification of the present application discloses nonobvious or unexpected results of the claimed methods in clinical studies with multiple myeloma patients. For example, Applicant invites the Examiner's attention to the methods using the recited compound and dexamethasone, which are disclosed in the specification, *e.g.*, page 20, line 19; page 24, line 30; page 25, lines 15-17; page 27, line 33 to page 28, line 6; page 31, lines 11-13 and 26-29; and page 51, lines 1-12, Section 6.5.6. "Treatment of Relapsed or Refractory Multiple Myeloma."

The unexpected results of the claimed invention are also evidenced by several references in the record of this application, published after the earliest filing date of the

application. For example, Applicant respectfully points out that the clinical benefits of the recited compound and dexamethasone administered to multiple myeloma patients are corroborated by the publications submitted on February 26, 2007, *e.g.*, Rajkumar *et al.*, "Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma," *Blood*, Dec. 15, 2005, 106 (13)4050-4053; WEBER *et al.*, "A multicenter, randomized, parallel-group, double-blind, placebo-controlled study of lenalidomide plus dexamethasone versus dexamethasone alone in previously treated subjects with multiple myeloma," *Abstract # PO.738, International Multiple Myeloma Workshop*, April 10-14, 2005; RICHARDSON *et al.*, "A multi-center, randomized, phase 2 study to evaluate the efficacy and safety of 2 CDC-5013 dose regimens when used alone or in combination with dexamethasone (Dex) for the treatment of relapsed or refractory multiple myeloma (MM)," *Blood, Abstract # 825, American Society of Hematology*, Dec. 6-9, 2003; WEBER, "Lenalidomide (CC-5013, Revlimid™) and other ImiDs," *Abstract # PL5.02, International Multiple Myeloma Workshop*, April 10-14, 2005; CELGENE CORPORATION, "Celgene receives fast track status from FDA for Revimid™ in multiple myloma," Press Release, February 2003; RICHARDSON *et al.*, "Novel biological therapies for the treatment of multiple myeloma," *Best Practice & Research Clinical Haematology,* 2005, 18 (4):619-634; HUSSEIN *et al.*, "Doxil (D), vincristine (V), reduced frequency dexamethasone (d) and Revlimid (DVd-R) a phase I/II trial in advanced relapsed/refractory multiple myeloma (Rmm) patients," *Blood, Abstract #208, American Society of Hematology*, Dec. 4-7, 2004; and BAZ *et al.*, "Doxil (D), vincristine (V), reduced frequency dexamethasone (d) and revlimid (R) (DVd-R) results in a high response rate in patients with refractory multiple myeloma (RMM)," *Blood, Abstract # 2559, American Society of Hematology*, December 10-13, 2005.

Also, Applicant submits additional publications to show such unexpected or superior results of the claimed invention. In phase III trials, multiple myeloma patients, who were refractory to prior thalidomide treatment and treated with the instant compound and dexamethasone as in the claimed method, had significantly improved overall survival and induced high response rates, compared with those treated with dexamethasone alone. *See* Weber *et al.*, Abstract #412, *American Society of Hematology*, December 8-11, 2007; Harousseau *et al.*, Abstract #3598, *American Society of Hematology*, December 8-11, 2007; Foa *et al.*, Abstract #4839, *American Society of Hematology*, December 8-11, 2007; Chanan-Khan *et al.*, Abstract #2721, *American Society of Hematology*, December 8-11, 2007; Wang *et al.*, Abstract #PO-662, *XI$^{th}$ International Myeloma Workshop and IV$^{th}$*

*International Workshop on Waldenstrom's Macroglobulinemia*, June 25-30, 2007; and Wang *et al.*, Abstract #3553, *American Society of Hematology*, December 9-12, 2006, submitted herewith.

In sum, the authors of the publications reported that the use of dexamethasone and the compound recited in the pending claims demonstrated good efficacy and tolerability in phase I, II and III studies with multiple myeloma patients.

Further, it is respectfully submitted that the use of the recited compound in combination with dexamethasone to treat multiple myeloma was approved by the U.S. Food and Drug Administration (FDA) in June 2006, in Europe in June 2007, and Australia in December 2007.

All the evidence rebuts even a *prima facie* case of obviousness.[4] In view of the unexpected or superior results of the present invention, the presently claimed invention is not obvious. *In re May*, at 1094; *In re Chupp*, at 646; and *Ortho-Mcneil Pharmaceutical v. Mylan Laboratories*, at 755. Therefore, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

## IV. The Double Patenting Rejections Should Be Withdrawn

Claims 24, 26, 29-33, 38-42, 57-75, and 77-80 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 and 22-40 of Application No. 10/534,324 (hereinafter '324 application) in view of the combination of Kyle and Davies, on the allegation that both applications claim common subject matter, because '324 application claims methods of treating a myeloproliferative disease such as smoldering myeloma using a cytokine inhibitory drug such as IMID3 (Revimid®) as disclosed in Davies and using additional agents such as dexamethasone. (Pages 8-9 of the Office Action). Applicant respectfully traverses this rejection.

Obviousness-type double patenting is a judicially created doctrine intended to prevent improper timewise extension of the patent right by prohibiting the issuance of claims in a second patent which are not "patentably distinct" from the claims of a first patent. *See In re Braat*, 19 U.S.P.Q.2d 1289, 1291-92 (Fed. Cir. 1991). In *General Foods Corp. v. Studiengesellschaft Kohle mbH*, the Federal Circuit further explained that in an obviousness-type double patenting rejection "it is important to bear in mind that comparison

3 These unexpected results should also be considered in the arguments for double patenting rejection below.

can be made only with what invention is *claimed* in the earlier patent, paying careful attention to the rules of claim interpretation to determine what invention a claim *defines* and not looking to the claim for anything that happens to be mentioned in it as though it were a prior art reference." *See, e.g., General Foods Corp.*, 23 U.S.P.Q.2d 1839, 1845 (Fed. Cir. 1992).

The claims of '324 application recite methods of treating a myeloproliferative disease using a selective cytokine inhibitory drug. The '324 application discloses selective cytokine inhibitory drugs, whose structure and characteristics are distinctive from 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione recited by the pending claims of the present application. (*See* the specification of '324 application, *e.g.*, page 10, line 21 to page 22.) The claims of the '324 application do not disclose or suggest the methods of treating multiple myeloma using the specific amounts of the recited compound with dexamethasone as in the instant claims of the instant application.[5] Applicant respectfully submits that the Patent Office is mistaken concerning what is claimed in the claims of the '324 application, and by not considering what the claims of the '324 application define, the Patent Office arrives at a legally improper double patenting rejection of the claims.

Nonetheless, the Office Action alleges that Revimid® is a cytokine inhibitory drug, referring to Davies, page 215, column 2, first paragraph. Applicant respectfully asserts that the Examiner erroneously interpreted the reference as teaching that the claimed compound is a cytokine inhibitory drug. Davies merely reports that thalidomide and IMiDs® inhibit cytokine secretions such as IL-6. Nowhere does Davies or Kyle teache or suggest that the instant compound 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione is a cytokine inhibitory drug, much less a method for treating multiple myeloma using the specific doses of the specific compound with dexamethasone, as recited in the present claims.

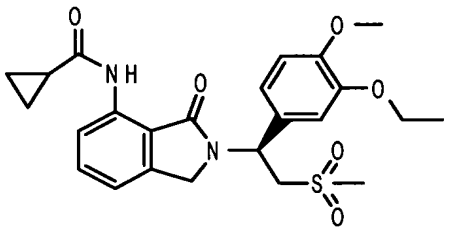
Further, a myeloproliferative disease recited in '324 application is distinct from, and is not an obvious variant of multiple myeloma. The claims of '324 application do not disclose or suggest methods of treating multiple myeloma using about 5 to 50 mg/day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione and dexamethasone. In sum, the subject matters of the claims of both applications are not encompassed by each

[5] The claims of '324 application will be amended in due course.

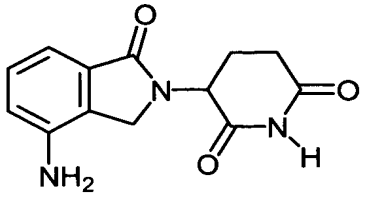
other. The Examiner has made no *prima facie* case that the pending claims are obvious over the claims of '324 application in view of the combination of Kyle and Davies.

Next, claims 24, 26, 29-33, 38-42, 57-75 and 77-80 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 and 18-32 of Application No. 10/515,270 (hereinafter '270 application) in view of combination of Kyle and Davies, on the ground that both applications claim common subject matter because the compounds share the same function of cytokine inhibition as diclosed in Davies. (Pages 9-10 of the Office Action). Applicant respectfully traverses this rejection.

Claims 1-32 of '270 application were canceled by the amendment filed on January 9. 2008. The pending claims of '270 application recite methods of treating non-Hodgkin's lymphoma using cyclopropanecarboxylic acid {2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1 *H*-isoindol-4-yl}-amide, which has the following structure:



The instant claims recite methods of treating multiple myeloma using dexamethasone and about 5 to 50 mg/day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione), which has the following formula:



Thus, the compound recited in '270 application is different from the compound recited in the instant claims 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione) in their structures and properties. Further, multiple myeloma as presently claimed is distinct from, and is not an obvious variant of, non-Hodgkin's lymphoma recited in the '270 application. Thus, the subject matters of the claims of both applications are not

encompassed by each other. Furthermore, the claims of the '270 application provide no suggestion or motivation for one skilled in the art to select the specific compound to treat the specific disease of the instant claims.

Davies or Kyle also fails to teach or suggest that the instant compound 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione inhibits cytokine, much less a method for treating multiple myeloma using the specific doses of the specific compound with dexamethasone, as recited in the present claims. The Examiner has made no *prima facie* case that the pending claims are obvious over the claims of the '270 application in view of the combination of Kyle and Davies. Thus, Applicant respectfully requests that this double patenting rejection be withdrawn.

Lastly, claims 24, 26, 29-33, 38-42, 57-75 and 77-80 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 and 21-37 of Application No. 10/531,552 (hereinafter '552 application) in view of combination of Kyle and Davies, on the ground that both applications claim common subject matter because the used compounds share same function of cytokine inhibition as diclosed in Davies. (Page 10 of the Office Action). Applicant respectfully traverses this rejection.

The claims of '552 application recite methods of treating myelodysplastic syndrome using selective cytokine inhibitory drugs. The selective cytokine inhibitory drugs are significantly different from 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione of the pending claims in their structures and properties. (*See* the specification of '552 application, *e.g.*, pages 9-21). The claims of the '552 application are directed to the treatment of a myelodysplastic syndrome with selective cytokine inhibitory drugs, whose structure and characteristics are distinctive from 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione recited by the pending claims of the present application. Further, a myelodysplastic syndrome recited in '552 application is distinct from, and is not an obvious variant of multiple myeloma. The claims of the '552 application do not disclose or suggest the use of about 5 to 50 mg/day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione and dexamethasone in multiple myeloma, as recited in the pending claims.[6] Thus, the subject matters of the claims of both applications are not encompassed by each other. Kyle and Davies are also devoid of teaching or suggestion of the claimed methods. The Examiner has made no *prima facie* case that the pending claims

[6] The claims of '552 application will be amended in due course.

are obvious over the claims of '552 application in view of the combination of Kyle and Davies.

In sum, Applicant respectfully submits that the rejection of the pending claims under judicially created obviousness-type double patenting should be withdrawn because no *prima facie* case of obviousness has been established for the pending claims over any of the cited applications. Furthermore, the policy behind a double patenting rejection—the prevention of an unjustified extension of the term of a patent—does not support the Examiner's rejection in this case. *See In re Braat*, 19 U.S.P.Q.2d at 1291-92; *see also In re Kaplan*, 789 F.2d 1574, 1579 (Fed. Cir. 1986) ("the basis for...obviousness-type double patenting rejections is timewise extension of the patent right"). Allowance of the instant claims would not result in the timewise extension of the term of any of the cited applications. Therefore, Applicants respectfully request that the double patenting rejection be withdrawn.

Nevertheless, solely to promote prosecution and without prejudice, terminal disclaimers can be submitted in the cited applications. In any event, Applicant respectfully requests that the rejection be held in abeyance until the claims of the present application are deemed otherwise allowable.

## V. Conclusion

In view of the foregoing, all the rejections of the claims should be withdrawn. Reconsideration, entry of the above amendment and remarks, and allowance of the pending claims are respectfully requested. Should the Examiner not agree that all claims are allowable, a personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application.

Respectfully submitted,

Date: February 20, 2008

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Interview Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/438,213 | ZELDIS, JEROME B. | |
| | Examiner | Art Unit | |
| | CHRIS E. SIMMONS | 1612 | |

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(1) *CHRIS E. SIMMONS*.

(2) *Frederick Krass* .

(3)*James Anderson*.

(4)*Yeah-Sil Moon (App. Rep.)*
*(5) Donna Robertson-Chow*.

Date of Interview: *07 March 2008*.

Type: a)☐ Telephonic b)☐ Video Conference
c)☒ Personal [copy given to: 1)☐ applicant 2)☒ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: ____.

Claim(s) discussed: *pending claims*.

Identification of prior art discussed: *Kyle et al. and Davies et al.*.

Agreement with respect to the claims f)☐ was reached. g)☒ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Obviousness-type double patenting rejections will be withdrawn. Regarding 35 USC 103, Applicant's arguments appear to support Applicant's position. Applicant will provide supporting evidence in the form of 1.132 affidavit for unexpected results and 2) 1.132 affidavit showing that IMID1, IMID2, and IMID3 could not positively be identified as Revimid.*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

/Frederick Krass/
Supervisor, Art Unit 1612
Examiner's signature, if required

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

03-28-08

1614

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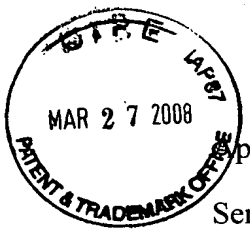



**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Application of: Jerome B. Zeldis

Continuation No.: 4802

Serial No.: 10/438,213

Group Art Unit: 1614

Filed: May 15, 2003

Examiner: Simmons, Chris E.

For: METHODS FOR TREATMENT OF MULTIPLE MYELOMA USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE (as amended)

Attorney Docket No.: 9516-074-999 (CAM: 501872-999073)

**RESPONSE, AMENDMENT AND STATEMENT OF INTERVIEW SUMMARY**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
Mail Stop Amendment

Sir:

Further to Examiner interview held on March 7, 2008, and to a response filed on February 20, 2008 to Non-final Office Action dated December 31, 2007, Applicant submits the following amendment and Remarks for the consideration by the Examiner and entry into the record of the above-captioned application. Submitted herewith are Declarations by Peter H. Schafer and Robert Knight under 37 C.F.R. § 1.132.

**Amendments to the Claims** are reflected in the listing of the claims that begins on page 2 of this paper.

**Remarks** begin on page 6 of this paper.

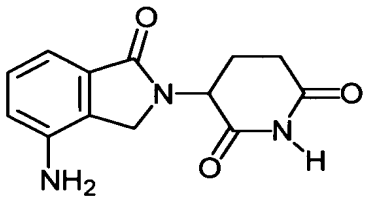
**Amendment to the Claims**:

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of the Claims:**

Claims 1-23. (canceled)

24. (previously presented) A method of treating multiple myeloma, which comprises administering to a patient having multiple myeloma about 5 to about 50 mg per day of a compound of the formula:



or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, and a therapeutically effective amount of dexamethasone.

25. (canceled)

26. (previously presented) The method of claim 24, wherein the multiple myeloma is smoldering myeloma, indolent myeloma, chemotherapy responsive multiple myeloma, refractory myeloma, relapsed myeloma, or relapsed and refractory Dune-Salmon stage III multiple myeloma.

27-28. (canceled)

29. (previously presented) The method of claim 24, wherein the compound is a pharmaceutically acceptable salt.

30. (previously presented) The method of claim 24, wherein the compound is a pharmaceutically acceptable solvate.

31. (previously presented) The method of claim 24, wherein the compound is a pharmaceutically acceptable stereoisomer.

32. (previously presented) The method of claim 31, wherein the stereoisomer is an enantiomerically pure R isomer.

33. (previously presented) The method of claim 31, wherein the stereoisomer is an enantiomerically pure S isomer.

34-37. (canceled)

38. (previously presented) The method of claim 24, which further comprises administering a therapeutically effective amount of an additional active agent.

39. (previously presented) The method of claim 38, wherein the additional active agent is hematopoietic growth factor, a cytokine, or an anti-cancer agent.

40. (previously presented) The method of claim 39, wherein the additional active agent is granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), erythropoietin (EPO), interleukin (IL), interferon (IFN), or a pharmacologically active mutant or derivative thereof.

41. (previously presented) The method of claim 39, wherein the additional active agent is oblimersen, melphalan, topotecan, pentoxifylline, taxotere, irinotecan, ciprofloxacin, doxorubicin, vincristine, dacarbazine, Ara-C, vinorelbine, prednisone, cyclophosphamide, bortezomib, arsenic trioxide or a combination thereof.

42. (previously presented) The method of claim 24, which further comprises administering radiation therapy, hormonal therapy, biological therapy or immunotherapy.

43-56. (canceled)

57. (currently amended) The method of claim 24, wherein the ~~cancer~~ multiple myeloma is relapsed, refractory or resistant to conventional therapy.

58. (previously presented) The method of claim 24, wherein the compound and dexamethasone are administered orally.

59. (previously presented) The method of claim 58, wherein the compound is administered in the form of a capsule or tablet.

60. (previously presented) The method of claim 24, wherein the compound is administered in an amount of from about 10 to about 25 mg per day.

61. (previously presented) The method of claim 24, wherein the compound is administered in an amount of about 5, 10, 20, 25, 30, or 50 mg per day.

62. (previously presented) The method of claim 24, wherein the compound is administered in an amount of from about 5 mg per day to about 25 mg per day.

63. (previously presented) The method of claim 60, wherein the compound is administered in an amount of about 25 mg per day.

64. (previously presented) The method of claim 24, wherein the compound and dexamethasone are administered cyclically.

65. (previously presented) The method of claim 64, wherein one cycle comprises four to six weeks.

66. (previously presented) The method of claim 64, wherein one cycle comprises the administration of the compound for 21 days followed by seven days rest.

67. (previously presented) The method of claim 64, wherein the compound is administered for four to twenty-four weeks with one to six weeks of rest.

68. (previously presented) The method of claim 24, wherein the compound is administered in an amount of from about 5 to about 25 mg per day for 21 days every 28 days for sixteen to twenty-four weeks.

69. (previously presented) The method of claim 64, wherein the compound is administered in an amount of about 25 mg per day for 21 days followed by seven days rest in a 28 day cycle; and dexamethasone is administered in an amount of about 40 mg once daily on Days 1 to 4, 9 to 12, and 17 to 20 of each cycle for first 4 cycles, and after the first 4 cycles dexamethasone is administered in an amount of about 40 mg once daily on Days 1 to 4 of each cycle.

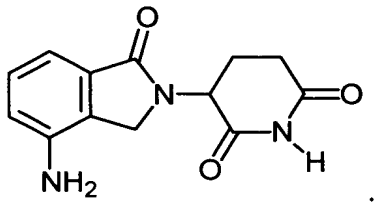
70. (previously presented) The method of claim 24, wherein the compound is administered in an amount of about 25 mg per day and dexamethasone is administered in an amount of about 40 mg per day on days 1-4 every four to six weeks.

71. (previously presented) The method of claim 24, wherein the compound is administered in an amount of 5 mg per day.

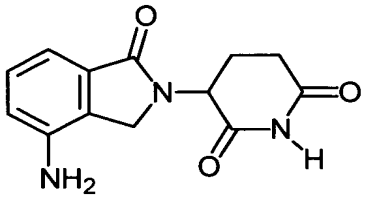
72. (previously presented) The method of claim 60, wherein the compound is administered in an amount of 10 mg per day.

73. (previously presented) The method of claim 24, wherein the compound is administered in a capsule of 5 mg, 10 mg, 15 mg or 25 mg.

74. (previously presented) The method of claim 24, wherein the compound is



75. (previously presented) A method of treating multiple myeloma, which comprises administering to a patient having multiple myeloma about 25 mg per day of a compound of the formula:



or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, and about 40 mg per day of dexamethasone.

76. (canceled).

77. (currently amended) The method of claim 24, wherein the compound is administered in an amount of about 15 mg~~/day~~ twice ~~or about 30 mg/day four times~~ a day.

78. (previously presented) The method of claim 24, which further comprises administering a therapeutically effective amount of doxorubicin and vincristine.

79. (previously presented) The method of claim 24, which further comprises administering a therapeutically effective amount of melphalan.

80. (previously presented) The method of claim 73, wherein the capsule comprises the compound, lactose anhydrous, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

## REMARKS

### I. Amendments to the Claims

Claims 1-23, 25, 27, 28, 34-37, 43-56 and 76 were previously canceled without prejudice. Applicant reserves the right to prosecute the subject matter of any canceled claims in one or more continuation, continuation-in-part, or divisional applications.

Claim 57 has been amended to clearly define the multiple myeloma. Claim 77 has been amended to clearly define the subject matter of the invention as to the dose of the compound administered, as discussed at the Examiner interview on March 7, 2008. No new matter has been added.

Claims 24, 26, 29-33, 38-42, 57-75 and 77-80 are pending. Applicant respectfully submits that the pending claims are allowable for the following reasons.

### II. Applicant's Statement of the Substance of Interview and Response to the Examiner's Interview Summary of Record

A personal interview with Supervisory Patent Examiner Frederick Krass, Patent Examiners Chris E. Simmons and James D. Anderson, Dr. Donna Robertson-Chow and Yeah-Sil Moon, attorney for Applicant, was held on March 7, 2008. Applicant appreciates the Examiner interview.

During the interview, the Examiners and attorney for Applicant discussed the amendment to the claims, the pending § 103 rejections and obviousness-type double patenting rejections.

First, the Examiners pointed out that claim 77 is indefinite. In this response, claim 77 has been amended to clarify the dose of the compound administered, as suggested by the Examiners.

Next, the Examiners and attorney for Applicant discussed the pending § 103 rejections. Attorney for Applicant pointed out that the primary reference Kyle et al. (*Semin. Oncol.*, 2001, "Kyle") teaches away from the selections of the instant compound, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, and the doses of the compound, by focusing on thalidomide and doses different from those of the present claims. Attorney for Applicant further explained that the secondary reference Davies et al. (*Blood*, 2001, "Davies"), alone or in combination with Kyle, fails to teach or suggest the use of the recited compound for treating multiple myeloma as claimed, and that the references fail to provide a reasonable expectation of success.

In addition to the reasons stated above, Attorney for Applicant stressed that the § 103 obviousness rejections also can be overcome by unexpected results of the claimed invention. Attorney for Applicant submitted and discussed several articles published after the filing date of the application, to evidence unexpected results of the claimed invention. The Examiners agreed that unexpected results of the claimed invention can overcome the § 103 rejections, and that Applicant's arguments appear to support Applicant's position in the § 103 rejections.

The Examiners suggested filing Declaration under 37 C.F.R. § 1.132 relating to unexpected results and Declaration that IMiD1, IMiD2 and IMiD3 disclosed in Davies could not positively be identified as the instant compound. Attorney for Applicant noted that she would submit such Declarations as proposed.

Next, Attorney for Applicant addressed the issue of obviousness-type double patenting rejections. Attorney for Applicant pointed out the differences of the compounds and diseases recited in the instant claims and the cited applications. The Examiners stated that the obviousness-type double patenting rejections would be withdrawn. Applicant's arguments and evidence are discussed below and presented herewith.

## III. Arguments and Response to Rejections

### The Claimed Invention is Not Obvious

Claims 24, 26, 29-33, 38-42, 57-75, and 77-80 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kyle et al. (*Semin. Oncol.*, 2001, "Kyle") in view of Davies et al. (*Blood*, 2001, "Davies"). (pages 3-5 of the Office Action). The Office Action states (1) that Kyle teaches the treatment of multiple myeloma with thalidomide and dexamethasone; (2) that Davies teaches that thalidomide derivatives, including Revimid®[1]-also known as IMID3, are useful in treating multiple myeloma; (3) and that it would have been obvious to one of ordinary skilled in the art to substitute Revimid® for thalidomide (pages 3-4 of Office Action). Applicant respectfully traverses this rejection.

Applicant respectfully reiterates that the pending claims are not obvious over Kyle in view of Davies for the reasons provided in the previous response filed on February 20, 2008. The amended claims recite, *inter alia*, methods of treating multiple myeloma,

[1] Applicant is assuming that, by referring to Revimid®, the Examiner is referring to 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, a species referenced by the registered trademark Revlimid®. Celgene Corporation presently markets pharmaceutical compositions comprising 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione under the mark Revlimid®.

comprising administering about 5 to 50 mg/day of a specific compound named 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, and a therapeutically effective amount of dexamethasone. Kyle discloses the use of thalidomide and dexamethasone. However, Kyle does not disclose or suggest the use of the specific compound, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione for treating multiple myeloma as recited in the instant claims.

In fact, Kyle teaches away from the selection of the recited compound by focusing on the use of compounds different from that recited by the present claims. Indeed, Kyle concludes that thalidomide and dexamethasone can be effective (page 586). Thus, one of skill in the art would have had no reason to specifically select 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, or to use it with dexamethasone in multiple myeloma, to arrive at the instant claims. Without such a teaching, a *prima facie* case of obviousness cannot be made.

Further, Kyle does not disclose or suggest the use of the specific doses (5 to 50 mg/day) of the specific compound, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione for treating multiple myeloma as recited in the instant claims. Kyle discloses that thalidomide was given at a dose of 200 mg/d for two weeks and then increased as tolerated by 200 mg/d every two weeks to a maximum dose of 800 mg/d (page 585). In fact, the doses used in Kyle are much higher than those recited in the instant claims (5 to 50 mg/day). Thus, Kyle teaches away from the selection of the instant doses of the recited compound by focusing on the doses different from those of the present claims. For purpose of obviousness analysis, a prior art that teaches away negates an obviousness rejection. "[A]n applicant may rebut a prima facie case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect." In *re Peterson*, 315 F.3d 1325, 1331 (Fed. Cir. 2003). (Emphasis added.) Thus, Applicant respectfully submits that the instant claims are not obvious over Kyle.

Next, the Office's reliance on Davies does not render the instant claims obvious. The Office has not pointed to any portion in Davies that would have led one skilled in the art towards the specific compound 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione of the instant claims. Davies purportedly discloses that multiple myeloma cells were incubated or cultured with thalidomide, or 3 IMiDs® immunomodulatory compounds (IMiD1, IMiD2 and IMiD3)[2]. *See*, page 212. Without

[2] Applicant respectfully directs the attention of the Examiner to the fact that IMiDs® refers to Celgene Corporation's registered trademark for immunomodulatory compounds.

identifying thalidomide analogs specifically by their chemical structures or names, Davies used the general terms, IMiD1, IMiD2, and IMiD3 to identify the compounds.

In this regard, Applicant invites the Examiner's attention to Declaration by PETER H. SCHAFER, Ph.D. under 37 C.F.R. § 1.132 ("Declaration") filed concurrently herewith. As evidenced by Dr. SCHAFER's Declaration and publications submitted herewith, IMiD1, IMiD2 and IMiD3 disclosed in Davies could not positively be identified as the instant compound 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione. Indeed, Celgene Corporation used the designation for different compounds at different times in different publications, in order not to reveal any specific IMiD compounds. For example, contrary to the Office's contention that IMiD3 is known as Revimid®, IMiD1 is used to designate Revimid® in Dredge *et al.* (page 1166) and Marriott *et al.* (page 182), wherein IMiD1 is used to designate CC4047 in Gupta *et al.* (page 1958), copies submitted herewith. Also, IMiD3 is used to designate different compound 4-amino-2-(3-methyl-2,6-dioxo-piperidine-3-yl)-isoindole-1,3-dione in Marriott *et al.* (page 182) and α-3-aminophthalimido-glutarimide in Tsenova *et al.* (page 1889), copies submitted herewith.

Thus, one skilled in the art would not have known which compounds were used in Davies from the disclosure of general terms, IMiD1, IMiD2, and IMiD3, without any specific chemical structures or names of the compounds tested. Thus, Davies, alone or in combination with Kyle, would not lead one skilled in the art to select the instant compound.

Davies also fails to teach or suggest the method of treating multiple myeloma using the specific amount (5 to 50 mg/day) of the recited compound within the instant claims. In Davies, there is no teaching or suggestion that the instant compound is effective to treat multiple myeloma, much less the combination therapy with dexamethasone as recited in the present claims. Applicant respectfully points out that the PTO bears the burden of establishing a case of *prima facie* obviousness against the claims as a whole. That is, all the claim elements must be considered in a 103 rejection.

Even when the teachings of Kyle and Davies are combined, all the elements of the claimed methods would not be arrived at by this combination. Further, the combined teachings do not provide the legally required reasonable expectation of success. When Kyle and Davies are combined, one skilled in the art is merely taught that thalidomide is effective with dexamethasone, or that unidentified IMiD1, IMiD2, and IMiD3 have been used in multiple myeloma cell cultures. As such, the prior art does not provide any reasonable expectation that the specific amount (5 to 50 mg/day) of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione with dexamethasone could be successfully used in treating multiple myeloma. In other words, the prior art does not provide any "direction as

to which of many possible choices is likely to be successful." This is precisely what the courts have held not to be a reasonable expectation of success. (*Medichem, S.A. v. Robaldo,* 437 F.3d 1157, 1165 (Fed. Cir. 2006); *O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988)). Further, since an expectation of success in the specifically claimed methods is completely lacking in Kyle and Davies, Applicant respectfully submits that the Office may be improperly relying on the instant disclosure as a basis for the rejection. (*See e.g. Velander v. Garner*, 348 F.3d 1359, 68 USPQ2d. 1769 (Fed. Cir. 2003), stating that a "reasonable expectation of success 'must be founded in the prior art, not the applicant's disclosure." (emphasis added)). Accordingly, because the Office has not demonstrated a reasonable expectation of success, the claimed invention is not obvious by the combination of Kyle and Davies.

Next, claims 59-63, 68-75, and 77 are rejected as being unpatentable over U.S. 2001/0022973 ("'973 publication") in view of the combination of Kyle and Davies (pages 5-6 of the Office Action). Applicant respectfully submits that '973 publication does not cure the deficiency of Kyle and Davies. The '973 publication teaches a pharmaceutical composition for certain piperidinoalkanol compounds having antihistaminic, antiallergic, bronchodilatory, or urticaria-reduction effects (column 5). However, the '973 publication is silent as to the instant compound, the specific amounts, and the use of the instant capsule for treating multiple myeloma. Thus, the '973 publication is completely irrelevant to the instant claims. The '973 publication suggests nothing about the combination therapy administering a capsule comprising the recited compound and dexamethasone in treating multiple myeloma as claimed. Accordingly, the '973 publication in view of the combination of Kyle and Davies does not render obvious the claimed methods administering the capsule comprising the recited compound in specific amounts and dexamethasone in treating multiple myeloma.

Claims 66-67 are rejected under 35 U.S.C. § 103(a) as being unpatentable over the combination of Kyle and Davies, in view of Broder et al. (*Am. J. Med.*, 1990, "Broder"). (page 6 of the Office Action). Broder teaches an alternating therapy with dideoxycytidine in treating HIV, AIDS or tuberculosis patients. However, Broder is silent as to the instant compound, let alone the administration of the specific amounts of the compound, much less the cycling therapy for treating multiple myeloma. Thus, Broder suggests nothing about the cycling therapy administering the recited compound and dexamethasone in treating multiple myeloma as claimed. Accordingly, the combination of Kyle and Davies in view of Broder does not render the claimed cycling methods obvious.

For at least the reasons set forth above, Applicant respectfully submits that the

instant claims are not obvious, and respectfully request that the rejection under 35 U.S.C. §103 be withdrawn.

**Unexpected Results and Commercial Success**

**Support the Nonobviousness of the Instant Claims**

Further, even assuming, *arguendo*, a *prima facie* case of obviousness is established by the cited references in combination, there is evidence of unexpected or superior results for the activity of the recited compound to rebut a *prima facie* case of obviousness. As the Examiner is well aware, such unexpected results can rebut even a *prima facie* case of obviousness. *In re May*, 574 F.2d 1082, 1094 (C.C.P.A. 1978); *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987); *Ortho-Mcneil Pharmaceutical v. Mylan Laboratories*, 348 F.Supp.2d 713, 755 (N.D.W.Va. 2004); and *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991).

As discussed at the interview, the evidence provided herein for treating multiple myeloma with the recited compound and dexamethasone, together with the evidence provided in the previous responses, supports unexpected results of the claimed invention. In this regard, Applicant invites the Examiner's attention to Declaration by Robert Knight, M.D. under 37 C.F.R. § 1.132 ("Declaration") filed concurrently herewith to support unexpected results in clinical studies with multiple myeloma patients treated with the recited compound and dexamethasone. As evidenced by Declaration and publications filed with the previous responses, which were also discussed at the Examiner interview, the claimed method is a superior and unexpectedly better method for treating multiple myeloma.

For example, Applicant respectfully submits that more than 113 Abstracts were presented at *American Society of Hematology* in 2007 and 25 oral presentations were made on updated clinical data for multiple myeloma patients treated with the recited compound and dexamethasone. *See* Press Release of Celgene Corporation, an assignee of the present application, a copy submitted herewith again. It reports that the combination therapy achieved an unprecedented two-year survival rate (87%) in an Eastern Cooperative Oncology Group Phase III trial in newly diagnosed multiple myeloma.

Applicant also submitted publications reporting that in phase III trials, multiple myeloma patients, who were refractory to prior thalidomide treatment and treated with the instant compound and dexamethasone as in the claimed method, had significantly improved overall survival and induced high response rates, compared with those treated with dexamethasone alone. *See* publications submitted with the response on February 20, 2008, Weber *et al.*, Abstract #412, *American Society of Hematology*, December 8-11, 2007; Harousseau *et al.*, Abstract #3598, *American Society of Hematology*, December 8-11, 2007;

Foa *et al.*, Abstract #4839, *American Society of Hematology*, December 8-11, 2007; Chanan-Khan *et al.*, Abstract #2721, *American Society of Hematology*, December 8-11, 2007; Wang *et al.*, Abstract #PO-662, *XI$^{th}$ International Myeloma Workshop and IV$^{th}$ International Workshop on Waldenstrom's Macroglobulinemia*, June 25-30, 2007; and Wang *et al.*, Abstract #3553, *American Society of Hematology*, December 9-12, 2006. Also see the publications submitted on February 26, 2007, Rajkumar *et al.*, "Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma," *Blood*, Dec. 15, 2005, 106 (13)4050-4053; WEBER *et al.*, "A multicenter, randomized, parallel-group, double-blind, placebo-controlled study of lenalidomide plus dexamethasone versus dexamethasone alone in previously treated subjects with multiple myeloma," *Abstract # PO.738, International Multiple Myeloma Workshop*, April 10-14, 2005; RICHARDSON *et al.*, "A multi-center, randomized, phase 2 study to evaluate the efficacy and safety of 2 CDC-5013 dose regimens when used alone or in combination with dexamethasone (Dex) for the treatment of relapsed or refractory multiple myeloma (MM)," *Blood, Abstract # 825, American Society of Hematology*, Dec. 6-9, 2003; WEBER, "Lenalidomide (CC-5013, Revlimid™) and other ImiDs," *Abstract # PL5.02, International Multiple Myeloma Workshop*, April 10-14, 2005; CELGENE CORPORATION, "Celgene receives fast track status from FDA for Revimid™ in multiple myloma," Press Release, February 2003; RICHARDSON *et al.*, "Novel biological therapies for the treatment of multiple myeloma," *Best Practice & Research Clinical Haematology,* 2005, 18 (4):619-634; HUSSEIN *et al.*, "Doxil (D), vincristine (V), reduced frequency dexamethasone (d) and Revlimid (DVd-R) a phase I/II trial in advanced relapsed/refractory multiple myeloma (Rmm) patients," *Blood, Abstract #208, American Society of Hematology*, Dec. 4-7, 2004; and BAZ *et al.*, "Doxil (D), vincristine (V), reduced frequency dexamethasone (d) and revlimid (R) (DVd-R) results in a high response rate in patients with refractory multiple myeloma (RMM)," *Blood, Abstract # 2559, American Society of Hematology*, December 10-13, 2005.

Therefore, the evidence provided supports unexpected results of the claimed invention for treating multiple myeloma with the recited compound and dexamethasone. As such, Applicant respectfully requests that the rejection be withdrawn.

Further, other secondary consideration, *e.g.*, commercial success supports non-obviousness of the claimed invention. *Pfizer Inc. v. Ranbaxy Labs. Ltd.*, 405 F.Supp.2d 495, 518 (D. Del. 2005), *aff'd & rev'd on other grounds*, 457 F.3d 1284 (Fed. Cir. 2006) (holding that secondary considerations, such as commercial success, support the nonobviousness of the claimed invention); *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*,

348 F.Supp.2d 713, 755-60 (N.D.W.V. 2004), *aff'd*, 161 Fed. App'x. 944 (Fed. Cir. 2005) (crediting evidence of other secondary considerations, including commercial success, as support for nonobviousness).

Applicant presented at the interview and submits herewith a copy of Press Release, which reports on REVLIMID® net product sales increased 141 Percent to $773.9 Million for 2007, compared to $320.6 Million for 2006. Further, it is respectfully submitted that the use of the recited compound in combination with dexamethasone to treat multiple myeloma was approved by the U.S. Food and Drug Administration (FDA) in June 2006, in Europe in June 2007, and Australia in December 2007.

Such evidence rebuts even a *prima facie* case of obviousness.[3] In view of the unexpected results and commercial success of the present invention, the presently claimed invention is not obvious. *In re May*, at 1094; *In re Chupp*, at 646; and *Ortho-Mcneil Pharmaceutical v. Mylan Laboratories*, at 755. Therefore, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

**The Double Patenting Rejections Should Be Withdrawn**

Claims 24, 26, 29-33, 38-42, 57-75, and 77-80 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 and 22-40 of Application No. 10/534,324 (hereinafter '324 application) in view of the combination of Kyle and Davies, on the allegation that both applications claim common subject matter, because '324 application claims methods of treating a myeloproliferative disease such as smoldering myeloma using a cytokine inhibitory drug such as IMID3 (Revimid®) as disclosed in Davies and using additional agents such as dexamethasone. (Pages 8-9 of the Office Action). Applicant respectfully traverses this rejection.

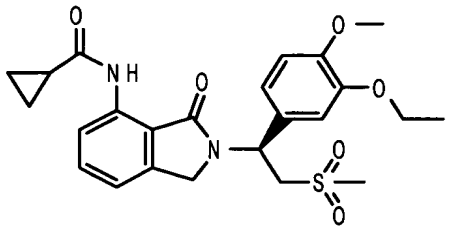
At the Examiner interview, Attorney for Applicant pointed out the differences of the compounds and diseases recited in the instant claims and the cited applications. The Examiners stated that the obviousness-type double patenting rejections would be withdrawn. Applicant respectfully reiterates that the claims of '324 application recite methods of treating a myeloproliferative disease using selective cytokine inhibitory drugs, whose structure and characteristics are distinct from 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione recited by the pending claims of the present application. (*See* the specification of '324 application, *e.g.*, page 10, line 21 to page 22.) Further, a

3 These unexpected results should also be considered in the arguments for double patenting rejection below.

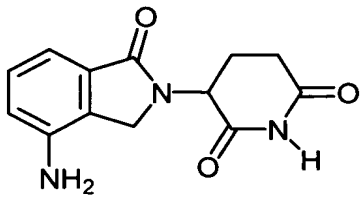
myeloproliferative disease recited in '324 application is distinct from, and is not an obvious variant of multiple myeloma. The claims of '324 application do not disclose or suggest methods of treating multiple myeloma using about 5 to 50 mg/day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione and dexamethasone. In sum, the subject matters of the claims of both applications are not encompassed by each other. The Examiner has made no *prima facie* case that the pending claims are obvious over the claims of '324 application.

Next, claims 24, 26, 29-33, 38-42, 57-75 and 77-80 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 and 18-32 of Application No. 10/515,270 (hereinafter '270 application) in view of combination of Kyle and Davies, on the ground that both applications claim common subject matter because the compounds share the same function of cytokine inhibition as disclosed in Davies. (Pages 9-10 of the Office Action). Applicant respectfully traverses this rejection.

Claims 1-32 of '270 application were canceled by the amendment filed on January 9. 2008. The pending claims of '270 application recite methods of treating non-Hodgkin's lymphoma using cyclopropanecarboxylic acid {2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1 *H*-isoindol-4-yl}-amide, which has the following structure:



The instant claims recite methods of treating multiple myeloma using dexamethasone and about 5 to 50 mg/day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione), which has the following formula:



Thus, the compound recited in '270 application is different from the compound recited in the instant claims 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-

dione) in their structures and properties. Further, multiple myeloma as presently claimed is distinct from, and is not an obvious variant of, non-Hodgkin's lymphoma recited in the '270 application. Thus, the subject matters of the claims of both applications are not encompassed by each other. Applicant respectfully requests that this double patenting rejection be withdrawn.

Lastly, claims 24, 26, 29-33, 38-42, 57-75 and 77-80 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 and 21-37 of Application No. 10/531,552 (hereinafter '552 application) in view of combination of Kyle and Davies, on the ground that both applications claim common subject matter because the used compounds share same function of cytokine inhibition as disclosed in Davies. (Page 10 of the Office Action). Applicant respectfully traverses this rejection.

The claims of '552 application recite methods of treating myelodysplastic syndrome using selective cytokine inhibitory drugs, which are distinct from 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione of the pending claims in their structures and properties. (*See* the specification of '552 application, *e.g.*, pages 9-21). Further, a myelodysplastic syndrome recited in '552 application is distinct from, and is not an obvious variant of multiple myeloma. The claims of the '552 application do not disclose or suggest the use of about 5 to 50 mg/day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione and dexamethasone in multiple myeloma, as recited in the pending claims. Thus, the subject matters of the claims of both applications are not encompassed by each other and the pending claims are not obvious over the claims of '552 application.

In sum, Applicant respectfully submits that the rejection of the pending claims under judicially created obviousness-type double patenting should be withdrawn because no *prima facie* case of obviousness has been established for the pending claims over any of the cited applications, as agreed by the Examiners at the interview.

## Conclusion

In view of the foregoing, all the rejections of the claims should be withdrawn. Reconsideration, entry of the above amendment and remarks, and allowance of the pending claims are respectfully requested. Should the Examiner not agree that all claims are allowable, a personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application.

Respectfully submitted,

Date: March 27, 2008

Yeah-Sil Moon (Reg. No. 52,042)
For Anthony M. Insogna (Reg. No. 35,203)
**JONES DAY**
222 East 41st Street
New York, NY 10017
Tel. (212) 326-3778

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Application of: | Jerome B. Zeldis | Confirmation No.: | 4802 |
| Serial No.: | 10/438,213 | Art Unit: | 1614 |
| Filed: | May 15, 2003 | Examiner: | Chris E. Simmons |
| For: | METHODS FOR TREATMENT OF A MULTIPLE MYELOMA USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE (as amended) | Attorney Docket No.: | 9516-074-999 (CAM 501872-999073) |

**DECLARATION BY PETER H. SCHAFER, PH.D. UNDER 37 C.F.R. § 1.132**

Mail Stop Amendment

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, PETER H. SCHAFER, Ph.D., declare as follows:

1. I received my Bachelor of Science degree in Biological Chemistry from University of Chicago, Chicago, Illinois in 1991. I received my Ph.D. degree from the Department of Biochemistry, Molecular Biology, and Cell Biology at Northwestern University, Evanston, Illinois in 1996.

2. From 1996 to 1999, I was a post-doctoral researcher at The R.W. Johnson Pharmaceutical Research Institute in Raritan, New Jersey. From 1999 to present, I have been employed by Celgene Corporation, Summit, New Jersey, as a Research Scientist, a Senior Research Scientist, a Group Leader, then as an Associate Director of Biology. Currently, I hold a position of the Director of Biology in the Department of Drug Discovery at Celgene Corporation.

3. I have published in peer-reviewed journals and made presentations at various academic conferences. I am also a named co-inventor of several patents and patent applications owned by Celgene Corporation and relating to immunomodulatory compounds.

4. I am affiliated with the International Society for the Biological Treatment of Cancer, American Association for the Advancement of Science, and American Association of Immunologists. I have been serving as a reviewer for academic journals such as Journal of Pharmacology and Experimental Therapeutics, European Journal of Hematology, and Leukemia and Lymphoma. My curriculum vitae is attached hereto as **Exhibit 1**.

5. I am familiar with the disclosure and claims of the above-identified patent application ("the '213 application"). I understand that the pending claims recite, *inter alia*, methods of treating multiple myeloma, comprising administering about 5 to 50 mg/day of a compound, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (known as REVLIMID®, REVIMID® or REVIMID™), and a therapeutically effective amount of dexamethasone. By training and experience, I am familiar with the compound recited in the claims, phamacological properties of the compound, and clinical studies of the compound in multiple myeloma patients.

6. I understand that an Office Action issued on December 31, 2007, in the '213 application, rejecting the claims as unpatentable over Kyle et al. (*Semin. Oncol.*, 2001, "Kyle") and Davies et al. (*Blood*, 2001, "Davies"). I understand that the Office Action states that IMiD3 disclosed in Davies is known as Revimid®. I have reviewed Kyle and Davies. Davies discloses 3 IMiDs® immunomodulatory compounds (IMiD1, IMiD2 and IMiD3) without identifying the compounds by their chemical structures or names. The Davies and Kyle papers do not identify which IMiD is IMiD3.

7. Contrary to the Office's contention that IMiD3 was known as Revimid®, at the time of the filing of this application (November 2003) the terms "IMiD1, IMiD2 and IMiD3" were not assigned to any one compound. For example, IMiD1 is used to designate lenalidomide in Dredge *et al.* (page 1166; copy submitted herewith) and Marriott *et al.* (page 182; copy submitted herewith) whereas IMiD1 is used to designate cc-4047 in Gupta *et al.* (copy submitted herewith). Conversely, IMiD3 is used to designate a different compound α-3-aminophthalimido-glutarimide in Tsenova *et al.* (page 1889), a copy submitted herewith.

8. I understand that certain studies published in whole or in part by Celgene Corporation and its collaborations used these designations of IMiD1, IMiD2 and

IMiD3 for different compounds at different times in different publications. Thus, it is my opinion that IMiD1, IMiD2 and IMiD3 disclosed in Davies could not positively be identified as the instant compound 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like may be punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent issuing from the present application.

Dated: 3/21/08

Peter H. Schafer

PETER H. SCHAFER, Ph.D.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | | | |
|---|---|---|---|
| Application of: | Jerome B. Zeldis | Confirmation No.: | 4802 |
| Serial No.: | 10/438,213 | Art Unit: | 1614 |
| Filed: | May 15, 2003 | Examiner: | Chris E. Simmons |
| For: | METHODS FOR TREATMENT OF A MULTIPLE MYELOMA USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE (as amended) | Attorney Docket No.: | 9516-074-999 (CAM 501872-999073) |

**DECLARATION BY ROBERT KNIGHT, M.D., UNDER 37 C.F.R. § 1.132**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Robert Knight, M.D., declare as follows:

1. I received my Bachelor of Science Degree from the United States Military Academy at West Point in 1973, and my Medical Degree from SUNY Downstate Medical Center in 1977. I completed an Internal Medicine Internship and Residency at Brooke Army Medical Center in San Antonio, Texas. Subsequently, I held a Research Fellowship in Hematology and Oncology at the Walter Reed Army Medical Center, Washington, D.C. Additionally, I have held academic appointments at The Uniformed Services University of the Health Sciences, Bethesda, Maryland. Presently, I hold the position of Vice President, Hematology at Celgene Corporation, Summit, NJ. My curriculum vitae is attached hereto as Exhibit 1.

2. I am familiar with the disclosure and claims of the above-identified patent application ("the '213 application"). I understand that the pending claims recite, *inter alia*, methods of treating multiple myeloma, comprising administering about 5 to 50 mg/day of a compound, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (known as REVLIMID®, REVIMID® or REVIMID™), and a therapeutically effective amount of dexamethasone. I understand that an Office Action issued on December 31, 2007, in the '213

application, rejecting the claims as unpatentable over Kyle et al. (*Semin. Oncol.*, 2001) and Davies et al. (*Blood*, 2001).

3. I am familiar with the compound recited in the claims and clinical studies of the compound in multiple myeloma patients. Phase I, II and III clinical trials were conducted by my colleagues at Celgene Corporation, the assignee of the application and by other scientists, sponsored by Celgene Corporation, to evaluate the efficacy and safety of the claimed methods.

4 In phase III trials, multiple myeloma patients, who were treated with the instant compound and dexamethasone as recited in the claimed methods, had significantly improved overall survival and induced high response rates. *See e.g.,* Weber *et al.*, Abstract #412, *American Society of Hematology*, December 8-11, 2007; Harousseau *et al.*, Abstract #3598, *American Society of Hematology*, December 8-11, 2007; Foa *et al.*, Abstract #4839, *American Society of Hematology*, December 8-11, 2007; Chanan-Khan *et al.*, Abstract #2721, *American Society of Hematology*, December 8-11, 2007; Wang *et al.*, Abstract #PO-662, *XI$^{th}$ International Myeloma Workshop and IV$^{th}$ International Workshop on Waldenstrom's Macroglobulinemia*, June 25-30, 2007; and Wang *et al.*, Abstract #3553, *American Society of Hematology*, December 9-12, 2006, submitted herewith.

5. It is my opinion that the results of the studies for treating multiple myeloma with the recited compound and dexamethasone as in the present claims would have been unexpected and surprising at the time the claimed invention was made.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like may be punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent issuing from the present application.

Dated: 26 March 2008

Robert Knight

Robert Knight, M.D.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/438,213 | 05/15/2003 | Jerome B. Zeldis | 9516-074-999 | 4802 |

20583 7590 08/06/2008

JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

| EXAMINER | |
|---|---|
| SIMMONS, CHRIS E | |
| ART UNIT | PAPER NUMBER |
| 1612 | |
| MAIL DATE | DELIVERY MODE |
| 08/06/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/438,213 | ZELDIS, JEROME B. | |
| | Examiner | Art Unit | |
| | CHRIS E. SIMMONS | 1612 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *24,26,29-33,38-42,57-75 and 77-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24,26,29-33,38-42,57-75 and 77-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicants' arguments, filed 03/27/2008, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 40 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See, e.g., In re Wilder, 22 USPQ 369, 372-3 (Fed. Cir. 1984). (Holding that a claim was not adequately described because the specification did 'little more than outline goals appellants hope the claimed invention achieves and the problems the invention will

hopefully ameliorate.')

Mere indistinct terms (such as "**pharmacologically active mutants and derivatives thereof**" used herein), however, may not suffice to meet the written description requirement. This is particularly true when a compound is claimed in purely functional terms. See Univ. of Rochester v. G.D. Searle, 69 USPQ2d 1886 (CAFC 2004) at 1892, stating:

> The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. A description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) described even in terms of its functioning of lessening inflammation of tissues fails to distinguish any steroid from others having the same activity or function. A description of what a material does, rather than of what it is, usually does not suffice…. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. (Emphasis added).

Conversely, a description of a chemical genus will usually comprise a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. See Univ. of Calf. V. Eli Lilly, 43 USPQ 2d 1398, 1406 (Fed. Cir. 1997). This is analogous to enablement of a genus under Section 112, ¶ 1, by showing the enablement of a representative number of species within the genus.

A chemical genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. *If the genus has substantial variance, the disclosure must describe a sufficient number of species to reflect the variation within that genus*. See MPEP 2163. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the

method of making the claimed invention. Disclosure of any *combination of such identifying characteristics that distinguish the claimed invention from other materials* and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. MPEP 2163.

Here, the specification does not provide a reasonably representative disclosure of useful "**pharmacologically active mutants and derivatives thereof"** generally, a potentially huge genus inclusive of many different compounds having widely divergent structures and functions. Specifically, the specification discloses only a limited number of species at page 15, line 19, and these are not viewed as being reasonably representative of the genus in its claimed scope because no readily apparent combination of identifying characteristics is provided, other than the disclosure of those specific species as examples of the claimed genus. This analysis may be applied to the proteins as well because their "**pharmacologically active mutants and derivatives thereof"** also encompasses a potentially huge genus inclusive of many different proteins having widely divergent structures and functions and may not suffice to meet the written description requirement.

Claims 24, 26, 30, 38-42, 57-75, and 77-80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See, e.g., In re Wilder, 22 USPQ 369, 372-3 (Fed. Cir. 1984). (Holding that a claim was not adequately described because the specification did 'little more than outline goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.')

Mere indistinct terms (such as "**solvate**" used herein), however, may not suffice to meet the written description requirement. This is particularly true when a compound is claimed in purely functional terms. See Univ. of Rochester v. G.D. Searle, 69 USPQ2d 1886 (CAFC 2004) at 1892, stating:

> The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. A description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) described even in terms of its functioning of lessening inflammation of tissues fails to distinguish any steroid from others having the same activity or function. A description of what a material does, rather than of what it is, usually does not suffice…. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. (Emphasis added).

Conversely, a description of a chemical genus will usually comprise a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. See Univ. of Calf. V. Eli Lilly, 43 USPQ 2d 1398, 1406 (Fed. Cir. 1997). This is analogous to enablement of a genus under Section 112, ¶ 1, by showing the enablement of a representative number of species within the genus.

A chemical genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. *If the genus has substantial variance, the disclosure must describe a sufficient number of species to reflect the variation within that genus*. See MPEP 2163. The MPEP lists factors that can

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Here, the specification does not provide a reasonably representative disclosure of useful "**solvates"** generally, a potentially huge genus inclusive of many different compounds having widely divergent structures and functions.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 24, 26, 29-33, 38, 39, 57-63, 71-74, 77, and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over USP 5,635,517 in view of Davies et al. (Prior art previously cited by examiner submitted on 12/31/2007).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The primary reference discloses that lenalidomide (1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline) is an effective compound in reducing the levels of TNF-alpha in mammals. See claims 1 and 10. Oral dosage forms include tablets, capsules, dragees,

and similar shaped, compressed pharmaceutical forms containing from 1 to 100 mg of drug per unit dosage. Isotonic saline solutions containing from 20 to 100 mg/mL can be used for parenteral administration (last paragraph at col. 5). Decreasing TNF-alpha levels and/or increasing cAMP levels constitute a valuable therapeutic strategy for the treatment of many inflammatory, infectious, immunological or malignant diseases. Examples are cancer and autoimmune diseases. The reference does not expressly teach treating multiple myeloma (MM). Microcrystalline cellulose is an excipient that can be added to the composition.

The secondary reference discloses that Thalidomide (Thal) and Thal analogues (IMiDs) can act directly on MM cells. These drugs induce a dose-dependent inhibition of proliferation even in MM cell lines and patient MM cells resistant to conventional chemotherapy, and they add to the effect of dexamethasone (Dex). For many years the immunomodulatory effects of Thal have provided the rationale for its use in the treatment of a broad range of diseases. Its mechanism of action was initially thought to be through the inhibition of cytokine production by monocytes, particularly tumor necrosis factor-alpha. New analogues of Thal have been produced that are 50,000 times more potent than Thal at inhibiting TNF-a secretion from peripheral blood mononuclear cells. (See page 210, columns 1 and 2). The authors concluded that their results show that Thal and its analogues may not only be useful in the treatment of refractory/relapsed disease, but also be effective in the maintenance of minimal residual disease after transplantation by enhancing NK-cell–mediated anti–MM cell immunity

(page 216, column 2, last sentence). The secondary reference does not expressly teach lenalidomide.

It would have been obvious to use lenalidomide in the treatment of MM at the time of the invention. One of ordinary skill in the art would have been motivated by the reasonable expectation that a thalidomide analogue effective in decreasing TNF-alpha would also be effective in the treatment of MM since the decrease in TNF-alpha has provided the rationale for treating many disease with Thal, including cancers, and more particularly, MM.

Claims 29-33 of the instant application recite the salt, solvate, stereoisomer, pure R isomer and pure S isomer. One of ordinary skill in the art would have a reasonable expectation that the salt, solvate, stereoisomer, pure R isomer and pure S isomer would also share similar anticancer effects of lenalidomide. A prima facie case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties. See MPEP 2144.08.

As for amounts claimed, generally, it is not patentable to optimize the amount of ingredients in a composition through routine experimentation. Differences in amount from what is disclosed in the reference, will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such amount is critical. It is not inventive to discover the optimum or workable ranges by routine

experimentation. *See MPEP 2144.05 [R-5] II A*.

Claims 38-42, 64-70, 75, and 78-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over USP 5,635,517 and Davies et al., the combination taken in view of Kyle et al. (Prior art previously cited by examiner submitted on 12/31/2007).

The disclosures for the primary and secondary references and the rationale for their combination are outlined *supra*. The references do not expressly teach additional the specific active agents.

The tertiary reference discloses, in the abstract, the treatment of multiple myeloma (MM) with thalidomide and dexamethasone. Thalidomide was administered in an initial dosage of 200 mg/d for 2 weeks and then increased as tolerated (in 200-mg increments at 2-week intervals) to a maximum daily dose of 800 mg. Dexamethasone was given orally in a dosage of 40 mg/d on days 1 through 4, 9 through 12, and 17 through 20 in odd cycles and 40 mg/d on days 1 through 4 in even cycles at monthly intervals. Patients with smoldering, indolent and relapsed myeloma showed results for thalidomide treatment. Signs of toxicity showed in some patients receiving 400 mg/day of thalidomide and the dosage had to be decreased, suggesting that the dosages must be altered depending on the side effects (see first paragraph on page 587). Table 2 at page 586 provides for potential strategies using thalidomide in MM treatment: Thalidomide may be used to treat MM in combination therapy with prednisone, vincristine, doxorubicin, melphalan, biological agents such as alpha2-interferon. The tertiary reference does not expressly teach lenalidomide.

It would have been obvious to one of ordinary skill in the art to use the Thal derivative, lenalidomide, in the dosage regimen disclosed in the tertiary reference. The motivation would have been the reasonable expectation of success in the treatment of MM using lenalidomide in a known effective dosage regimen. It is within the skill of the skilled artisan to tweak the regimen depending on the level of disease of the patient and the potency of the lenolidamide.

As for claims 38-42, Applicant claims a composition with both Lenalidomide and dexamethasone and an additional active agent selected from agents or methods known to be used for cancer therapy. However, as outlined above, Table 2 suggests treatment of MM using thalidomide in combination with several agents, including dexamethasone. Generally, it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose; the idea of combining them flows logically from their having been individually taught in the prior art. Conversely, there is no evidence in the record establishing the Applicant's combination of agents is any more effective or in any way different than any single member of that combination.

Claims 24, 26, 29-33, 38, 39, 57-63, 71-74, 77, and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over USP 6,555,554 in view of Davies et al.

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome

by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The primary reference discloses a composition comprising a therapeutic agent and 1 to 100 mg of lenalidomide, or its enantiomers, in a single or multidose regimen to reduce TNF-alpha and to improve oncogenic or cancerous conditions. The reference does not expressly teach treating MM.

The disclosure of the secondary reference is outlined *supra.* The secondary reference does not expressly teach lenalidomide.

It would have been obvious to use lenalidomide in the treatment of MM at the time of the invention. One of ordinary skill in the art would have been motivated by the reasonable expectation that a thalidomide analogue effective in decreasing TNF-alpha would also be effective in the treatment of MM since the decrease in TNF-alpha has

provided the rationale for treating many disease with Thal, including cancers, and more particularly, MM.

Claims 24, 26, 29-33, 38, 39, 57-63, 71-74, 77, and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over USP 6,281,230 in view of Davies et al.

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The primary reference discloses combination therapy comprising administering between 1 to 100 mg of lenalidomide (and its enantiomers) and an active agent in the treatment of an oncogenic or cancerous condition (claims 18-26). It is further disclosed

that lenalidomide is effective in decreasing TNF-alpha (paragraph bridging columns 4 and 5). The reference does not expressly teach treating MM.

The disclosure for the secondary reference is outlined above. It does not expressly teach lenalidomide.

It would have been obvious to use lenalidomide in the treatment of MM at the time of the invention. One of ordinary skill in the art would have been motivated by the reasonable expectation that a thalidomide analogue effective in decreasing TNF-alpha would also be effective in the treatment of MM since the decrease in TNF-alpha has provided the rationale for treating many disease with Thal, including cancers, and more particularly, MM.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 24, 26, 29-33, 38, 39, 57-63, 71-74, 77, and 80 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 5,635,517 in view of Davies et al. The references' disclosures are outlined above. It would have been obvious to use lenalidomide in the treatment of MM at the time of the invention. One of ordinary skill in the art would have been motivated by the reasonable expectation that a thalidomide analogue effective in decreasing TNF-alpha would also be effective in the treatment of MM since the decrease in TNF-alpha has provided the rationale for treating many disease with Thal, including cancers, and more particularly, MM.

Claims 24, 26, 29-33, 38, 39, 57-63, 71-74, 77, and 80 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 18-26 of U.S. Patent No. 6,281,230 in view of Davies et al. The disclosures of the references are outlined above. It would have been obvious to use lenalidomide in the treatment of MM at the time of the invention. One of ordinary skill in the art would have been motivated by the reasonable expectation that a thalidomide analogue effective in decreasing TNF-alpha would also be effective in the treatment of MM since the decrease in TNF-alpha has provided the rationale for treating many disease with Thal, including cancers, and more particularly, MM.

Claims 24, 26, 29-33, 38, 39, 57-63, 71-74, 77, and 80 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 6,555,554 in view of Davies et al. The disclosures of the references are outlined above. It would have been obvious to use lenalidomide in the treatment of MM at the time of the invention. One of ordinary skill in the art would have been motivated by the reasonable expectation that a thalidomide analogue effective in decreasing TNF-alpha would also be effective in the treatment of MM since the decrease in TNF-alpha has provided the rationale for treating many disease with Thal, including cancers, and more particularly, MM.

Claims 24, 26, 29-33, 38, 39, 57-63, 71-74, 77, and 80 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 7,119,106 in view of Davies et al.

The patented claims disclose a composition comprising 1 to 100 mg of lenalidomide. The patent teaches that the compounds of the invention are effective in decreasing TNF-alpha (paragraph bridging col. 4 and 5). The patent does not expressly teach treating MM.

It would have been obvious to use lenalidomide in the treatment of MM at the time of the invention. One of ordinary skill in the art would have been motivated by the reasonable expectation that a thalidomide analogue effective in decreasing TNF-alpha would also be effective in the treatment of MM since the decrease in TNF-alpha has

provided the rationale for treating many disease with Thal, including cancers, and more particularly, MM.

Claims 24, 26, 29-33, 38, 39, 57-63, 71-74, 77, and 80 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-34 of U.S. Patent No. 7,189,740. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are embraced by the patented claims. The term "myelodysplastic syndromes" or "MDS" means hematopoietic stem cell disorders characterized by one or more of the following: ineffective blood cell production, progressive cytopenias, risk of progression to acute leukemia or cellular marrow with impaired morphology and maturation (dysmyelopoiesis) (col. 6, lines 41-46). MM would then be a species of this definition.

Claims 24, 26, 29-33, 38, 39, 57-63, 71-74, 77, and 80 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 7,393,862. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are embraced by the patented claims. The term "leukemia" refers to malignant neoplasms of the blood-forming tissues (col. 13, lines 9-10 of the patent), of which MM is a specie.

***Conclusion***

No claims are allowed.

***Correspondence***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRIS E. SIMMONS whose telephone number is (571)272-9065. The examiner can normally be reached on Monday - Friday from 7:30 - 5:00 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/C. E. S./

Examiner, Art Unit 1612

***/Frederick Krass/***
***Supervisory Patent Examiner, Art Unit 1612***

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| Application of: Jerome B. Zeldis | Continuation No.: 4802 |
| Serial No.: 10/438,213 | Group Art Unit: 1614 |
| Filed: May 15, 2003 | Examiner: Simmons, Chris E. |
| For: METHODS FOR TREATMENT OF multiple myeloma USING 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (as amended) | Attorney Docket No.: 9516-074-999 (CAM: 501872-999073) |

**RESPONSE**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
Mail Stop Amendment

Sir:

In response to Office Action dated August 6, 2008, Applicant submits the following amendment and remarks for the consideration by the Examiner and entry into the record of the above-captioned application.

**Amendments to the Claims** are reflected in the listing of the claims that begins on page 2 of this paper.

**Remarks** begin on page 6 of this paper.

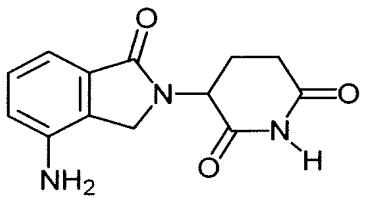
**Amendment to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of the Claims:**

Claims 1-23. (canceled)

24. (currently amended) A method of treating multiple myeloma, which comprises cyclically administering to a patient having multiple myeloma about 5 to about 50 mg per day of a compound of the formula:



or a pharmaceutically acceptable salt, ~~solvate~~ or stereoisomer thereof, and a therapeutically effective amount of dexamethasone.

25. (canceled)

26. (previously presented) The method of claim 24, wherein the multiple myeloma is smoldering myeloma, indolent myeloma, chemotherapy responsive multiple myeloma, refractory myeloma, relapsed myeloma, or relapsed and refractory Dune-Salmon stage III multiple myeloma.

27-28. (canceled)

29. (previously presented) The method of claim 24, wherein the compound is a pharmaceutically acceptable salt.

30. (canceled)

31. (previously presented) The method of claim 24, wherein the compound is a pharmaceutically acceptable stereoisomer.

32. (previously presented) The method of claim 31, wherein the stereoisomer is an enantiomerically pure R isomer.

33. (previously presented) The method of claim 31, wherein the stereoisomer is an enantiomerically pure S isomer.

34-37. (canceled)

38. (previously presented) The method of claim 24, which further comprises administering a therapeutically effective amount of an additional active agent.

39. (previously presented) The method of claim 38, wherein the additional active agent is hematopoietic growth factor, a cytokine, or an anti-cancer agent.

40. (currently amended) The method of claim 39, wherein the additional active agent is granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), erythropoietin (EPO), interleukin (IL), interferon (IFN), or a ~~pharmacologically active mutant or derivative~~ combination thereof.

41. (previously presented) The method of claim 39, wherein the additional active agent is oblimersen, melphalan, topotecan, pentoxifylline, taxotere, irinotecan, ciprofloxacin, doxorubicin, vincristine, dacarbazine, Ara-C, vinorelbine, prednisone, cyclophosphamide, bortezomib, arsenic trioxide or a combination thereof.

42. (previously presented) The method of claim 24, which further comprises administering radiation therapy, hormonal therapy, biological therapy or immunotherapy.

43-56. (canceled)

57. (previously presented) The method of claim 24, wherein the multiple myeloma is relapsed, refractory or resistant to conventional therapy.

58. (previously presented) The method of claim 24, wherein the compound and dexamethasone are administered orally.

59. (previously presented) The method of claim 58, wherein the compound is administered in the form of a capsule or tablet.

60. (previously presented) The method of claim 24, wherein the compound is administered in an amount of from about 10 to about 25 mg per day.

61. (previously presented) The method of claim 24, wherein the compound is administered in an amount of about 5, 10, 20, 25, 30, or 50 mg per day.

62. (previously presented) The method of claim 24, wherein the compound is administered in an amount of from about 5 mg per day to about 25 mg per day.

63. (previously presented) The method of claim 60, wherein the compound is administered in an amount of about 25 mg per day.

64. (canceled)

65. (currently amended) The method of claim ~~64~~ 24, wherein one cycle comprises four to six weeks.

66. (currently amended) The method of claim ~~64~~ 24, wherein one cycle comprises the administration of the compound for 21 days followed by seven days rest.

67. (currently amended) The method of claim ~~64~~ 24, wherein the compound is administered for four to twenty-four weeks with one to six weeks of rest.

68. (previously presented) The method of claim 24, wherein the compound is administered in an amount of from about 5 to about 25 mg per day for 21 days every 28 days for sixteen to twenty-four weeks.

69. (currently amended) The method of claim ~~64~~ 24, wherein the compound is administered in an amount of about 25 mg per day for 21 days followed by seven days rest in a 28 day cycle; and dexamethasone is administered in an amount of about 40 mg once daily on Days 1 to 4, 9 to 12, and 17 to 20 of each cycle for first 4 cycles, and after the first 4 cycles dexamethasone is administered in an amount of about 40 mg once daily on Days 1 to 4 of each cycle.

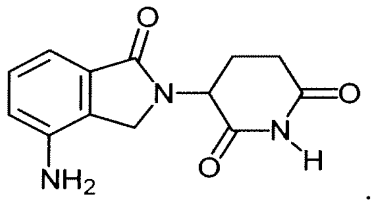
70. (previously presented) The method of claim 24, wherein the compound is administered in an amount of about 25 mg per day and dexamethasone is administered in an amount of about 40 mg per day on days 1-4 every four to six weeks.

71. (previously presented) The method of claim 24, wherein the compound is administered in an amount of 5 mg per day.

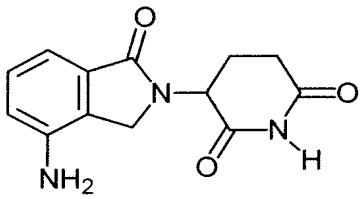
72. (previously presented) The method of claim 60, wherein the compound is administered in an amount of 10 mg per day.

73. (previously presented) The method of claim 24, wherein the compound is administered in a capsule of 5 mg, 10 mg, 15 mg or 25 mg.

74. (previously presented) The method of claim 24, wherein the compound is




75. (currently amended) A method of treating multiple myeloma, which comprises administering, on a 28 day cycle, to a patient having multiple myeloma: (a) about 25 mg per day of a compound of the formula:



or a pharmaceutically acceptable salt, ~~solvate~~ or stereoisomer thereof for 21 consecutive days followed by seven consecutive days of rest, and; (b) about 40 mg per day of dexamethasone on days 1-4 every 28 days.

76. (canceled).

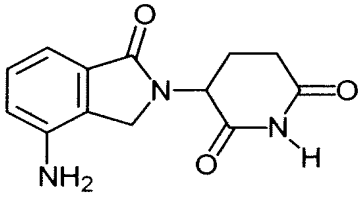
77. (previously presented) The method of claim 24, wherein the compound is administered in an amount of about 15 mg twice a day.

78. (previously presented) The method of claim 24, which further comprises administering a therapeutically effective amount of doxorubicin and vincristine.

79. (previously presented) The method of claim 24, which further comprises administering a therapeutically effective amount of melphalan.

80. (previously presented) The method of claim 73, wherein the capsule comprises the compound, lactose anhydrous, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

81. (new) A method of treating multiple myeloma using a 28 day cycle, which comprises administering to a patient having multiple myeloma; (a) for 21 consecutive days about 25 mg per day of a compound of the formula:



followed by seven consecutive days of rest; and (b) dexamethasone in an amount of about 40 mg once per day on days 1, 8, 15 and 22 of the 28 day cycle.

## REMARKS

### I. Amendments to the Claims

Claims 24, 40 and 75 have been amended and claim 81 has been added to clearly define the subject matter of the invention. Accordingly, claims 30 and 64 have been canceled, and claims 65-67 and 69 have been amended. The amended claims are supported by the originally filed specification, for example, pages 12, 23-24, 27-28, 31-33, 43-44, 46-48 and 51, and claims 64-70. No new matter has been added.

Claims 24, 26, 29, 31-33, 38-42, 57-63, 65-75 and 77-81 are pending. Applicant respectfully submits that the pending claims are allowable for the following reasons.

### II. The Rejections Under 35 U.S.C. §112 Should be Withdrawn

Claim 40 is rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. (Office Action, pages 2-4). Specifically, the Office appears to have rejected the terms 'pharmacologically active mutant or derivative thereof.' (Office Action, pages 3-4).

Without acquiescing to the rejection and solely to promote allowance of this case, Applicant has deleted the terms in claim 40. Thus, the rejection of the Claims is now moot and should be withdrawn.

Next, claims 24, 26, 30, 38-42, 57-75 and 77-80 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. (Office Action, pages 4-6). Specifically, the Office appears to have rejected the term solvate. (Office Action, pages 5-6).

Without acquiescing to the rejection and solely to promote allowance of this case, Applicant has deleted the term solvate in the pending claims. Thus, this rejection is moot and should be withdrawn.

### III. The Claimed Invention is Not Obvious

#### The Rejection over USP 5,635,517 in view of Davies Should be Withdrawn

Claims 24, 26, 29-33, 38, 39, 57-63, 71-74, 77 and 80 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,635,517 ("'517 Patent") in view of Davies et al. (*Blood*, 2001, "Davies"). (pages 7-9 of the Office Action). Applicant respectfully traverses this rejection.

Applicant respectfully appreciates that claims 64-70 reciting the cyclic administrations of the recited compound (3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-

piperidine-2,6-dione or lenalidomide) and dexamethasone were not rejected over the '517 Patent in view of Davies. Page 7 of the Office Action.

Without acquiescing to the rejection and solely to promote allowance of this case, Applicant has amended the rejected claims to recite the cyclic administration of the recited compound and dexamethasone.[1] Thus, the rejection of the claims over the '517 Patent in view of Davies is now moot and should be withdrawn.

**The Rejection over USP 5,635,517 and Davies in view of Kyle Should be Withdrawn**

Claims 38-42, 64-70, 75 and 78-79 are rejected under 35 U.S.C. § 103(a) as being unpatentable over the '517 Patent and Davies in view of Kyle et al. (*Semin. Oncol.*, 2001, "Kyle"). (pages 10-11 of the Office Action). The Office Action states that: (1) the '517 Patent teaches lenalidomide is effective in reducing TNF-α levels; (2) Davies teaches that thalidomide and its analogues (IMiDs®) can act directly on multiple myeloma cells and inhibit TNF-α; (3) Kyle teaches the treatment of multiple myeloma with thalidomide and dexamethasone; and (4) it would have been obvious to one of ordinary skilled in the art to substitute lenalidomide for thalidomide (pages 7-11 of Office Action). Applicant respectfully traverses this rejection.

The current standard of obviousness takes into account (1) whether there would have been a "reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does;" and (2) whether the combination of elements would have yielded "predictable results" *i.e.*, whether there would have been a reasonable expectation of success. *See e.g., PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d at 1342, 1360 (Fed. Cir. 2007) ("The burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, and would have had a reasonable expectation of success in doing so.") (emphasis added, internal quotations omitted). Applicant respectfully submits that the pending claims are not obvious over the '517 Patent and Davies in view of Kyle for the following reasons.

The amended claims recite, *inter alia*, methods of treating multiple myeloma, by cyclically administering about 5 to 50 mg/day of a specific compound named lenalidomide, (3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione), and a therapeutically

[1] Applicant will address the arguments as to the differences of the claimed invention from the '517 Patent and Davies in the following section.

effective amount of dexamethasone. First, Applicant respectfully submits that the cited references would not have provided any reason to specifically select the combination of the specific drugs in specific amounts for treating the particular disease, much less the claimed cyclic therapy using the combination.

The Office alleges that the '517 Patent discloses that the recited compound is effective in reducing TNF-α levels and decreasing TNF-α levels constitutes a valuable therapeutic strategy for treatments of many diseases such as cancer. (Office Action, pages 7-8). While the '517 Patent discloses the recited compound and a genus that encompasses the compound (*e.g.*, column 4, Formula I), the Office has not pointed to any reason that would have prompted a person skilled in the art to specifically select the claimed compound in specific amounts for treating multiple myeloma by cyclic administration in combination with dexamethasone.

As well settled, the legally required "reason" to select a species or subspecies from a genus for purposes of 35 U.S.C. §103 does not exist unless there was "[s]ome motivation to select the claimed species or subgenus [from] the prior art." *In re Deuel*, 51 F.3d 1552, 1558-9, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995) ("No particular one of these DNA's can be obvious unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared.") (emphasis added); *In re Baird*, 16 F.3d 380, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994) ("Absent anything in the cited prior art suggesting which of the $10^{36}$ possible sequences corresponds to [a gene], the PTO has not met its burden of establishing that the prior art would have suggested the claimed sequences."); *see also* MPEP §2144.08.

Nothing in the '517 Patent even hints at the desirability of singling out the instant compound for use in treating multiple myeloma, much less using the claimed doses. While the '517 Patent discloses that the compounds may be used as a valuable therapeutic strategy for various disorders by decreasing TNF-α levels (columns 3-4), it does not teach or suggest multiple myeloma, much less treating the specific disease, as the Office Action admitted (page 8). Thus, even assuming, *arguendo*, that one skilled in the art would be motivated to select the compound disclosed in the '517 Patent, there is no teaching or suggestion that the compound would be useful for treating multiple myeloma – a distinctive disease which is not mentioned in the '517 Patent.

Applicant further respectfully submits that the Office has not pointed to any portion in the '517 Patent that would have provided the impetus to one of skill in the art to specifically select the combination of the instant compound and dexamethasone for treating multiple myeloma, much less the cyclic therapy using the combination as claimed.

Next, the Office's reliance on Davies does not cure the defects of the first reference. The Office alleges that Davies teaches that thalidomide and its analogues (IMiDs®) can act directly on multiple myeloma cells and inhibit TNF-α. However, the Office has not pointed to any portion in Davies that would have led one skilled in the art towards the specific compound 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione of the instant claims. In Davies, there is no teaching or suggestion that the instant compound is effective to treat multiple myeloma. Davies merely discloses that multiple myeloma cells were incubated or cultured with thalidomide, or 3 IMiDs® or immunomodulatory compounds (IMiD1, IMiD2 and IMiD3)[2]. *See*, page 212. Applicant reiterates that without identifying thalidomide analogs specifically by their chemical structures or names, Davies used the general terms, IMiD1, IMiD2, and IMiD3 to identify the compounds. As evidenced by Dr. SCHAFER's Declaration and publications submitted on March 27, 2008, IMiD1, IMiD2 and IMiD3 disclosed in Davies could not positively be identified as the instant compound 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, because Celgene Corporation used the designation for different compounds at different times in different publications, in order not to reveal any specific IMiD compounds.

Thus, one skilled in the art would not have known which compounds were used in Davies from the disclosure of general terms, IMiD1, IMiD2, and IMiD3, without any specific chemical structures or names of the compounds tested. Thus, Davies would not lead one skilled in the art to select the instant compound.

Davies also fails to teach or suggest the claimed method of treating multiple myeloma, using (1) the specific amounts (5 to 50 mg/day) of the recited compound, (2) in combination with dexamethasone, and (3) by cyclically administering them in particular dosing regimens. Applicant respectfully points out that the PTO bears the burden of establishing a case of *prima facie* obviousness against the claims as a whole. That is, all the claim elements must be considered in a 103 rejection.

Nonetheless, the PTO alleges that one skilled in the art would select the recited compound for the claimed methods over the '517 Patent and Davies, because thalidomide analogue effective in decreasing TNF-α would also be effective in treating multiple myeloma, since the decrease in TNF-α has provided the rationale for treating multiple myeloma (Office Action, page 9).

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[2] Applicant respectfully directs the attention of the Examiner to the fact that IMiDs® refers to Celgene Corporation's registered trademark for immunomodulatory compounds.

Applicant respectfully disagrees with the PTO's position that is contrary to the law of obviousness. The law requires a motivation to select the references and to combine them in the particular claimed manner to reach the claimed invention. *Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc.*, 471 F.3d 1369, 1379 (Fed. Cir. 2006). (Emphasis added). In this case, the Examiner has provided no specific source of motivation to combine the teachings of the '517 Patent and Davies in "the particular claimed manner"– a method of treating multiple myeloma, using the particular cyclic dosing regimens with the specific amounts (5 to 50 mg/day) of the recited compound in combination with dexamethasone.

As stated above, neither the '517 Patent nor Davies teach cyclically administering the specific amounts of lenalidomide and dexamethasone for treating multiple myeloma. Accordingly, there is no motivation to combine the teachings of the '517 Patent and Davies to reach the claimed invention.

Further, TNF-α inhibition is not the only motivating factor to move ahead in clinical development for multiple myeloma. Indeed the recited compound has a number of mechanisms working in multiple myeloma. For example, Palumbo (*Cancer Treatment Reviews*, 34, 283-91, 2008) explains that antitumor activity of lenalidomide against multiple myeloma (MM) includes inducing apoptosis, decreasing the binding of MM cells to bone marrow stromal cells, inhibiting IL-6 and VEGF, enhancing dexamethasone cytotoxicity, stimulating host anti-MM natural killer cell immunity, inhibiting osteoclast differentiation, and direct antiproliferative effects on MM cell lines. A copy of the article is submitted herewith.[3] Indeed, Davis discusses that his study together with other reports may help better understanding of MM pathogenesis and to define the stage of disease for a therapy (page 216, last paragraph). Thus, the cited references have not provided any reason or motivation to combine the teachings to arrive at the claimed methods for treating multiple myeloma using the particular cyclic dosing regimens with the specific combination of drugs, which are not taught in the references.

Nonetheless, the Office contends that Kyle teaches the treatment of multiple myeloma with thalidomide and dexamethasone; and it would have been obvious to one of ordinary skilled in the art to use lenalidomide in the dosing regimen disclosed in Kyle (pages 10-11 of Office Action). Nor does Kyle cure the defects of the first and secondary references.

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[3] Applicant requests that the references submitted be made of record in the file history of the application and that the Examiner execute the 1449 Form enclosed.

Kyle discloses the use of thalidomide and dexamethasone. However, Kyle does not disclose or suggest the use of the specific compound, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione for treating multiple myeloma as recited in the instant claims. Further, Kyle does not disclose or suggest the use of the specific doses (5 to 50 mg/day) of the compound, much less cyclically administering the compound with dexamethasone for treating multiple myeloma as recited in the instant claims.

In fact, Kyle teaches away from the selection of the recited compound by focusing on the use of compounds different from that recited by the present claims, because Kyle concludes that thalidomide and dexamethasone can be effective (page 586). Thus, one of skill in the art would have had no reason to specifically select lenalidomide, much less to use it with dexamethasone in multiple myeloma, to arrive at the instant claims.

Further, Kyle discloses that thalidomide was given at a dose of 200 mg/d for two weeks and then increased as tolerated by 200 mg/d every two weeks to a maximum dose of 800 mg/d (page 585). The doses used in Kyle are much higher than those recited in the instant claims (5 to 50 mg/day). Thus, Kyle teaches away from the claimed dosage range. Prior art is said to teach away from a claimed invention "[w]hen a piece of prior art 'suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant....'" *Medichem*, 437 F.3d at 1165 (*quoting In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)) (emphasis added); *See also KSR,* 127 S.Ct. at 1740 (*citing United States v. Adams*, 383 U.S. 39, 40 (1966)); MPEP § 2145 (citing *In re Grasselli*, 713 F.2d 731, 743, 218 U.S.P.Q. 769, 779 (Fed. Cir. 1983)).

In view of the foregoing, even when the teachings of the '517 Patent, Davies and Kyle are combined, there would have been no reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does. All the elements of the claimed methods would not be arrived at by the combination. Thus, the *prima facie* case of obviousness has not been established.

Next, Applicant respectfully submits that the combined teachings would not have provided the legally required reasonable expectation of success. The Office Action fails to explain how one skilled in the art would have had a reasonable expectation that the instant claimed methods would be effective in treating multiple myeloma. The Federal Circuit, following the landmark case of *KSR International Co. v. Teleflex Inc.* 127 S.Ct. 1727, 167 L.Ed.2d 705, 75 USLW 4289, 82 U.S.P.Q.2d 1385 (2007), reaffirmed the guidelines for determining "whether the expectation of success from a particular line of inquiry is great

enough to render a resulting invention obvious" as previously set forth by the same Court. *PharmaStem*, 491 F.3d at 1364. As the Federal Circuit explained:

> an invention would not be invalid for obviousness if the inventor would have been motivated to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. Likewise, an invention would not be deemed obvious if all that was suggested was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

*Id.* (citing *In re O'Farrell*, 953 F.2d 894, 903 (Fed. Cir. 1988))(internal quotations omitted) (emphasis added).

In the instant case, when the references are combined, one skilled in the art is merely taught that thalidomide is effective with dexamethasone against multiple myeloma, or that unidentified IMiD1, IMiD2, and IMiD3 have been used in multiple myeloma cell culture assays. As such, the references do not provide any reasonable expectation that the cyclic administrations of the specific amounts (5 to 50 mg/day) of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione and dexamethasone could be successfully used in treating multiple myeloma. None of the cited references would have provided any "indication of which parameters were critical" or any "direction as to which of [the] many possible choices is likely to be successful." This is particularly significant since the instant claims relate to the chemical arts, which are known to be unpredictable. Indeed, the Federal Circuit has recently pointed out the importance of considering the unpredictable nature of the chemical arts in the context of an analysis under 35 U.S.C. §103. *See Eisai Co., Ltd. v. Dr. Reddy's Laboratories, Ltd.*, No. 2007-1397 (Fed. Cir. Jul. 21, 2008) ("To the extent an art is unpredictable, as the chemical arts often are, [the] focus on...'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable."). Accordingly, because the Office has not demonstrated a reasonable expectation of success, the claimed invention is not obvious by the combination of the cited references.

**The Rejection over USP 6,555,554 in view of Davies Should be Withdrawn**

Claims 24, 26, 29-33, 38, 39, 57-63, 71-74, 77 and 80 are rejected as being unpatentable over U.S. Patent No. 6,555,554 ("'554 Patent") in view of Davies (pages 11-13 of the Office Action). Applicant respectfully traverses this rejection.

Applicant appreciates that claims 64-70 reciting the cyclic administration of the recited compound (3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione) and dexamethasone were not rejected over the '554 Patent in view of Davies. Page 11 of the Office Action.

Without acquiescing any rejection and solely to promote allowance of this case, Applicant has amended the rejected claims to recite the cyclic administration of the recited compound and dexamethasone. Thus, any rejection over the '554 Patent in view of Davies is moot and should be withdrawn.

Applicant reserves the right to present further arguments demonstrating the differences between the claimed invention and the '554 Patent in view of Davies. However, in view of the amendments, the rejection must be withdrawn.

**The Rejection over USP 6,281,230 in view of Davies Should be Withdrawn**

Claims 24, 26, 29-33, 38, 39, 57-63, 71-74, 77 and 80 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,281,230 ("'230 Patent") in view of Davies. (page 13-14 of the Office Action). Applicant respectfully traverses this rejection.

Applicant appreciates that claims 64-70 reciting the cyclic administration of the recited compound (3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione) and dexamethasone were not rejected over the '230 Patent in view of Davies. Page 13 of the Office Action.

Without acquiescing any rejection and solely to promote allowance of this case, Applicant has amended the rejected claims to recite the cyclic administration of the recited compound and dexamethasone. Thus, this rejection over the '280 Patent in view of Davies is now moot and should be withdrawn.

Applicant reserves the right to present further arguments demonstrating the differences between the claimed invention and the '280 Patent in view of Davies. However, in view of the amendments, the rejection must be withdrawn.

For at least the reasons set forth above, Applicant respectfully submits that the instant claims are not obvious, and respectfully request that the rejections under 35 U.S.C. §103 be withdrawn.

**Unexpected Results and Commercial Success Support the Nonobviousness of the Instant Claims**

Further, even assuming, *arguendo*, a *prima facie* case of obviousness is established by the cited references in combination, there is evidence of unexpected or superior results for the claimed method sufficient to rebut a *prima facie* case of obviousness. *In re May*,

574 F.2d 1082, 1094 (C.C.P.A. 1978); *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987); *Ortho-Mcneil Pharmaceutical v. Mylan Laboratories*, 348 F.Supp.2d 713, 755 (N.D.W.Va. 2004); and *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991).

In the responses filed on March 27, 2008, February 20, 2008 and February 26, 2007, Applicant submitted numerous publications which support that the claimed combination therapy showed surprising, unexpected and synergistic effects for treating multiple myeloma patients.[4]

Applicant respectfully submit new articles herewith reporting that the cyclic therapy of the instant compound and dexamethasone as in the claimed method had significantly improved overall survival and induced high response rates in multiple myeloma patients, who were refractory to prior thalidomide treatment, when compared with those treated with dexamethasone alone or in combination with thalidomide. *See* Press Release by UMHS and Celgene Corporation, Medical News Today News Article, and the following articles:

Antonio Palumbo, *et al.*, *Cancer Treatment Reviews*, 34, 283-91 (2008) ("Palumbo") reports: "Combined with dexamethasone, oral lenalidomide has proved highly effective in patients whose disease has become resistant to conventional therapy." Palumbo at 283. Palumbo states that, "[i]n patients who failed to respond to lenalidomide monotherapy, after the addition of oral dexamethasone 29% responded," demonstrating synergy, in certain cases, between the combination treatment of lenalidomide and dexamethasone over treatment with lenalidomide alone. *Id.* at 285. Palumbo also states that "two phase III randomized clinical trials (MM-009 and MM-010) have demonstrated the superiority of lenalidomide plus dexamethasone, compared with dexamethasone alone," demonstrating synergy, in certain cases, between the combination treatment of lenalidomide and dexamethasone over treatment with dexamethasone alone. *Id.*

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[4] *See* the publications submitted, Weber *et al.*, Abstract #412, *American Society of Hematology*, December 8-11, 2007; Harousseau *et al.*, Abstract #3598, *American Society of Hematology*, December 8-11, 2007; Foa *et al.*, Abstract #4839, *American Society of Hematology*, December 8-11, 2007; Chanan-Khan *et al.*, Abstract #2721, *American Society of Hematology*, December 8-11, 2007; Wang *et al.*, Abstract #PO-662, *XI$^{th}$ International Myeloma Workshop and IV$^{th}$ International Workshop on Waldenstrom's Macroglobulinemia*, June 25-30, 2007; and Wang *et al.*, Abstract #3553, *American Society of Hematology*, December 9-12, 2006. Also see the publications submitted on February 26, 2007, Rajkumar *et al.*, *Blood*, Dec. 15, 2005, 106 (13)4050-4053; WEBER *et al.*, *Abstract # PO.738, International Multiple Myeloma Workshop*, April 10-14, 2005; RICHARDSON *et al.*, *Blood, Abstract # 825, American Society of Hematology*, Dec. 6-9, 2003; WEBER, *Abstract # PL5.02, International Multiple Myeloma Workshop*, April 10-14, 2005; CELGENE CORPORATION Press Release, February 2003; RICHARDSON *et al., Best Practice & Research Clinical Haematology*, 2005, 18 (4):619-634; HUSSEIN *et al.*, *Blood, Abstract #208, American Society of Hematology*, Dec. 4-7, 2004; and BAZ *et al.*, "*Blood, Abstract # 2559, American Society of Hematology*, December 10-13, 2005

Palumbo also describes the synergistic effects of combinations of lenalidomide with other second active agents, including doxorubicin, vincristine, adriamycin, pegfilgrastim, cyclophosphamide, and bortezomib. *Id.* at 287-88. Palumbo also describes the synergistic effects of combinations of lenalidomide with melphalan and prednisone. *Id.* at 289.

Gareth Morgan, *et al.* (Abstract, European Hematology Association, 13th Cong. June 12-15, 2008) describes that "the significantly better efficacy of Len+Dex" (i.e., lenalidomide plus dexamethasone) as compared to dexamethasone alone, and concludes that lenalidomide delivers significantly larger survival in this life-limiting orphan disease.

X. Armoiry, *et al.* (*Journal of Clinical Pharmacy and Therapeutics*, 33, 219-26 2008) reports: "In relapsed or refractory multiple myeloma (MM), lenalidomide, combined with standard dose dexamethasone, is superior to dexamethasone alone in terms of time to progression, response rate and overall survival.... Lenalidomide does not trigger the limiting toxicities of thalidomide." *Id.* at 219.

Weber, *et al.* (*New England Journal of Medicine*, 357, 2133-42, 2007) reports that the claimed combination therapy had significant clinical activity in increasing response rate, time to progression and overall survival in patients with multiple myeloma, and was superior even among patients treated previously with thalidomide. Weber at 2139-42.

Meletios Dimopoulos, *et al.* (*New England Journal of Medicine*, 357, 2123-32, 2007) notes that "[l]enalidomide, a derivative or thalidomide, is less toxic and more potent than the parent drug," and further notes that "dexamethasone plus lenalidomide is more effective than either agent alone in refractory multiple myeloma." Dimopolous at 2124. Dimopolous reports that lenalidomide can be administered to patients previously treated with thalidomide without deterioration of thalidomide's side effects. Dimopolous at 2131.

Martha Q. Lacy, *et al.* (*Mayo Clinic Proceedings*, 82, 1179-84, 2007) reports that the "remarkably high response rate (91%) with oral Rev-Dex [i.e., lenalidomide plus dexamethasone] in newly diagnosed myeloma . . . compares favorably to those previously reported with Thal-Dex [i.e., thalidomide plus dexamethasone]." and treatment with Rev-Dex was well tolerated in contrast to results reported with thalidomide. Lacy at 1183.

In sum, the publications support that the cyclic therapy of the recited compound and dexamethasone as claimed significantly increased response rate and survival rate, reduced toxicity compared to thaldidomide therapy, and overcame resistance to thalidomide and conventional chemotherapy in treating patients with multiple myeloma. This evidence as a whole supports unexpected results of the claimed invention.

Further, Applicant invites the Examiner's attention to Declaration by Robert Knight, M.D. under 37 C.F.R. § 1.132 ("Declaration") filed on March 27, 2008. The Declaration states that unexpected results were obtained in clinical studies with multiple myeloma patients when they were treated with the recited compound and dexamethasone as recited in the instant claims. As evidenced by Declaration and publications submitted all together, the claimed method is a superior and unexpectedly better method for treating multiple myeloma.

The PTO must consider the evidence provided for unexpected results of the claimed invention.[5] As such, Applicant respectfully requests that the obviousness rejection be withdrawn.

Further, other secondary consideration, *e.g.*, commercial success supports non-obviousness of the claimed invention. *Pfizer Inc. v. Ranbaxy Labs. Ltd.*, 405 F.Supp.2d 495, 518 (D. Del. 2005), *aff'd & rev'd on other grounds*, 457 F.3d 1284 (Fed. Cir. 2006) (holding that secondary considerations, such as commercial success, support the nonobviousness of the claimed invention); *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 348 F.Supp.2d 713, 755-60 (N.D.W.V. 2004), *aff'd*, 161 Fed. App'x. 944 (Fed. Cir. 2005) (crediting evidence of other secondary considerations, including commercial success, as support for nonobviousness).

Applicant submitted on March 27, 2008 a copy of Press Release, which reports on REVLIMID® net product sales increased 141 Percent to $773.9 Million for 2007, compared to $320.6 Million for 2006. Further, it is respectfully submitted that the cyclic use of the recited compound in combination with dexamethasone to treat multiple myeloma was approved by the U.S. Food and Drug Administration (FDA) in June 2006, in Europe in June 2007, and Australia in December 2007.

Such evidence rebuts even a *prima facie* case of obviousness. In view of the unexpected results and commercial success of the present invention, the presently claimed invention is not obvious. *In re May*, at 1094; *In re Chupp*, at 646; and *Ortho-Mcneil Pharmaceutical v. Mylan Laboratories*, at 755. Therefore, Applicant respectfully requests that the rejections under 35 U.S.C. § 103(a) be withdrawn.

## IV. The Double Patenting Rejections Should Be Withdrawn

Claims 24, 26, 29-33, 38, 39, 57-63, 71-74, 77 and 80 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of

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4 These unexpected results should also be considered in the arguments for double patenting rejection below.

Muller et al. (the '517 Patent) in view of Davies et al.; over claims 18-26 of Muller et al. (the '230 Patent) in view of Davies et al.; over claims 1-17 of Muller et al. (the '554 Patent) in view of Davies et al.; over claims 1-7 of Muller et al. (U.S. Patent No. 7,119,106) in view of Davies et al.; over claims 1-34 of Zeldis (U.S. Patent No. 7,189,740); and over claims 1-25 of Zeldis (U.S. Patatent No. 7,393,862). (page 14-17 of the Office Action). Applicant respectfully traverses this rejection.

Applicant respectfully appreciates that claims 64-70 reciting the cyclic administrations of the recited compound (3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione) and dexamethasone were not rejected over the cited Patents. Pages 15-17 of the Office Action.

Without acquiescing to the rejections and solely to promote allowance of this case, Applicant has amended the rejected claims to recite the cyclic administrations of the recited compound and dexamethasone. Thus, all these rejections over the cited Patents are moot and should be withdrawn.

Applicant reserves the right to present further arguments demonstrating the differences between the claimed invention and the cited Patents. However, in view of the amendments, Applicant respectfully submits that the rejections of the pending claims under judicially created obviousness-type double patenting should be withdrawn, because no *prima facie* case of obviousness has been established for the pending claims over any of the cited Patents.

## Conclusion

In view of the foregoing, all the rejections of the claims should be withdrawn. Reconsideration, entry of the above amendment and remarks, and allowance of the pending claims are respectfully requested. Should the Examiner not agree that all claims are allowable, a personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application.

Respectfully submitted,

Date: October 28, 2008

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/438,213 | 05/15/2003 | Jerome B. Zeldis | 9516-074-999 | 4802 |

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| EXAMINER | |
|---|---|
| SIMMONS, CHRIS E | |
| ART UNIT | PAPER NUMBER |
| 1612 | |
| MAIL DATE | DELIVERY MODE |
| 02/27/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Interview Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/438,213 | ZELDIS, JEROME B. | |
| | Examiner | Art Unit | |
| | CHRIS E. SIMMONS | 1612 | |

All participants (applicant, applicant's representative, PTO personnel):

(1) *CHRIS E. SIMMONS*.

(2) *BRANDON FETTEROLF*.

(3) *YEAH-SIL MOON*.

(4) *DONNA ROBERTSON-CHOW*.

Date of Interview: *17 February 2009*.

Type: a)☐ Telephonic b)☐ Video Conference
c)☒ Personal [copy given to: 1)☐ applicant 2)☒ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: _____.

Claim(s) discussed: *24,26,29,31-33,38-42,57-63,65-75 and 77-81*.

Identification of prior art discussed: *See Continuation Sheet*.

Agreement with respect to the claims f)☐ was reached. g)☒ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Discussed unexpected results of combination therapy in treating multiple myeloma using lenalidomide together with dexamethasone. Also discussed 103 and ODP rejections. Applicant pointed out that no references cited in the Office actions show that lenalidomide is useful in treating multiple myeloma*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

| /Chris E Simmons/<br>Examiner, Art Unit 1612 | |
|---|---|

# Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

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The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

## Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Continuation of Identification of prior art discussed: Kyle et al., Davies, et al. Palumbo et al., US Patents 6,555,554, 5,635,517, 6,281,230, 7,119,106, 7,189,740, and 7,393,862.

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Application of: Jerome B. Zeldis

Serial No.: 10/438,213

Filed: May 15, 2003

For: METHODS FOR TREATMENT OF MULTIPLE MYELOMA USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE (AS AMENDED)

Continuation No.: 4802

Group Art Unit: 1614

Examiner: Simmons, Chris E.

Attorney Docket No.: 9516-074-999
(CAM: 501872-999073)

## RESPONSE AND STATEMENT OF INTERVIEW SUMMARY

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
Mail Stop Amendment

Sir:

Further to Examiner interview held on February 17, 2009, and to a response filed on October 28, 2008 to Office Action dated August 6, 2008, Applicant submits the following remarks for the consideration by the Examiner and entry into the record of the above-captioned application.

The listing of the claims begins on page 2 of this paper.

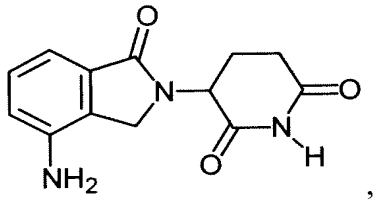
**Remarks** begin on page 6 of this paper.

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of the Claims:**

Claims 1-23. (canceled)

24. (previously presented) A method of treating multiple myeloma, which comprises cyclically administering to a patient having multiple myeloma about 5 to about 50 mg per day of a compound of the formula:



or a pharmaceutically acceptable salt or stereoisomer thereof, and a therapeutically effective amount of dexamethasone.

25. (canceled)

26. (previously presented) The method of claim 24, wherein the multiple myeloma is smoldering myeloma, indolent myeloma, chemotherapy responsive multiple myeloma, refractory myeloma, relapsed myeloma, or relapsed and refractory Dune-Salmon stage III multiple myeloma.

27-28. (canceled)

29. (previously presented) The method of claim 24, wherein the compound is a pharmaceutically acceptable salt.

30. (canceled)

31. (previously presented) The method of claim 24, wherein the compound is a pharmaceutically acceptable stereoisomer.

32. (previously presented) The method of claim 31, wherein the stereoisomer is an enantiomerically pure R isomer.

33. (previously presented) The method of claim 31, wherein the stereoisomer is an enantiomerically pure S isomer.

34-37. (canceled)

38. (previously presented) The method of claim 24, which further comprises administering a therapeutically effective amount of an additional active agent.

39. (previously presented) The method of claim 38, wherein the additional active agent is hematopoietic growth factor, a cytokine, or an anti-cancer agent.

40. (previously presented) The method of claim 39, wherein the additional active agent is granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), erythropoietin (EPO), interleukin (IL), interferon (IFN), or a combination thereof.

41. (previously presented) The method of claim 39, wherein the additional active agent is oblimersen, melphalan, topotecan, pentoxifylline, taxotere, irinotecan, ciprofloxacin, doxorubicin, vincristine, dacarbazine, Ara-C, vinorelbine, prednisone, cyclophosphamide, bortezomib, arsenic trioxide, or a combination thereof.

42. (previously presented) The method of claim 24, which further comprises administering radiation therapy, hormonal therapy, biological therapy or immunotherapy.

43-56. (canceled)

57. (previously presented) The method of claim 24, wherein the multiple myeloma is relapsed, refractory or resistant to conventional therapy.

58. (previously presented) The method of claim 24, wherein the compound and dexamethasone are administered orally.

59. (previously presented) The method of claim 58, wherein the compound is administered in the form of a capsule or tablet.

60. (previously presented) The method of claim 24, wherein the compound is administered in an amount of from about 10 to about 25 mg per day.

61. (previously presented) The method of claim 24, wherein the compound is administered in an amount of about 5, 10, 20, 25, 30, or 50 mg per day.

62. (previously presented) The method of claim 24, wherein the compound is administered in an amount of from about 5 mg per day to about 25 mg per day.

63. (previously presented) The method of claim 60, wherein the compound is administered in an amount of about 25 mg per day.

64. (canceled)

65. (previously presented) The method of claim 24, wherein one cycle comprises four to six weeks.

66. (previously presented) The method of claim 24, wherein one cycle comprises the administration of the compound for 21 days followed by seven days rest.

67. (previously presented) The method of claim 24, wherein the compound is administered for four to twenty-four weeks with one to six weeks of rest.

68. (previously presented) The method of claim 24, wherein the compound is administered in an amount of from about 5 to about 25 mg per day for 21 days every 28 days for sixteen to twenty-four weeks.

69. (previously presented) The method of claim 24, wherein the compound is administered in an amount of about 25 mg per day for 21 days followed by seven days rest in a 28 day cycle; and dexamethasone is administered in an amount of about 40 mg once daily on Days 1 to 4, 9 to 12, and 17 to 20 of each cycle for first 4 cycles, and after the first 4 cycles dexamethasone is administered in an amount of about 40 mg once daily on Days 1 to 4 of each cycle.

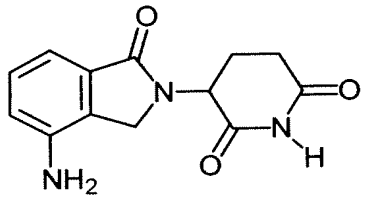
70. (previously presented) The method of claim 24, wherein the compound is administered in an amount of about 25 mg per day and dexamethasone is administered in an amount of about 40 mg per day on days 1-4 every four to six weeks.

71. (previously presented) The method of claim 24, wherein the compound is administered in an amount of 5 mg per day.

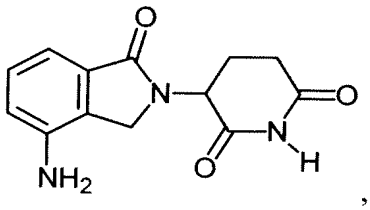
72. (previously presented) The method of claim 60, wherein the compound is administered in an amount of 10 mg per day.

73. (previously presented) The method of claim 24, wherein the compound is administered in a capsule of 5 mg, 10 mg, 15 mg or 25 mg.

74. (previously presented) The method of claim 24, wherein the compound is




75. (previously presented) A method of treating multiple myeloma, which comprises administering, on a 28 day cycle, to a patient having multiple myeloma: (a) about 25 mg per day of a compound of the formula:



or a pharmaceutically acceptable salt or stereoisomer thereof for 21 consecutive days followed by seven consecutive days of rest from administration of this compound, and; (b) about 40 mg per day of dexamethasone on days 1-4 every 28 days.

76. (canceled).

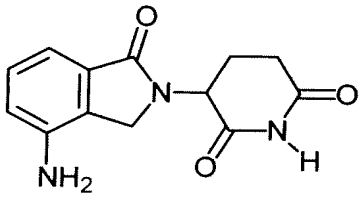
77. (previously presented) The method of claim 24, wherein the compound is administered in an amount of about 15 mg twice a day.

78. (previously presented) The method of claim 24, which further comprises administering a therapeutically effective amount of doxorubicin and vincristine.

79. (previously presented) The method of claim 24, which further comprises administering a therapeutically effective amount of melphalan.

80. (previously presented) The method of claim 73, wherein the capsule comprises the compound, lactose anhydrous, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

81. (previously presented) A method of treating multiple myeloma using a 28 day cycle, which comprises administering to a patient having multiple myeloma: (a) for 21 consecutive days about 25 mg per day of a compound of the formula:



followed by seven consecutive days of rest from administration of this compound; and (b) dexamethasone in an amount of about 40 mg once per day on days 1, 8, 15 and 22 of the 28 day cycle.

## REMARKS

### I. Applicant's Statement of the Substance of Interview and Response to the Examiner's Interview Summary of Record

A personal interview with Supervisory Patent Examiner Brandon Fetterolf, Patent Examiner Chris E. Simmons, Dr. Donna Robertson-Chow and Yeah-Sil Moon, attorney for Applicant, was held on February 17, 2009. Applicant appreciates the Examiner interview.

During the interview, the Examiners and attorney for Applicant discussed the amendment to the claims, the pending § 112 and § 103 rejections, and obviousness-type double patenting rejections.

First, Applicant pointed out that § 112 rejections, as failing to comply with the written description requirement, are moot in view of the amendments of the claims by deleting the terms 'pharmacologically active mutant or derivative thereof' and 'solvate.'

Next, the Examiners and attorney for Applicant discussed the pending § 103 rejections. Attorney for Applicant explained that U.S. Patent No. 5,635,517 ("'517 Patent") and Davies et al. (*Blood*, 2001, "Davies"), alone or in combination with Kyle *et al.* (*Semin. Oncol.*, 2001, "Kyle"), fail to suggest the claimed methods, which require the use of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione and dexamethasone for treating multiple myeloma in specific amounts and specific dosing regimens. Further, Attorney for Applicant pointed out that Kyle teaches away from the selections of the instant compound, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, and the doses of the compound, by focusing on thalidomide and doses different from those of the present claims.

In addition, Attorney for Applicant stressed that the § 103 obviousness rejections also can be overcome by unexpected results of the claimed invention. Attorney for Applicant discussed several articles previously submitted to evidence unexpected results of the claimed invention. The Examiners agreed that unexpected results of the claimed invention can overcome the § 103 rejections, and that Applicant's arguments appear to support Applicant's position in the § 103 rejections.

Attorney for Applicant pointed out that Declaration by Dr. Robert Knight was filed on March 27, 2008, and that it also supports unexpected results of the claimed invention. Attorney for Applicant stressed that other secondary consideration, *e.g.*, commercial success further supports non-obviousness of the claimed invention. Applicant presented at the interview and submits herewith a copy of Press Release of Celgene Corporation, which reports on REVLIMID® net product sales increased 71 percent to $1.325 billion in 2008.

Next, Attorney for Applicant addressed that the obviousness-type double patenting rejections should be withdrawn in view of the amendment and the unexpected results of the claimed invention. Applicant's arguments and evidence are discussed below and presented herewith.

## II. Arguments and Response to Rejections

### The Rejections Under 35 U.S.C. §112 Should be Withdrawn

The Office rejected the terms 'pharmacologically active mutant or derivative thereof' recited in claim 40. (Office Action, pages 3-4). Without acquiescing to the rejection and solely to promote allowance of this case, Applicant deleted the terms in claim 40. Thus, the rejection of the claim is now moot and should be withdrawn.

Next, claims 24, 26, 30, 38-42, 57-75 and 77-80 are rejected under 35 U.S.C. § 112, first paragraph, on the ground that the term solvate fails to comply with the written description requirement. (Office Action, pages 4-6). Without acquiescing to the rejection and solely to promote allowance of this case, Applicant deleted the term solvate in the rejected claims. Thus, this rejection is moot and should be withdrawn.

### The Claimed Invention is Not Obvious

Claims 24, 26, 29-33, 38, 39, 57-63, 71-74, 77 and 80 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,635,517 ("'517 Patent") in view of Davies et al. (*Blood*, 2001, "Davies"). (pages 7-9 of the Office Action).

Claims 24, 26, 29-33, 38, 39, 57-63, 71-74, 77 and 80 are rejected as being unpatentable over U.S. Patent No. 6,555,554 ("'554 Patent") in view of Davies (pages 11-13 of the Office Action).

Claims 24, 26, 29-33, 38, 39, 57-63, 71-74, 77 and 80 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,281,230 ("'230 Patent") in view of Davies. (page 13-14 of the Office Action). Applicant respectfully traverses the rejections.

Applicant notes that claims 64-70 reciting the cyclic administration of the recited compound (3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione) and dexamethasone were not rejected over the '517 Patent, '554 Patent or '230 Patent, in view of Davies. Without acquiescing to the rejections and solely to promote allowance of this case, Applicant amended the rejected claims to recite the cyclic administration of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione and dexamethasone. Thus, the rejections of the claims over the '517 Patent, '554 Patent or '230 Patent in view of Davies, are now moot and should be withdrawn.

Claims 38-42, 64-70, 75 and 78-79 are rejected under 35 U.S.C. § 103(a) as being unpatentable over the '517 Patent and Davies in view of Kyle et al. (*Semin. Oncol.*, 2001, "Kyle"). (pages 10-11 of the Office Action). Applicant submitted the arguments as to the differences of the claimed invention from the cited references in the October 28, 2008 response, the entireties of which are incorporated herein by reference.

As discussed at the interview held on February 17, 2009, the PTO has failed to establish a *prima facie* case of obviousness, since the claimed elements are not found in any of the cited references. Indeed, the cited references, alone or in combination, do not teach or suggest the treatment of multiple myeloma using (1) the specific amounts (5 to 50 mg/day) of the recited compound 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, (2) in combination with dexamethasone, and (3) by cyclically administering them in particular dosing regimens. Applicant respectfully points out that the PTO bears the burden of establishing a case of *prima facie* obviousness against the claims as a whole. That is, all the claim elements must be considered in a 103 rejection. For this reason alone, the rejection is in error.

Further, Kyle teaches away from the selection of the recited compound by focusing on the use of compounds different from that recited by the present claims, because Kyle concludes that thalidomide and dexamethasone can be effective (page 586). Thus, one of skill in the art would have had no reason to use a compound other than thalidomide, much less to specifically select lenalidomide, and use it with dexamethasone in multiple myeloma.

Furthermore, Kyle discloses that thalidomide was given at a dose of 200 mg/d for two weeks and then increased as tolerated by 200 mg/d every two weeks to a maximum dose of 800 mg/d (page 585). The doses used in Kyle are much higher than those recited in the instant claims (5 to 50 mg/day). Thus, even if Kyle motivated one to select lenalidomide, and it does not, Kyle teaches away from the claimed dosage range. Prior art is said to teach away from a claimed invention "[w]hen a piece of prior art 'suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant....'" *Medichem*, 437 F.3d at 1165 (*quoting In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)) (emphasis added); *See also KSR*, 127 S.Ct. at 1740 (*citing United States v. Adams*, 383 U.S. 39, 40 (1966)); MPEP § 2145 (citing *In re Grasselli*, 713 F.2d 731, 743, 218 U.S.P.Q. 769, 779 (Fed. Cir. 1983)).

In view of the foregoing, even when the teachings of the '517 Patent, Davies and Kyle are combined, there would have been no reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention

does. All the elements of the claimed methods would not be arrived at by the combination. Thus, the *prima facie* case of obviousness has not been established.

**Unexpected Results Support the Nonobviousness of the Instant Claims**

Further, even assuming, *arguendo*, a *prima facie* case of obviousness is established by the cited references in combination, Applicant provided evidence of unexpected results of the claimed method sufficient to rebut a *prima facie* case of obviousness. *In re May*, 574 F.2d 1082, 1094 (C.C.P.A. 1978); *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987); *Ortho-Mcneil Pharmaceutical v. Mylan Laboratories*, 348 F.Supp.2d 713, 755 (N.D.W.Va. 2004); and *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991).

As well settled, even if a *prima facie* case of obviousness is established, the Examiner is required to consider all rebuttal evidence submitted by Applicant. *See In re Sullivan*, 498 F.3d 1345 (Fed. Cir. 2007); *see also* MPEP §2145. This requirement remains unchanged following the decision in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007), as the Federal Circuit has made clear in *In re Sullivan.* 498 F.3d at 1351. As the Court explained, "[w]hen a patent applicant puts forth rebuttal evidence, the Board must consider that evidence." *Id.* Such rebuttal evidence includes "evidence of unexpected results." *Id.*, citing *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1369 (Fed. Cir. 2007).

In the responses filed on October 28, 2008, March 27, 2008, February 20, 2008 and February 26, 2007, Applicant submitted publications, which support that the claimed combination therapy showed surprising, unexpected and synergistic effects for treating multiple myeloma patients.

For example, Rajkumar *et al.* which was submitted on February 26, 2007, report that the combination of lenalidomide plus dexamethasone resulted in an overall 91% objective response rate (*see* abstract); and that "Responses were observed with even in patients in whom thalidomide had previously failed. Thus, lenalidomide (Rev)/Dex may be a safer and more effective alternative to Thal/Dex in newly diagnosed myeloma." Rajkumar at p. 4050, column 2, lines 10-13, a copy submitted herewith again. Rajkumar also commented that "The observed response rate [for Rev/Dex] compares favorably with those previously reported with Thal/Dex." Rajkumar at p. 4053, column 1, lines 20-22.

Rajkumar also notes an additional unexpected result of lenalidomide/dexamethasone therapy as compared to thalidomide/dexamethasone therapy. Thalidomide/dexamethasone was found to have significant toxicities. For example, in reporting their thalidomide/ dexamethasone studies, Kyle *et al.* noted: "Major grade 3 or 4 toxicities [with Thal/Dex] included rash in three patients, and sedation, constipation, and myaldias in one patient

each." (Kyle et al., p. 586, column 1, lines 13-15). By contrast, lenalidomide/dexamethasone therapy exhibits surprisingly fewer toxicities. Rajkumar, for example, noted: "Unlike thalidomide, side effects such as constipation and neuropathy were uncommon and sedation was not seen; no patient developed grade III or higher neuropathy." (Rajkumar at p. 4053, column 1, lines 25-27). These results are sufficient to rebut the alleged *prima facie* case of obviousness over thalidomide and dexamethasone therapy as allegedly disclosed in Kyle.

In addition, at the interview held on February 17, 2009, Applicant also explained unexpectedly superior effects of the claimed invention reported in the publications, which were submitted with a response on October 28, 2008.

For example, Weber, *et al.* (*New England Journal of Medicine*, 357, 2133-42, 2007) reports that the claimed combination therapy had significant clinical activity in increasing response rate, time to progression and overall survival in patients with multiple myeloma, and was superior even among patients treated previously with thalidomide. Weber at 2139-42.

Meletios Dimopoulos, *et al.* (*New England Journal of Medicine*, 357, 2123-32, 2007) notes that lenalidomide, a derivative or thalidomide, is less toxic and more potent than the parent drug, and that lenalidomide in combination with dexamethasone can be administered to patients previously treated with thalidomide without deterioration of thalidomide's side effects. Dimopolous at 2124 and 2131. X. Armoiry, *et al.* (*Journal of Clinical Pharmacy and Therapeutics*, 33, 219-26 2008) reports that lenalidomide in combination with dexamethasone does not trigger the limiting toxicities of thalidomide. *Id.* at 219.

Martha Q. Lacy, *et al.* (*Mayo Clinic Proceedings*, 82, 1179-84, 2007) reports that the "remarkably high response rate (91%) with oral Rev-Dex [i.e., lenalidomide plus dexamethasone] in newly diagnosed myeloma . . . compares favorably to those previously reported with Thal-Dex [i.e., thalidomide plus dexamethasone]." and treatment with Rev-Dex was well tolerated in contrast to results reported with thalidomide. Lacy at 1183. *Also see* Richardson *et al.*, at page 1170 (*Expert Rev. Anticancer Ther.*, 1165-73. 2006), a copy submitted herewith.

Accordingly, the claimed therapy using lenalidomide and dexamethasone has been reported to be unexpectedly superior to thalidomide plus dexamethasone therapy used in Kyle *et al.*, both with respect to efficacy (*e.g.*, objective response rate) as well as certain toxicities (*e.g.*, constipation, neuropathy and sedation). These unexpected results should overcome any allegations of *a prima facie* obviousness.

Further, no reference cited by the PTO is sufficient to render the claimed combination therapy obvious. Applicant submitted publications describing unexpected and superior results of the claimed combination therapy over monotherapy of lenalidomide or dexamethasone alone, as discussed at the examiner interview. For example, Armoiry, *et al.* at 219 reports that in relapsed or refractory multiple myeloma (MM), lenalidomide, combined with standard dose dexamethasone, is superior to dexamethasone alone in terms of time to progression, response rate and overall survival. Gareth Morgan, *et al.* (Abstract, European Hematology Association, 13th Cong. June 12-15, 2008) describes that "the significantly better efficacy of Len+Dex" (*i.e.*, lenalidomide plus dexamethasone) as compared to dexamethasone alone, and concludes that lenalidomide delivers significantly larger survival in this life-limiting orphan disease. Dimopoulos, *et al.* at 2124 notes that dexamethasone plus lenalidomide is more effective than either agent alone (lenalidomide or dexamethasone) in refractory multiple myeloma. Also see Richardson, 2006 page 1170.

Antonio Palumbo, *et al.*, *Cancer Treatment Reviews*, 34, 283-91 (2008) ("Palumbo") reports: "Combined with dexamethasone, oral lenalidomide has proved highly effective in patients whose disease has become resistant to conventional therapy." Palumbo at 283. Palumbo states that, "[i]n patients who failed to respond to lenalidomide monotherapy, after the addition of oral dexamethasone 29% responded," demonstrating synergy between the combination treatment of lenalidomide and dexamethasone over treatment with lenalidomide alone. *Id.* at 285. Palumbo also states that "two phase III randomized clinical trials (MM-009 and MM-010) have demonstrated the superiority of lenalidomide plus dexamethasone, compared with dexamethasone alone," demonstrating synergy between the combination treatment of lenalidomide and dexamethasone over treatment with dexamethasone alone. *Id.*

Palumbo also describes the synergistic effects of combinations of lenalidomide with other second active agents, including doxorubicin, vincristine, adriamycin, pegfilgrastim, cyclophosphamide, and bortezomib. *Id.* at 287-88. Palumbo also describes the synergistic effects of combinations of lenalidomide with melphalan and prednisone. *Id.* at 289.

In sum, these publications support that the claimed therapy of the recited compound and dexamethasone significantly increased response rate and survival rate, and reduced toxicity, when compared to thaldidomide/dexamethasone therapy, or monotherapy of thaldidomide, lenalidomide or dexamethasone alone, in treating multiple myeloma. The publications also support that the claimed method overcame resistance to thalidomide

therapy and conventional chemotherapy in treating multiple myeloma. This evidence as a whole supports unexpected results of the claimed invention.

Further, Applicant invites the Examiner's attention to Declaration by Robert Knight, M.D. under 37 C.F.R. § 1.132 ("Declaration") filed on March 27, 2008. The Declaration states that unexpected results were obtained in clinical studies with multiple myeloma patients when they were treated with the recited compound and dexamethasone as recited in the instant claims. As evidenced by Declaration and publications submitted all together, the claimed method is a superior and unexpectedly better method for treating multiple myeloma. The PTO must consider the evidence provided for unexpected results of the claimed invention.[1]

**Commercial Success Support the Nonobviousness of the Instant Claims**

Further, other secondary consideration, *e.g.*, commercial success supports non-obviousness of the claimed invention. *Pfizer Inc. v. Ranbaxy Labs. Ltd.*, 405 F.Supp.2d 495, 518 (D. Del. 2005), *aff'd & rev'd on other grounds*, 457 F.3d 1284 (Fed. Cir. 2006) (holding that secondary considerations, such as commercial success, support the nonobviousness of the claimed invention); *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 348 F.Supp.2d 713, 755-60 (N.D.W.V. 2004), *aff'd*, 161 Fed. App'x. 944 (Fed. Cir. 2005) (crediting evidence of other secondary considerations, including commercial success, as support for nonobviousness).

At the interview held on February 17, 2009, Applicant discussed commercial success of the claimed invention. Applicant presented a copy of Press Release of Celgene Corporation, reporting the claimed method of the instant compound and dexamethasone as number 1 therapy in multiple myeloma worldwide, and Year 2008 financial results (Revlimid® net product sales increased 71 percent to $1.325 billion in 2008). *See* a copy of Press Release submit herewith.[2] Further, it is respectfully submitted that the use of the recited compound in combination with dexamethasone to treat multiple myeloma was approved by the U.S. Food and Drug Administration (FDA) in June 2006, in Europe in June 2007, and Australia in December 2007.

Such evidence rebuts even a *prima facie* case of obviousness. In view of the unexpected results and commercial success of the present invention, the presently claimed

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1 These unexpected results should also be considered in the arguments for double patenting rejections below.

2 Applicant submitted on March 27, 2008 a copy of Press Release, which reports on REVLIMID® net product sales increased 141 Percent to $773.9 Million for 2007, compared to $320.6 Million for 2006.

invention is not obvious. *In re May*, at 1094; *In re Chupp*, at 646; and *Ortho-Mcneil Pharmaceutical v. Mylan Laboratories*, at 755. Therefore, Applicant respectfully requests that the rejections under 35 U.S.C. § 103(a) be withdrawn.

**The Double Patenting Rejections Should Be Withdrawn**

Claims 24, 26, 29-33, 38, 39, 57-63, 71-74, 77 and 80 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of Muller et al. (the '517 Patent) in view of Davies et al.; over claims 18-26 of Muller et al. (the '230 Patent) in view of Davies et al.; over claims 1-17 of Muller et al. (the '554 Patent) in view of Davies et al.; over claims 1-7 of Muller et al. (U.S. Patent No. 7,119,106) in view of Davies et al.; over claims 1-34 of Zeldis (U.S. Patent No. 7,189,740); and over claims 1-25 of Zeldis (U.S. Patatent No. 7,393,862). (page 14-17 of the Office Action). Applicant respectfully traverses this rejection.

Applicant notes that claims 64-70 reciting the cyclic administrations of the recited compound (3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione) and dexamethasone were not rejected over the cited Patents. Pages 15-17 of the Office Action. Without acquiescing to the rejections and solely to promote allowance of this case, Applicant amended the rejected claims to recite the cyclic administrations of the recited compound and dexamethasone. Thus, all these rejections over the cited Patents are moot and should be withdrawn.

Applicant reserves the right to present further arguments demonstrating the differences between the claimed invention and the cited Patents. However, in view of the amendments and unexpected results of the claimed invention, Applicant respectfully submits that the rejections of the pending claims under judicially created obviousness-type double patenting should be withdrawn.

## Conclusion

In view of the foregoing, all the rejections of the claims should be withdrawn. Reconsideration, entry of the above amendment and remarks, and allowance of the pending claims are respectfully requested. Should the Examiner not agree that all claims are allowable, a personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application.

Respectfully submitted,

Date: February 27, 2009

Yeah-Sil Moon (Reg. No. 52,042)
For Anthony M. Insogna (Reg. No. 35,203)
**JONES DAY**
222 East 41st Street
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Tel. (212) 326-3778

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/438,213 | 05/15/2003 | Jerome B. Zeldis | 9516-074-999 | 4802 |

84802 7590 03/27/2009

JONES DAY
222 E. 41ST. STREET
NEW YORK, NY 10017

| EXAMINER | |
|---|---|
| SIMMONS, CHRIS E | |
| ART UNIT | PAPER NUMBER |
| 1612 | |
| MAIL DATE | DELIVERY MODE |
| 03/27/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

UNITED STATES DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450

| APPLICATION NO./ CONTROL NO. | FILING DATE | FIRST NAMED INVENTOR / PATENT IN REEXAMINATION | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 10438213 | 5/15/2003 | ZELDIS, JEROME B. | 9516-074-999 |

JONES DAY
222 E. 41ST. STREET
NEW YORK, NY 10017

| EXAMINER | |
|---|---|
| CHRIS E. SIMMONS | |
| **ART UNIT** | **PAPER** |
| 1612 | 20090319 |

**DATE MAILED:**

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner for Patents**

REJECTIONS ARE WITHDRAWN

At this time, all prior rejections are withdrawn. However, in order for the examiner to sufficiently consider patentability of the claimed invention under 35 USC §§ 102 and 103, additional information regarding this issue is hereby requested.

REQUEST FOR INFORMATION

Applicant and the assignee of this application are required under 37 CFR 1.105 to provide the following information that the examiner has determined is reasonably necessary to the examination of this application.

BACKGROUND

Davies et al. ("Thalidomide and immunomodulatory derivatives augment naturl killer cell cytotoxicity in multiple myeloma"; Blood (2001); 98(1):210-216), at page 211, under the section titled 'Preparation of Thal and IMIDs', state that the Thal (thalidomide) and IMIDs (immonomodulatory compounds designated as IMID 1, 2 and 3) were provided to them by the assignee, i.e., Celgene Corp.

REQUEST

In responding to this requirement for information, applicant is required to provide: Shipment records (if available) regarding the transfer of the IMlD compounds from Celgene to Davies, including the identity of the compounds shipped;

and (whether shipment records are available or not)

information indicating what particular compounds were designated "IMID 1, IMlD 2 and IMID3" by Celgene prior to the shipment to Davies.

In responding to those requirements that require copies of documents, where the document is a bound text or a single article over 50 pages, the requirement may be met by providing copies of those pages that provide the particular subject matter indicated in the requirement, or where such subject matter is not indicated, the subject matter found in applicant's disclosure.

The applicant is reminded that the reply to this requirement must be made with candor and good faith under 37 CFR 1.56. Where the

applicant does not have or cannot readily obtain an item of required information, a statement that the item is unknown or cannot be readily obtained may be accepted as a complete reply to the requirement for that item.

This requirement is subject to the provisions of 37 CFR 1.134, 1.135 and 1.136 and has a shortened statutory period of 2 months. EXTENSIONS OF THIS TIME PERIOD MAY BE GRANTED UNDER 37 CFR 1.136(a).

CORRESPONDENCE

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRIS E. SIMMONS whose telephone number is (571)272-9065. The examiner can normally be reached on M-F from 9 to 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass, can be reached on M-F at (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free)..

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612

/C. E. S./
Examiner, Art Unit 1612

PTO-90C (Rev.04-03)

**ELECTRONIC FILING**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| Application of: Jerome B. Zeldis | Continuation No.: 4802 |
| Serial No.: 10/438,213 | Group Art Unit: 1612 |
| Filed: May 15, 2003 | Examiner: Simmons, Chris E. |
| For: METHODS FOR TREATMENT OF MULTIPLE MYELOMA USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE (AS AMENDED) | Attorney Docket No.: 9516-074-999 (CAM: 501872-999073) |

**INFORMATION DISCLOSURE STATEMENT**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the duty of disclosure provisions of 37 C.F.R. §1.56, there is hereby provided certain information which the Examiner may consider material to the examination of the subject U.S. patent application. It is requested that the Examiner make this information of record if it is deemed material to the examination of the application.

1. Enclosures accompanying this Information Disclosure Statement are:

1a. ☒ A list of all patents, publications, applications, or other information submitted for consideration by the office.

1b. A legible copy of :

☒ Each publication or that portion which caused it to be listed on the PTO-1449;

☐ For each cited pending unpublished U.S. application, the application specification including the claims, and any drawing of the application, or portion of the application which caused it to be listed on the PTO-1449 including any claims directed to that portion that have been checked to be unavailable at the USPTO's private PAIR system;

☐ An English language copy of search report(s) from a counterpart foreign application or PCT International Search Report;

☐ Explanations of relevancy (ATTACHMENT 1(d), hereto) or English language abstracts of the non-English language publications;

☐ All other information or portion which caused it to be listed on the PTO-1449.

1c. ☐ Pursuant to 37 C.F.R. § 1.98(a)(2)(ii), copies of the cited U.S. patents and U.S. patent application publications are not submitted herewith unless required by the office.

1d. ☐ Pursuant to 1287 OG 163, copies of cited pending unpublished applications that are available at the USPTO's private PAIR system are not submitted herewith.

2. ☐ This Information Disclosure Statement is filed under 37 C.F.R. §1.97(b):

☐ Within three months of the filing date of a national application other than a continued prosecution application under §1.53(d);

☐ Within three months of the date of entry of the national stage as set forth in §1.491 in an international application;

☐ Before the mailing of the first Office action on the merits;

☐ Before the mailing of a first Office action after the filing of a request for continued examination under §1.114.

3. ☒ This Information Disclosure Statement is filed under 37 C.F.R. §1.97(c) after the period specified in 37 C.F.R §1.97(b), but before the mailing date of any of a final action under 37 C.F.R. §1.113, a notice of allowance under 37 C.F.R. §1.311 or an action that otherwise closes prosecution in the application.

*(Check either Item 3a or 3b)*

3a. ☒ The Certification Statement in Item 5 below is applicable. Accordingly, no fee is required.

3b. ☐ The $180.00 fee set forth in 37 C.F.R. §1.17(p) in accordance with 37 C.F.R. §1.97(c) is:

☐ enclosed.
☐ to be charged to Jones Day Deposit Account No. 50-3013.

*(Item 3b to be checked if any reference known for more than 3 months)*

4. ☐ This Information Disclosure Statement is filed under 37 C.F.R. §1.97(d) after the period specified in 37 C.F.R. §1.97(c), but on or before the date of payment of the issue fee.

The Certification Statement in Item 5 below is applicable.

The $180.00 fee set forth in 37 C.F.R. §1.17(p) is:
☐ enclosed.
☐ to be charged to Jones Day Deposit Account No. 50-3013.

5. ☒ Certification Statement (applicable if Item 3a or Item 4 is checked):

*(Check either Item 5a or 5b)*

5a. ☒ In accordance with 37 C.F.R. §1.97(e)(1), it is certified that each item of information contained in this Information Disclosure Statement was first cited in a communication from the Israeli patent office in a counterpart Israeli application not more than three months prior to the filing of this Information Disclosure Statement.

5b. ☐ Each item of information contained in this information disclosure statement was cited in a communication from a foreign patent office in a counterpart application, and the communication was not **received** by any individual designated in 37 C.F.R. §1.56(c) more than thirty days prior to the filing of this information disclosure statement.

5c. ☐ Pursuant to 37 C.F.R. §1.704(d), each item of information contained in this information disclosure statement was cited in a communication from a foreign patent office in a counterpart application, and the communication was not

**received** by any individual designated in 37 C.F.R. §1.56(c) more than thirty days prior to the filing of this information disclosure statement.

6. ☐ This application is a continuation application under 37 C.F.R. §1.53(b) or (d).

*(Check appropriate Items 6a, 6b and/or 6c)*

6a. ☐ A Petition to Withdraw from issue under 37 C.F.R. §1.313(b)(5) is concurrently filed herewith.

6b. ☐ Copies of publications listed on Form PTO-1449 from prior application Serial No. , filed on , of which this application claims priority under 35 U.S.C. §120, are not being submitted pursuant to 37 C.F.R. §1.98(d).

6c. ☐ Copies of the publications listed on Form PTO-1449 were not previously cited in prior application Serial No. , filed on , and are provided herewith.

7. ☒ This is a Supplemental Information Disclosure Statement. (Check Item 7a)

7a. ☒ This Supplemental Information Disclosure Statement under 37 C.F.R. §1.97(f) supplements the Information Disclosure Statement filed on February 26, 2007.

8. ☐ In accordance with 37 C.F.R. §1.98, a concise explanation of what is presently understood to be the relevance of each non-English language publication is:

*( Check Item 8a, 8b, or 8c)*

8a. ☐ Satisfied because all non-English language publications were cited on the enclosed English language copy of the PCT International Search Report or the search report from a counterpart foreign application indicating the degree of relevance found by the foreign office.

8b. ☐ Set forth in the application.

8c. ☐ Enclosed as an attachment hereto.

9. ☒ The Commissioner is authorized to charge any additional fee required or credit any overpayment for this Information Disclosure Statement and/or Petition to Jones Day Deposit Account No. 50-3013.

10. ☒ No admission is made that the information cited in this Statement is, or is considered to be, material to patentability and no representation is made that a search has been made (other than a search report of a foreign counterpart application or PCT International Search Report if submitted herewith). 37 C.F.R. §§1.97(g) and (h).

Respectfully submitted,

Date: April 29, 2009

52,042

Yeahsil Moon (Reg. No.)
JONES DAY
222 East 41st Street
New York, New York 10017-6702
(212) 326-3939

# LIST OF REFERENCES CITED BY APPLICANT

(Use several sheets if necessary)

| | |
|---|---|
| **Application Number** | 10/438,213 |
| **Filing Date** | May 15, 2003 |
| **First Named Inventor** | Jerome B. Zeldis |
| **Art Unit** | 1612 |
| **Examiner Name** | Chris E. Simmons |
| **Attorney Docket No.** | 9516-074-999 |

## U.S. PATENT DOCUMENTS

| *Examiner Initials | Cite No. | Document Number – Kind Code | Publication Date mm/dd/yyyy | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | A01 | | | | |
| | A02 | | | | |

## FOREIGN PATENT DOCUMENTS

| *Examiner Initials | Cite No. | Foreign Patent Document Country Code, Number, Kind Code (if known) | Publication Date mm/dd/yyyy | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear | T |
|---|---|---|---|---|---|---|
| | B01 | | | | | |
| | B02 | | | | | |

## NON PATENT LITERATURE DOCUMENTS

| *Examiner Initials | Cite No. | Include name of the author (in CAPITAL LETTERS), (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T |
|---|---|---|---|
| | C205 | "Celgene drug promises activity in solid tumors," *Marketletter*, June 18, 2001 | |
| | | | |

NYI-4179606v1

| EXAMINER SIGNATURE | DATE CONSIDERED |
|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Application of: Jerome B. Zeldis

Serial No.: 10/438,213

Filed: May 15, 2003

For: METHODS FOR TREATMENT OF MULTIPLE MYELOMA USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE (AS AMENDED)

Continuation No.: 4802

Group Art Unit: 1614

Examiner: Simmons, Chris E.

Attorney Docket No.: 9516-074-999
(CAM: 501872-999073)

**RESPONSE**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
Mail Stop Amendment

Sir:

In response to Office Communication mailed March 27, 2009, Applicant respectfully submits the following remarks for consideration by the Examiner and entry into the file of the above-referenced application.

**Remarks** begin on page 2 of this paper.

## REMARKS

On page 2 of the Office Communication, the Examiner has withdrawn all prior rejections. However, the Examiner requested applicant and the assignee of the application to provide shipment records (if available) regarding the transfer of Celgene compounds to the authors of Davies *et al.* ( "Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma," *Blood*, 2001;98:210-216), including the identity of the compounds shipped, and information indicating what particular compounds were designated "IMID1, IMID2 and IMID3" by Celgene prior to the shipment to the authors of Davies *et al.*

In complying to the request, Applicant submits herewith communications between Celgene Corporation to the authors of Davies *et al.* as Exhibits 1 to 6. As the Examiner will see, Celgene Corporation and the authors of Davies *et al.* used the designations of "Celgene compounds, IMiDs, IMiD, 4047, 7062, 5013 and CC-5013" for the transfer of the compounds to be tested. There is no information in the communications indicating what particular compounds were designated "IMID1, IMID2 and IMID3" by Celgene prior to the shipment to the authors of Davies *et al.* Celgene did not use "IMID1, IMID2 and IMID3" as an internal reference for its compounds. The authors of Davies *et al.* randomly used "IMID1, IMID2 and IMID3" for designating different Celgene compounds in their paper (*Blood*, 2001;98:210-216).

## Conclusion

In view of the foregoing, allowance of the pending claims are respectfully requested. Should the Examiner not agree that all claims are allowable, a personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application.

Respectfully submitted,

Date: May 20, 2009

Yean-Sil Moon (Reg. No. 52,042)
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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/438,213 | 05/15/2003 | Jerome B. Zeldis | 9516-074-999 | 4802 |

84802 7590 09/09/2009

JONES DAY
222 E. 41ST. STREET
NEW YORK, NY 10017

| EXAMINER | |
|---|---|
| SIMMONS, CHRIS E | |
| ART UNIT | PAPER NUMBER |
| 1612 | |
| MAIL DATE | DELIVERY MODE |
| 09/09/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/438,213 | ZELDIS, JEROME B. | |
| | Examiner | Art Unit | |
| | CHRIS E. SIMMONS | 1612 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/29/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicants' arguments, filed 02/27/2009, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

### *Response to Request for Information*

Applicant's responses on 4/29/2009 and 5/30/2009 to the Request for Information filed 3/27/2009 are acknowledged.

### *Claim Rejections - 35 USC § 112 - New Matter*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 81 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The originally filed specification does not appear to have adequate support for a 28 day cycle where dexamethasone is administered on days 1, 8, 15 and 22 of the cycle. Accordingly, the claim introduces new matter.

***Claim Rejections - 35 USC § 103***

Claims 24, 26, 29, 31-33, 38-42, 57-63, 65-75, and 77-81 are rejected under 35 U.S.C. 103(a) as being unpatentable over USP 5,635,517 in view of Davies et al. (Prior art previously cited by examiner submitted on 12/31/2007), the combination taken in view of Kyle et al. (Prior art previously cited by examiner submitted on 12/31/2007).

The primary reference discloses, in the abstract, the treatment of multiple myeloma (MM) with thalidomide and dexamethasone. Thalidomide was administered in an initial dosage of 200 mg/d for 2 weeks and then increased as tolerated (in 200-mg increments at 2-week intervals) to a maximum daily dose of 800 mg. Dexamethasone was given orally in a dosage of 40 mg/d on days 1 through 4, 9 through 12, and 17 through 20 in odd cycles and 40 mg/d on days 1 through 4 in even cycles at monthly intervals. Patients with smoldering, indolent and relapsed myeloma showed results for thalidomide treatment. Signs of toxicity showed in some patients receiving 400 mg/day of thalidomide and the dosage had to be decreased, suggesting that the dosages must be altered depending on the side effects (see first paragraph on page 587). Table 2 at page 586 provides for potential strategies using thalidomide in MM treatment: Thalidomide may be used to treat MM in combination therapy with prednisone, vincristine, doxorubicin, melphalan, biological agents such as alpha2-interferon. The primary reference does not expressly teach lenalidomide (LEN).

The secondary reference discloses that Thalidomide (Thal) and Thal analogues (IMiDs) can act directly on MM cells. These drugs induce a dose-dependent inhibition

of proliferation even in MM cell lines and patient MM cells resistant to conventional chemotherapy, and they add to the effect of dexamethasone (Dex). For many years the immunomodulatory effects of Thal have provided the rationale for its use in the treatment of a broad range of diseases. Its mechanism of action was initially thought to be through the inhibition of cytokine production by monocytes, particularly tumor necrosis factor-alpha. New analogues of Thal have been produced that are 50,000 times more potent than Thal at inhibiting TNF-a secretion from peripheral blood mononuclear cells. (See page 210, columns 1 and 2). The authors concluded that their results show that Thal and its analogues may not only be useful in the treatment of refractory/relapsed disease, but also be effective in the maintenance of minimal residual disease after transplantation by enhancing NK-cell–mediated anti–MM cell immunity (page 216, column 2, last sentence). The secondary reference does not expressly teach LEN.

The tertiary reference discloses that the Thal analogue, LEN (1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline), is an effective compound in reducing the levels of TNF-alpha in mammals. See claims 1 and 10. Oral dosage forms include tablets, capsules, dragees, and similar shaped, compressed pharmaceutical forms containing from 1 to 100 mg of drug per unit dosage. Isotonic saline solutions containing from 20 to 100 mg/mL can be used for parenteral administration (last paragraph at col. 5). Decreasing TNF-alpha levels and/or increasing cAMP levels constitute a valuable therapeutic strategy for the treatment of many inflammatory, infectious, immunological or malignant diseases. Examples are cancer and autoimmune diseases.

Microcrystalline cellulose is an excipient that can be added to the composition. The tertiary reference does not expressly teach treating multiple myeloma (MM).

It would have been obvious to use the Thal analogue, LEN, in the cyclical treatment of MM at the time of the invention. One of ordinary skill in the art would have been motivated by the reasonable expectation that the thalidomide analogue, LEN, which is effective in decreasing TNF-alpha as disclosed in the tertiary reference would also be effective in the treatment of MM since the decrease in TNF-alpha provided the rationale for treating many disease with Thal as disclosed in the secondary reference, including cancers, and more particularly, the cyclical treatment of MM as disclosed in the primary reference.

It would have been obvious to one of ordinary skill in the art to use the Thal derivative, LEN, in the dosage regimen disclosed in the primary reference. The motivation would have also been the reasonable expectation of success in the treatment of MM using LEN in a known effective dosage regimen. It is within the skill of the skilled artisan to adjust the regimen depending on the level of disease of the patient and the potency of the drug being used.

Claims 29, 30-33 of the instant application recite the salt, stereoisomer, pure R isomer and pure S isomer. Due to their structural similarities, one of ordinary skill in the art would have a reasonable expectation that the salt, stereoisomer, pure R isomer and pure S isomer would also share similar anticancer effects of LEN. See MPEP 2144.08.

One of ordinary skill in the art would have found it obvious to adjust the amount of the drug depending on its efficacy and side effects as outlined in the primary

reference (see first paragraph on page 587). Accordingly, the differences in claimed amount from the amounts disclosed in the reference will not support the patentability unless there is evidence indicating such amount is critical. *See MPEP 2144.05 [R-5] II A*.

Claims 24, 26, 29, 31-33, 38-42, 57-63, 65-75, and 77-81 are rejected under 35 U.S.C. 103(a) as being unpatentable over USP 5,635,517, Davies et al., the combination taken further in view of USP 6,555,554.

The disclosures of the primary and secondary references are outlined *supra.* The combination does not expressly teach LEN.

The tertiary reference discloses a composition comprising a therapeutic agent and 1 to 100 mg of LEN, or its enantiomers, in a single or multidose regimen to reduce TNF-alpha and to improve oncogenic or cancerous conditions. The reference does not expressly teach treating MM.

It would have been obvious to use the Thal analogue, LEN, in the cyclical treatment of MM at the time of the invention. One of ordinary skill in the art would have been motivated by the reasonable expectation that the thalidomide analogue, LEN, which is effective in decreasing TNF-alpha as disclosed in the tertiary reference would also be effective in the treatment of MM since the decrease in TNF-alpha provided the rationale for treating many disease with Thal as disclosed in the secondary reference, including cancers, and more particularly, the cyclical treatment of MM as disclosed in the primary reference.

It would have been obvious to one of ordinary skill in the art to use the Thal derivative, LEN, in the dosage regimen disclosed in the primary reference. The motivation would have also been the reasonable expectation of success in the treatment of MM using LEN in a known effective dosage regimen. It is within the skill of the skilled artisan to adjust the regimen depending on the level of disease of the patient and the potency of the drug being used.

One of ordinary skill in the art would have found it obvious to adjust the amount of the drug depending on its efficacy and side effects as outlined in the primary reference (see first paragraph on page 587). Accordingly, the differences in claimed amount from the amounts disclosed in the reference will not support the patentability unless there is evidence indicating such amount is critical. *See MPEP 2144.05 [R-5] II A*.

Claims 24, 26, 29, 31-33, 38-42, 57-63, 65-75, and 77-81 are rejected under 35 U.S.C. 103(a) as being unpatentable over USP 5,635,517, Davies et al., the combination taken further in view of USP 6,281,230.

The disclosures of the primary and secondary references are outlined *supra.* The combination does not expressly teach LEN.

The tertiary reference discloses combination therapy comprising administering between 1 to 100 mg of LEN (and its enantiomers) and an active agent in the treatment of an oncogenic or cancerous condition (claims 18-26). It is further disclosed that LEN is

effective in decreasing TNF-alpha (paragraph bridging columns 4 and 5). The reference does not expressly teach treating MM.

It would have been obvious to use the Thal analogue, LEN, in the cyclical treatment of MM at the time of the invention. One of ordinary skill in the art would have been motivated by the reasonable expectation that the thalidomide analogue, LEN, which is effective in decreasing TNF-alpha as disclosed in the tertiary reference would also be effective in the treatment of MM since the decrease in TNF-alpha provided the rationale for treating many disease with Thal as disclosed in the secondary reference, including cancers, and more particularly, the cyclical treatment of MM as disclosed in the primary reference.

It would have been obvious to one of ordinary skill in the art to use the Thal derivative, LEN, in the dosage regimen disclosed in the primary reference. The motivation would have also been the reasonable expectation of success in the treatment of MM using LEN in a known effective dosage regimen. It is within the skill of the skilled artisan to adjust the regimen depending on the level of disease of the patient and the potency of the drug being used.

One of ordinary skill in the art would have found it obvious to adjust the amount of the drug depending on its efficacy and side effects as outlined in the primary reference (see first paragraph on page 587). Accordingly, the differences in claimed amount from the amounts disclosed in the reference will not support the patentability unless there is evidence indicating such amount is critical. *See MPEP 2144.05 [R-5] II A*.

***Response to Arguments***

Applicant argues that Kyle et al. teach away from selecting the instant compound because art teaches that Thal and Dex are effective. Thus the skilled artisan has no reason to select another compound. This argument is not found to be persuasive because a disclosure of the success of one compound does not teach away from the use of a different compound. Only a reasonable expectation of success is required for a prima facie case of obviousness. Indeed, the skill artisan would reasonably expect the successful treatment of MM using a structurally similar analog of a compound known to treat MM, especially where both are known to decrease TNF-alpha.

Applicant further argues that Kyle et al. teach amounts of Thal that are "much higher" than instantly claimed. This is not found to be persuasive because 1) the instant claims are directed to amounts for LEN not Thal and 2) the tertiary reference discloses effective amounts for LEN that are not "much higher" than instantly claimed.

Applicant asserts that publications submitted on 10/28/2008, 03/27/2008, 02/20/2008, and 02/26/2007 show unexpected results that would overcome any prima facie case of obviousness. Applicant cites Rajkumar et al. - allegedly submitted on 02/26/2007 - who report that the combination of LEN and Dex resulted in overall 91% objective response rate; and that responses were observed with even in patients in whom Thal and Dex had previously failed. Rajkumar et al. according to applicant recites that because of this "unexpected" result, LEN/Dex may be safer than Thal/Dex in treating MM. The examiner first notes that there is not Rajkumar et al. cited in the IDS

of 02/26/2007. Secondly, Corral et al. (submitted as evidence on 05/20/2009) demonstrates that LEN is exponentially more potent than Thal in decreasing TNF-alpha. Therefore, it is necessarily unexpected that MM would be treated more effectively than Thal. It would also be expected to have lower toxic effects since less LEN can be used than the less potent Thal. Accordingly, unexpected results are not considered to have been demonstrated in Rajkumar et al. or the other references cited on page 10 of the response for the same reasons. None of the references at the top of page 11 demonstrate a proper side by side comparison to demonstrate unexpected results in treating MM by combining LEN with Dex. Essentially, more anticancer agent was used when LEN and Dex were combined as compared to each agent individually.

Applicant states that Palumbo et al. supports a showing of unexpected results.

Palumbo reports: "Combined with dexamethasone, oral lenalidomide has proved highly effective in patients whose disease has become resistant to conventional therapy." Palumbo at 283. Palumbo states that, "[i]n patients who failed to respond to lenalidomide monotherapy, after the addition of oral dexamethasone 29% responded," demonstrating synergy between the combination treatment of lenalidomide and dexamethasone over treatment with lenalidomide alone, according to applicant. Palumbo also states that "two phase III randomized clinical trials (MM-009 and MM-010) have demonstrated the superiority of lenalidomide plus dexamethasone, compared with dexamethasone alone," demonstrating synergy between the combination treatment of lenalidomide and dexamethasone over treatment with dexamethasone alone, according to applicant.

The examiner does not agree that these statements in Palumbo demonstrate a proper showing of unexpected results. There is no data on whether or not the 29% who "responded" is responding due to the Dex in Len/Dex combination treatment. There was only a comparison in this study of the combination of Len/Dex to Len alone - not Dex alone. Additionally, it is not clear in what way the patients "responded". The statement in Palumbo that phase III clinical trials "demonstrated the superiority of lenalidomide plus dexamethasone, compared with dexamethasone alone" is not considered analogous to unexpected results. Len and Dex are known to be effective in MM treatment. Their addition in combinatory treatment of MM would reasonably be expected to be superior as compared to their individual use.

Applicant asserts that Palumbo describes at pages 287 and 288 synergistic results when Len is combined with other anticancer agents. The examiner does not readily identify such teachings in Palumbo.

Applicant refers to the declaration filed 03/27/2008, asserting it supports the position of unexpected results. However, the examiner does not find one example of a proper showing of unexpected results in the multitude of publications submitted.

Applicant argues that the showing of commercial success overcomes any prima facie case of obviousness. In this case, however, the examiner does not believe a sufficient case of commercial success has been demonstrated. An applicant who is asserting commercial success to support its contention of nonobviousness bears the burden of proof of establishing a nexus between the claimed invention and evidence of commercial success. The claimed invention is the treatment of MM by administering a

combination Len/Dex. There is no sufficient connection between the evidence of commercial success and the claimed invention. Accordingly, the evidence is not of probative value in the determination of nonobviousness.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 24, 26, 29, 31-33, 38-42, 57-63, 65-75, and 77-81 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 18-26 of Patent No. 6,281,230 in view of U.S. Patent No. 5,635,517 and Davies et al. The references' disclosures are outlined above. It would have been obvious to use LEN in the treatment of MM at the time of the invention. One of ordinary skill in the art would have been motivated by the reasonable expectation that a thalidomide

analogue effective in decreasing TNF-alpha would also be effective in the treatment of MM since the decrease in TNF-alpha has provided the rationale for treating many disease with Thal, including cancers, and more particularly, MM.

Claims 24, 26, 29, 31-33, 38-42, 57-63, 65-75, and 77-81 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 6,555,554 230 in view of U.S. Patent No. 5,635,517 and Davies et al. The disclosures of the references are outlined above. It would have been obvious to use LEN in the treatment of MM at the time of the invention. One of ordinary skill in the art would have been motivated by the reasonable expectation that a thalidomide analogue effective in decreasing TNF-alpha would also be effective in the treatment of MM since the decrease in TNF-alpha has provided the rationale for treating many disease with Thal, including cancers, and more particularly, MM.

Claims 24, 26, 29, 31-33, 38-42, 57-63, 65-75, and 77-81 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 7,119,106 in 230 in view of U.S. Patent No. 5,635,517 and Davies et al.

The patented claims disclose a composition comprising 1 to 100 mg of LEN. The patent teaches that the compounds of the invention are effective in decreasing TNF-alpha (paragraph bridging col. 4 and 5). The patent does not expressly teach treating MM. It would have been obvious to use LEN in the treatment of MM at the time of the

invention. One of ordinary skill in the art would have been motivated by the reasonable expectation that a thalidomide analogue effective in decreasing TNF-alpha would also be effective in the treatment of MM since the decrease in TNF-alpha has provided the rationale for treating many disease with Thal, including cancers, and more particularly, MM.

Claims 24, 26, 29, 31-33, 38-42, 57-63, 65-75, and 77-81 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-34 of U.S. Patent No. 7,189,740 in view of U.S. Patent No. 5,635,517 and Davies et al.

The references' disclosures are outlined above. It would have been obvious to use LEN in the treatment of MM at the time of the invention. One of ordinary skill in the art would have been motivated by the reasonable expectation that a thalidomide analogue effective in decreasing TNF-alpha would also be effective in the treatment of MM since the decrease in TNF-alpha has provided the rationale for treating many disease with Thal, including cancers, and more particularly, MM.

Claims 24, 26, 29, 31-33, 38-42, 57-63, 65-75, and 77-81 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 7,393,862 in view of U.S. Patent No. 5,635,517 and Davies et al.

The references' disclosures are outlined above. It would have been obvious to use LEN in the treatment of MM at the time of the invention. One of ordinary skill in the art would have been motivated by the reasonable expectation that a thalidomide analogue effective in decreasing TNF-alpha would also be effective in the treatment of MM since the decrease in TNF-alpha has provided the rationale for treating many disease with Thal, including cancers, and more particularly, MM.

## *Conclusion*

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

***Correspondence***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRIS E. SIMMONS whose telephone number is (571)272-9065. The examiner can normally be reached on Monday - Friday from 7:30 - 5:00 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/C. E. S./
Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612

**ELECTRONIC FILING**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| Application of: Jerome B. Zeldis | Continuation No.: 4802 |
| Serial No.: 10/438,213 | Group Art Unit: 1612 |
| Filed: May 15, 2003 | Examiner: Simmons, Chris E. |
| For: METHODS FOR TREATMENT OF MULTIPLE MYELOMA USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE (AS AMENDED) | Attorney Docket No.: 9516-074-999 (CAM: 501872-999073) |

**INFORMATION DISCLOSURE STATEMENT**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the duty of disclosure provisions of 37 C.F.R. §1.56, there is hereby provided certain information which the Examiner may consider material to the examination of the subject U.S. patent application. It is requested that the Examiner make this information of record if it is deemed material to the examination of the application.

1. Enclosures accompanying this Information Disclosure Statement are:

1a. ☒ A list of all patents, publications, applications, or other information submitted for consideration by the office.

1b. A legible copy of :

☒ Each publication or that portion which caused it to be listed on the PTO-1449;

☐ For each cited pending unpublished U.S. application, the application specification including the claims, and any drawing of the application, or portion of the application which caused it to be listed on the PTO-1449 including any claims directed to that portion that have been checked to be unavailable at the USPTO's private PAIR system;

☒ An English language copy of search report(s) from a counterpart foreign application or PCT International Search Report;

☐ Explanations of relevancy (ATTACHMENT 1(d), hereto) or English language abstracts of the non-English language publications;

☐ All other information or portion which caused it to be listed on the PTO-1449.

1c. ☐ Pursuant to 37 C.F.R. § 1.98(a)(2)(ii), copies of the cited U.S. patents and U.S. patent application publications are not submitted herewith unless required by the office.

1d. ☐ Pursuant to 1287 OG 163, copies of cited pending unpublished applications that are available at the USPTO's private PAIR system are not submitted herewith.

2. ☐ This Information Disclosure Statement is filed under 37 C.F.R. §1.97(b):

☐ Within three months of the filing date of a national application other than a continued prosecution application under §1.53(d);

☐ Within three months of the date of entry of the national stage as set forth in §1.491 in an international application;

☐ Before the mailing of the first Office action on the merits;

☐ Before the mailing of a first Office action after the filing of a request for continued examination under §1.114.

3. ☐ This Information Disclosure Statement is filed under 37 C.F.R. §1.97(c) after the period specified in 37 C.F.R §1.97(b), but before the mailing date of any of a final action under 37 C.F.R. §1.113, a notice of allowance under 37 C.F.R. §1.311 or an action that otherwise closes prosecution in the application.

*(Check either Item 3a or 3b)*

3a. ☐ The Certification Statement in Item 5 below is applicable. Accordingly, no fee is required.

3b. ☐ The $180.00 fee set forth in 37 C.F.R. §1.17(p) in accordance with 37 C.F.R. §1.97(c) is:

☐ enclosed.
☐ to be charged to Jones Day Deposit Account No. 50-3013.

*(Item 3b to be checked if any reference known for more than 3 months)*

4. ☒ This Information Disclosure Statement is filed under 37 C.F.R. §1.97(d) after the period specified in 37 C.F.R. §1.97(c), but on or before the date of payment of the issue fee.

The Certification Statement in Item 5 below is applicable.

The $180.00 fee set forth in 37 C.F.R. §1.17(p) is:
☐ enclosed.
☒ to be charged to Jones Day Deposit Account No. 50-3013.

5. ☐ Certification Statement (applicable if Item 3a or Item 4 is checked):

*(Check either Item 5a or 5b)*

5a. ☐ In accordance with 37 C.F.R. §1.97(e)(1), it is certified that each item of information contained in this Information Disclosure Statement was first cited in a communication from the Israeli patent office in a counterpart Israeli application not more than three months prior to the filing of this Information Disclosure Statement.

5b. ☐ Each item of information contained in this information disclosure statement was cited in a communication from a foreign patent office in a counterpart application, and the communication was not **received** by any individual designated in 37 C.F.R. §1.56(c) more than thirty days prior to the filing of this information disclosure statement.

5c. ☐ Pursuant to 37 C.F.R. §1.704(d), each item of information contained in this information disclosure statement was cited in a communication from a foreign patent office in a counterpart application, and the communication was not

**received** by any individual designated in 37 C.F.R. §1.56(c) more than thirty days prior to the filing of this information disclosure statement.

6. ☐ This application is a continuation application under 37 C.F.R. §1.53(b) or (d).

*(Check appropriate Items 6a, 6b and/or 6c)*

6a. ☐ A Petition to Withdraw from issue under 37 C.F.R. §1.313(b)(5) is concurrently filed herewith.

6b. ☐ Copies of publications listed on Form PTO-1449 from prior application Serial No. , filed on , of which this application claims priority under 35 U.S.C. §120, are not being submitted pursuant to 37 C.F.R. §1.98(d).

6c. ☐ Copies of the publications listed on Form PTO-1449 were not previously cited in prior application Serial No. , filed on , and are provided herewith.

7. ☒ This is a Supplemental Information Disclosure Statement. (Check Item 7a)

7a. ☒ This Supplemental Information Disclosure Statement under 37 C.F.R. §1.97(f) supplements the Information Disclosure Statement filed on April 29, 2009.

8. ☐ In accordance with 37 C.F.R. §1.98, a concise explanation of what is presently understood to be the relevance of each non-English language publication is:

*( Check Item 8a, 8b, or 8c)*

8a. ☐ Satisfied because all non-English language publications were cited on the enclosed English language copy of the PCT International Search Report or the search report from a counterpart foreign application indicating the degree of relevance found by the foreign office.

8b. ☐ Set forth in the application.

8c. ☐ Enclosed as an attachment hereto.

9. ☒ The Commissioner is authorized to charge any additional fee required or credit any overpayment for this Information Disclosure Statement and/or Petition to Jones Day Deposit Account No. 50-3013.

10. ☒ No admission is made that the information cited in this Statement is, or is considered to be, material to patentability and no representation is made that a search has been made (other than a search report of a foreign counterpart application or PCT International Search Report if submitted herewith). 37 C.F.R. §§1.97(g) and (h).

Respectfully submitted,

Date: November 20, 2009

52,042 (Reg. No.)

Yeahsil Moon
JONES DAY
222 East 41st Street
New York, New York 10017-6702
(212) 326-3939

# LIST OF REFERENCES CITED BY APPLICANT

**(Use several sheets if necessary)**

| | |
|---|---|
| **Application Number** | 10/438,213 |
| **Filing Date** | May 15, 2003 |
| **First Named Inventor** | Jerome B. Zeldis |
| **Art Unit** | 1612 |
| **Examiner Name** | Chris E. Simmons |
| **Attorney Docket No.** | 9516-074-999 |

## U.S. PATENT DOCUMENTS

| *Examiner Initials | Cite No. | Document Number – Kind Code | Publication Date mm/dd/yyyy | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | A02 | | | | |
| | A03 | | | | |

## FOREIGN PATENT DOCUMENTS

| *Examiner Initials | Cite No. | Foreign Patent Document Country Code, Number, Kind Code (if known) | Publication Date mm/dd/yyyy | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear | T |
|---|---|---|---|---|---|---|
| | B02 | | | | | |
| | B03 | | | | | |

## NON PATENT LITERATURE DOCUMENTS

| *Examiner Initials | Cite No. | Include name of the author (in CAPITAL LETTERS), (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T |
|---|---|---|---|
| | C206 | Meregalli *et al.*, "High-dose dexamethasone as first line therapy of multiple myeloma?", *Recenti Progressi in Medicina*, 1998, 89(1):18-20 | |
| | C207 | Copy of Official Action in corresponding Canadian Application No. 2,476,983 | |

| EXAMINER SIGNATURE | DATE CONSIDERED |
|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| Application of: Jerome B. Zeldis | Continuation No.: 4802 |
| Serial No.: 10/438,213 | Group Art Unit: 1612 |
| Filed: May 15, 2003 | Examiner: Simmons, Chris E. |
| For: METHODS FOR TREATMENT OF MULTIPLE MYELOMA USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE (AS AMENDED) | Attorney Docket No.: 9516-074-999 (CAM: 501872-999073) |

**AMENDMENT, RESPONSE AND REQUEST FOR CONTINUED EXAMINATION**

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to Final Action dated September 9, 2009, Applicant submits the following amendment and remarks for the consideration by the Examiner and entry into the record of the above-captioned application. Submitted herewith are Request for Continued Examination with the required fee, Supplemental Information Disclosure Statement with fee, and Petition for extension of term from December 9, 2009 to and including March 9, 2010 with fee.

**Amendments to the Claims** are reflected in the listing of the claims that begins on page 2 of this paper.

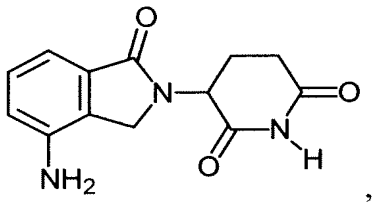
**Remarks** begin on page 5 of this paper.

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of the Claims:**

Claims 1-23. (canceled)

24. (currently amended) A method of treating multiple myeloma, which comprises cyclically administering to a patient having multiple myeloma about 5 to about 50 mg per day of a compound of the formula:



or a pharmaceutically acceptable salt ~~or stereoisomer~~ thereof, and a therapeutically effective amount of dexamethasone.

25. (canceled)

26. (previously presented) The method of claim 24, wherein the multiple myeloma is smoldering myeloma, indolent myeloma, chemotherapy responsive multiple myeloma, refractory myeloma, relapsed myeloma, or relapsed and refractory Dune-Salmon stage III multiple myeloma.

27-28. (canceled)

29. (previously presented) The method of claim 24, wherein the compound is a pharmaceutically acceptable salt.

30-56. (canceled)

57. (previously presented) The method of claim 24, wherein the multiple myeloma is relapsed, refractory or resistant to conventional therapy.

58. (previously presented) The method of claim 24, wherein the compound and dexamethasone are administered orally.

59. (previously presented) The method of claim 58, wherein the compound is administered in the form of a capsule or tablet.

60. (previously presented) The method of claim 24, wherein the compound is administered in an amount of from about 10 to about 25 mg per day.

61. (previously presented) The method of claim 24, wherein the compound is administered in an amount of about 5, 10, 20, 25, 30, or 50 mg per day.

62. (previously presented) The method of claim 24, wherein the compound is administered in an amount of from about 5 mg per day to about 25 mg per day.

63. (previously presented) The method of claim 60, wherein the compound is administered in an amount of about 25 mg per day.

64. (canceled)

65. (previously presented) The method of claim 24, wherein one cycle comprises four to six weeks.

66. (previously presented) The method of claim 24, wherein one cycle comprises the administration of the compound for 21 days followed by seven days rest.

67. (previously presented) The method of claim 24, wherein the compound is administered for four to twenty-four weeks with one to six weeks of rest.

68. (currently amended) The method of claim 24, wherein the compound is administered in an amount of from about 5 to about 25 mg per day for 21 days every 28 days ~~for sixteen to twenty-four weeks~~.

69. (currently amended) The method of claim 24, wherein the compound is administered in an amount of about 25 mg per day for 21 days followed by seven days rest in a 28 day cycle; and dexamethasone is administered in an amount of about 40 mg ~~once daily on Days 1 to 4, 9 to 12, and 17 to 20 of each cycle for first 4 cycles, and after the first 4 cycles dexamethasone is administered in an amount of about 40 mg once daily on Days 1 to 4 of each cycle~~.

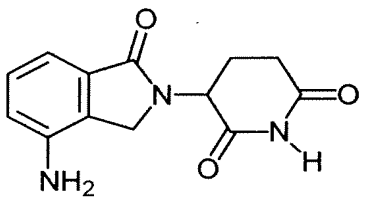
70. (currently amended) The method of claim 24, wherein the compound is administered in an amount of about 25 mg per day and dexamethasone is administered in an amount of about 40 mg per day on days 1 to 4 ~~every four to six weeks~~.

71. (previously presented) The method of claim 24, wherein the compound is administered in an amount of 5 mg per day.

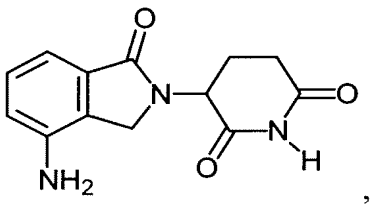
72. (previously presented) The method of claim 60, wherein the compound is administered in an amount of 10 mg per day.

73. (previously presented) The method of claim 24, wherein the compound is administered in a capsule of 5 mg, 10 mg, 15 mg or 25 mg.

74. (previously presented) The method of claim 24, wherein the compound is



75. (currently amended) A method of treating multiple myeloma, which comprises administering, on a 28 day cycle, to a patient having multiple myeloma: (a) about 25 mg per day of a compound of the formula:



or a pharmaceutically acceptable salt ~~or stereoisomer~~ thereof for 21 consecutive days followed by seven consecutive days of rest from administration of ~~this~~ said compound, and; (b) about 40 mg per day of dexamethasone on days 1-4 every 28 days.

76. (canceled)

77. (previously presented) The method of claim 24, wherein the compound is administered in an amount of about 15 mg twice a day.

78. (canceled)

79. (previously presented) The method of claim 24, which further comprises administering a therapeutically effective amount of melphalan.

80. (previously presented) The method of claim 73, wherein the capsule comprises the compound, lactose anhydrous, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

81. (canceled)

## REMARKS

### I. Amendments to the Claims

Claims 1-23, 25, 27, 28, 30, 34-37, 43-56, 64, and 76 were previously canceled without prejudice. Claims 31-33, 38-42, 78 and 81 have been canceled without prejudice in this response. Applicant reserves the right to prosecute the subject matter of any canceled claims in one or more continuation, continuation-in-part, or divisional applications.

Claims 24, 68-70 and 75 have been amended to clearly define the subject matter of the invention. No new matter has been added.

Claims 24, 26, 29, 57-63, 65-75, 77, and 79-80 are pending. Applicant respectfully submits that the pending claims are allowable for the following reasons.

### II. Summary of the Invention

The claimed invention relates, *inter alia*, to a very specific method of treating multiple myeloma by cyclically administering specific amounts (about 5 to 50 mg/day) of a specific compound known as "lenalidomide" or (3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione), and a therapeutically effective amount of dexamethasone. This specific method relates to an FDA approved use of lenalidomide (product named Revlimid®). (Exhibit 1). This method has resulted in one of the newest and most effective treatments available for multiple myeloma. Indeed, since the approval of lenalidomide for multiple myeloma in 2006, the sales of the drug have increased from $320.6 Million in 2006 to $1.71 Billion in 2009.

### III. Response to Rejections

#### 1. The PTO Has Made Numerous Factual Errors

First, Applicant points out that the Patent Office has made numerous errors of fact in its obviousness rejections. Once these errors are corrected, the § 103 rejections must be withdrawn, as discussed herein. Second, the reasoning applied in the obviousness rejections are inconsistent at best, that is, the Patent Office changes the logic or the factual basis in each rejection. Third, the Patent Office has summarily (and improperly) rejected the clear evidence of unexpected results over the cited art, which evidence was submitted by way of declaration and peer-reviewed third party publications. Indeed, the Examiner has even dismissed the commercial success of the claimed method by making the conclusory statement that there is "no nexus" between this commercial success and the claimed invention despite the fact that the claimed method covers an FDA approved indication.

Applicant points all this out before its detailed argument so that the Patent Office may carefully consider these errors and conduct a proper examination of the record.

**2. The Finality of the Action Is Improper**

On February 27, 2009, Applicant filed Response to Office Action of August 6, 2008, further to Examiner interview held on February 17, 2009 and to a response filed on October 28, 2008. Then, a March 27, 2009 Office Communication issued and stated that all the prior rejections ***were withdrawn*** (see page 2 of the Office Communication).

However, the March 27, 2009 Office Communication requested Applicant to provide information regarding the transfer of Celgene compounds to the authors of Davies *et al.* ( "Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma," *Blood*, 2001;98:210-216), including the identity of the compounds shipped, and information indicating what particular compounds were designated "IMID1, IMID2 and IMID3" by Celgene prior to the shipment to the authors of Davies *et al.*

In complying to the request, Applicant filed a response on May 20, 2009, submitting communications between Celgene Corporation and the authors of Davies *et al.* as Exhibits 1 to 6 (see Response and Exhibits filed).

Because Applicant complied with the request of the March 27, 2009 Office Communication and all prior rejections were withdrawn, the Patent Office should have allowed all the pending claims. Contrary to March 27, 2009 Office Communication, the Patent Office issued the current Final Action on September 9, 2009, allegedly based on Response filed February 27, 2009 (see page 2 of the Final Action).

The Office alleges that Applicant's amendment necessitated the new ground of rejection and made this action final (page 15 of the Final Action). However, the February 27, 2009 and May 20, 2009 Responses do not make amendments to the claims or to the specification. The February 27, 2009 Response includes previously presented claims only. Therefore, this Final Action is improper.

Furthermore, the Final Action states that "Applicant's responses on April 29, 2009 and May 30, 2009 to the Request for Information filed March 27, 2009 are acknowledged" (see page 2 of the Final Action). There were no responses filed on these dates.

In view of the foregoing, the current Final Action was improperly issued. Applicant respectfully requests at a minimum that the finality be withdrawn and that the fee for the RCE be refunded.

### 3. The Unexpected Results Evidence Must be Considered

The Office alleges that the publications previously submitted do not support unexpected results of the claimed invention (pages 9-11 of the Final Action). At a personal interview that was held on February 17, 2009 with Supervisory Patent Examiner Brandon Fetterolf, and Patent Examiner Chris E. Simmons, the publications were discussed in detail to support unexpected results of the claimed invention. The Examiners agreed that unexpected results of the claimed invention can overcome the § 103 rejections, and that Applicant's arguments appear to support Applicant's position in the § 103 rejections. See, page 6 of Response filed on February 27, 2009. The record is replete with evidence of unexpected results from publications, declaration and commercial success. Yet, all such evidence is summarily dismissed or ignored by the examiner. Proper consideration of the evidence and facts of record is respectfully requested.

With that said, Applicant now turns to the substance of the rejections.

### 4. The Rejection Under 35 U.S.C. §112 Should be Withdrawn

The Office rejected claim 81 as new matter. (Final Action, page 2). Without acquiescing to the rejection and solely to promote allowance of this case, claim 81 has been canceled. Thus, the rejection of the claim is now moot and should be withdrawn.

### 5. The Claimed Invention is Not *Prima Facie* Obvious

#### The rejection over the combination of '517 Patent, Davies and Kyle

Claims 24, 26, 29, 31-33, 38-42, 57-63, 65-75, and 77-81 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,635,517 ("'517 Patent") in view of Davies *et al.* (*Blood*, 2001, "Davies"), the combination taken in view of Kyle *et al.* (*Semin. Oncol.*, 2001, "Kyle"). (pages 3-6 of the Final Action). Applicant respectfully traverses the rejection.[1]

The Office alleges that the primary reference discloses, in the abstract, the treatment of multiple myeloma with thalidomide and dexamethasone (Page 3 of the Final Action). The Office also alleges that the tertiary reference discloses that the thalidomide ("Thal") analogue, LEN (lenalidomide) is effective in reducing TNF-α levels and that decreasing TNF-α levels constitutes a valuable therapeutic strategy for treatments of many diseases such as cancer. (Final Action, page 4).[2]

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[1] Many of the claims have been canceled, thus rendering the rejections moot as to those claims. The rejections as applied to the pending claims are discussed.

[2] The Office's designations of the references are vague and ambiguous throughout the Office Action, as to whether it refers the primary reference to the first cited '517 Patent or the third cited Kyle, and whether it

Specifically, the Office alleges that "one of ordinary skilled in the art would have been motivated by the reasonable expectation that the thalidomide analogue, LEN, which is effective in decreasing TNF-α as disclosed in the tertiary reference, would also be effective in the treatment of multiple myeloma, since the decrease in TNF-α provided the rationale for treating many diseases with Thal as disclosed in the secondary reference including cancers, and more particularly, the cyclical treatment of multiple myeloma as disclosed in the primary reference." Page 5 of the Action. Applicant disagrees.

As discussed in detail below, Applicant respectfully submits that the cited references would not have provided any reason to specifically select the combination of the specific drugs in specific amounts for treating the particular disease multiple myeloma, much less the claimed cyclic therapy using the combination.

Kyle appears to be a review article that discusses previous trials using thalidomide alone in treating refractory multiple myeloma, and thalidomide plus dexamethasone as first-line therapy in treating multiple myeloma. On page 586, last paragraph to page 587, first paragraph, Kyle concludes that thalidomide is a useful agent for treating refractory multiple myeloma since approximately one third of patients will obtain an objective response. However, patients remain refractory to thalidomide, and according to Kyle, some of those refractory patients may respond to thalidomide plus dexamethasone:

> The addition of dexamethasone to thalidomide may produce a response in patients who are refractory to thalidomide. [Emphasis added.]

Thus, Kyle concludes, at best, that thalidomide may be useful in the treatment of multiple myeloma. The reference does not state, as the PTO seems to suggest, that the thalidomide plus dexamethasone combination is better than thalidomide alone. For example, the response rate of using thalidomide alone in retractory multiple myeloma reported in a Cheng study is 78% (page 585, Table 2), while the response rate of the combination of thalidomide with dexamethasone is 77% (page 586, Column 1). That is, no difference by the addition of dexamethasone is reported. In sum, Kyle does not direct the skilled person to use a combination of thalidomide with dexamethasone in the treatment of multiple myeloma. The PTO has missed this fact.

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refers the tertiary reference to the '517 Patent or Kyle. Applicant makes several assumptions in deciding to which reference the PTO refers. These are spelled out in the response. For this rejection, in view of the page numbers of the primary reference and column numbers of the tertiary reference that are mentioned in the Final Action, Applicant assumes that the PTO refers Kyle as the primary reference, Davies as the secondary reference, and '517 Patent as the tertiary reference for this rejection.

The PTO recognizes that Kyle does not teach the use of lenalidomide or 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione for treating multiple myeloma (Page 3 of Final Action). Indeed, Kyle does not mention lenalidomide, even though according to the PTO analogues of Thal were well known in 2001 as being more potent TNF-alpha inhibitors.[3]

In Applicant's view, Kyle clearly teaches away (1) from the selection of the recited compound, (2) from combining it with dexamethasone, and (3) from using the doses recited by the claims. The PTO improperly ignores all these facts and fails to recognize such facts teach away from the claimed invention in several material respects. Any one of these would be sufficient alone to rebut a *prima facie* case of obviousness based upon Kyle. *In re Peterson*, 315 F.3d 1325, 1331 (Fed. Cir. 2003).

Nevertheless, the PTO alleges that Kyle does not teach away and that a skilled artisan would reasonably expect the successful treatment of multiple myeloma using a structurally similar analog of a compound known to treat multiple myeloma (*e.g.*, thalidomide), especially since both are known to decrease TNF-α (Final Action, page 9). Applicant respectfully disagrees.

The Office's "structural similarly" premise is not consistent with the current standard of obviousness. As the Federal Circuit made clear in *Takeda* and *Eisai*, allegations of structural similarity alone are insufficient to support the obviousness of a chemical modification. *Eisai Co., Ltd. v. Dr. Reddy's Laboratories, Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008); *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361, *cert denied*, 128 S. Ct. 1739 (2008). Instead, "it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound.") (emphasis added). *Takeda*, 492 F.3d at 1357. Further, the mere existence of a common core structure is not enough to render a modification obvious. *Eisai*, 533 F.3d at 1359; *Takeda*, 492 F.3d at 1361. Thus, it is not proper for the Office to rely on the "structurally similarity" to support the obviousness of using lenalidomide instead of thalidomide in the claimed method. Under *Takeda* and *Eisai*, the Office must establish that there would have been a reason for, and reasonable expectation of success for the claimed methods using the recited compound.

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[3] Further, Kyle does not disclose or suggest the use of the specific doses (5 to 50 mg/day) of lenalidomide, much less cyclically administering it with dexamethasone for treating multiple myeloma as recited in the instant claims. And, the doses (200 to 800 mg/d) used in Kyle are much higher than those recited in the instant claims (5 to 50 mg/day).

The Office fails to adequately explain why a person of ordinary skill in the art would have had a reason to specifically use the instant compound for treating multiple myeloma, and have a reasonable expectation of success in doing so.

To the extent the PTO relies on TNF-α inhibition as the basis, the PTO is factually wrong. Indeed, a person of ordinary skill in the art as of May or November 2002 would have had *no* motivation to choose more potent TNF-α inhibitors in treating multiple myeloma based on the cited references, because decreasing TNF-α was not considered as motivating factor in multiple myeloma studies reported in Kyle, much less Davies. For example, Kyle discloses that Singhal, *et al.* studied the use of thalidomide in the treatment of multiple myeloma and that thalidomide was used because of its anti-angiogenesis properties (see page 584, first column, last paragraph to second column, first paragraph). Further, Davies studied immunomodulatory effects (*e.g.*, natural killer cell cytotoxicity) of thalidomide and its derivatives in multiple myeloma. More importantly, Applicants submitted several publications showing that potent known TNF-α inhibitors failed in treating multiple myeloma (see Kast and Tsimberdou submitted herewith). For example, Enbrel® is a well known TNF-α antagonist. *See* Tsimberdou, page 375. Ten patients with refractory multiple myeloma were treated with Enbrel®. Enbrel® did not have anti-myleoma activity. *Id.* Also, see Kast. Thus, not all TNF-α inhibitors treat multiple myeloma. Therefore, the Office cannot rely on the cited art to support the current rejection. For this additional reason the rejection fails.

Next, the Office alleges that the secondary reference teaches that thalidomide and its IMiDs® analogues can act directly on multiple myeloma cells, and that new analogues are 50,000 times more potent than thalidomide in inhibiting TNF-α. (Pages 3-5 of Final Action). The Office's reliance on the secondary reference (Davies) does not cure the defects of the primary reference.

First, Davies explicitly states that the rational for the use of thalidomide in multiple myeloma was anti-angiogenesis, not TNF-α. *See* Davies, page 210, abstract ("The angiogenic activity of thalidomide, coupled with an increase in bone marrow angiogenesis in multiple myeloma, provided the rational for the use of thalidomide in multiple myeloma"). The PTO has simply failed to provide any references that suggest the use of the recited compound as an anti-angiogenesis agent like thalidomide. Moreover, irrespective of mechanisms, there is no suggestion in the cited art that the instant compound is effective to treat multiple myeloma and no suggestion to combine it with dexamethasone. Davies merely discloses that the compounds studied are thalidomide, and 3 other IMiDs® or

immunomodulatory compounds (IMiD1, IMiD2 and IMiD3). [4] *See*, page 212. Without identifying thalidomide analogs by their chemical structures or chemical names, Davies used the general terms, IMiD1, IMiD2, and IMiD3 to identify the compounds.

As evidenced by Response and Exhibits submitted on May 20, 2009, Dr. SCHAFER's Declaration and publications submitted on March 27, 2008, Celgene Corporation used the general terms to designate different compounds at different times in different publications, in order not to reveal the structures of any specific IMiDs® compounds. The Office admits that the secondary reference does not teach LEN (lenalidomide) (page 4 of Final Action). Thus, Davies would not lead one skilled in the art to select the instant compound.

Next, the Office alleges that "one of ordinary skilled in the art would have been motivated by the reasonable expectation that the thalidomide analogue, LEN, would also be effective in the treatment of multiple myeloma, since the decrease in TNF-α provided the rationale for treating many diseases with Thal as disclosed in the secondary reference including cancers" (page 5 of Final Action). Again, Davies did ***not*** study TNF-α activity. Instead, Davies studied other mechanisms including immunomodulatory effects and reported on NK-cell-mediated lysis of multiple myeloma cell lines and patient cells by the tested compounds (pages 213-216). In addition, Davies does not teach or suggest that lenalidomide is more effective than thalidomide in the treatment of multiple myeloma. There would be no basis in Davies to select one compound over the other. Thus, the PTO's reliance on Davies is misplaced and the rationale for the rejection is simply factually incorrect.

As described in Kyle and Davies, and explained above, TNF-α inhibition is not what they discuss as an important factor in studying the compounds in multiple myeloma. Indeed, they state that multiple myeloma involves many complex mechanisms of actions. Since 2002, many mechanisms have been proposed as the basis for the treatment of multiple myeloma. For example, see Palumbo (*Cancer Treatment Reviews*, 34, 283-91, 2008). Palumbo explains that antitumor activity of lenalidomide against multiple myeloma includes inducing apoptosis, decreasing the binding of multiple myeloma cells to bone marrow stromal cells, inhibiting IL-6 and VEGF, enhancing dexamethasone cytotoxicity, stimulating host anti- multiple myeloma natural killer cell immunity, inhibiting osteoclast

[4] Applicant respectfully submits that IMiDs® refers to Celgene Corporation's registered trademark for its proprietary immunomodulatory compounds.

differentiation, and direct antiproliferative effects on multiple myeloma cell lines. (Page 284 and Figure 1).

Thus, the cited art does not provide a rationale for treating multiple myeloma based on TNF-α activity, and it would not have been obvious to use the recited compound with dexamethasone for treating multiple myeloma as claimed.

The claimed method requires at least: (1) using the specific amounts (5 to 50 mg/day) of the recited compound for treating multiple myeloma, (2) in combination with dexamethasone, and (3) by cyclically administering them in particular dosing regimens. Applicant respectfully points out that the PTO bears the burden of establishing a case of *prima facie* obviousness against the claims as a whole. That is, all the claim elements must be considered in a 103 rejection. Kyle plus Davies simply fails to do so.

As to the tertiary reference, the Office alleges that it discloses lenalidomide is an effective compound in reducing TNF-α levels (claims 1 and 10), and that decreasing TNF-α levels constitutes a valuable therapeutic strategy for the treatments of many inflammatory, infectious, immunological or malignant diseases such as cancer. (Final Action, page 4). The flaw in relying on TNF-α in Kyle and Davies has been discussed. Applicant has shown why TNF-α is not the issue in these cited references.

The Office also admits that that the tertiary reference does not teach treating multiple myeloma. (page 5 of the Action). The law requires a motivation to select the references and to combine them in the particular claimed manner to reach the claimed invention. *Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc.*, 471 F.3d 1369, 1379 (Fed. Cir. 2006). The Examiner has provided no specific source of motivation to combine the teachings of the three references in the particular claimed manner. Clearly, TNF-α is not a proper basis.

Further, even if the cited references were combined as the PTO alleges, the combination would not have provided the requisite expectation of success. Such is required to establish a *prima facie* case of obviousness. *See e.g., PharmaStem* at 1360 (Fed. Cir. 2007). When the cited references are combined, one skilled in the art is merely taught that thalidomide may be used for treating multiple myeloma or that certain unidentified immunomodulatory compounds can be explored further. The combination of references would not have provided any indication to combine a compound other than thalidomide with dexamethasone for treating multiple myeloma, much less specific amounts (5 to 50 mg/day) of the recited compound combined with dexamethasone using particular cyclic

dosing regimens. Because the Office has not demonstrated such, the claimed invention is not obvious by the combination of the cited references.

In view of the foregoing, a *prima facie* case of obviousness has not been established and the rejection under 35 U.S.C. § 103(a) be withdrawn.

**The rejection over the combination of '517 Patent, Davies and '554 Patent**

Claims 24, 26, 29, 31-33, 38-42, 57-63, 65-75, and 77-81 are rejected as being unpatentable over the '517 Patent, Davies, the combination taken further in view of U.S. Patent No. 6,555,554 ("'554 Patent"). (Pages 6-7 of the Final Action). Applicant respectfully traverses the rejection.

The Office repeated the same allegation that "one of ordinary skilled in the art would have been motivated by the reasonable expectation that the thalidomide analogue, LEN, which is effective in decreasing TNF-α as disclosed in the tertiary reference would also be effective in the treatment of multiple myeloma, since the decrease in TNF-α provided the rationale for treating many diseases with Thal as disclosed in the secondary reference including cancers, and more particularly, the cyclical treatment of multiple myeloma as disclosed in the primary reference." Page 6 of the Action. Applicant disagrees.

Applicant assumes that the Examiner refers to the '517 Patent as the primary reference, Davies as the secondary reference, and the '554 Patent as the tertiary reference. However, none of the references disclose or suggest the cyclical treatment of multiple myeloma, as the examiner alleges is disclosed in the primary reference. It appears that without proper analyses of the cited references, the examiner simply copied the same allegation from page 5 of the Final Action based on the '517 Patent in view of Davies, the combination taken in view of Kyle. [5]

As discussed above, the secondary reference does not disclose the instant compound and does not focus on or study TNF-α activity. Also, Applicant has shown that TNF inhibitors failed against multiple myeloma (see Kast and Tsimberdou). Further, methods of actions of the instant compound and multiple myeloma involve more mechanisms than TNF-α (see Palumbo, page 284). Thus, the secondary reference does not provide the rationale for treating multiple myeloma based on TNF-α activity.

The '554 Patent does not cure the lack of teaching or suggestion of the claimed methods. The Office alleges that "the tertiary reference discloses a composition comprising

[5] Kyle was not cited as a reference in this rejection; however, page 7 of the Final Action refers to page 587 of the primary reference in alleging that it would have been obvious to adjust the amount of the drug. There is no page 587 in any of the references cited in this rejection.

a therapeutic agent and 1 to 100 mg of LEN to reduce TNF-α and to improve oncogenic or cancerous condition." (Final Action, page 6). Applicant does not dispute this disclosure. However, without using improper hindsight, it does not cure the deficiency of the '517 Patent or Davies (or Kyle), as the record shows not all TNF-α inhibitors work in treating multiple myeloma and many elements of the claimed method are simply missing from even a combination of the references. Therefore, a *prima facie* case of obviousness has not been established and the rejection under 35 U.S.C. § 103(a) be withdrawn.

**The rejection over the combination of '517 Patent, Davies and '230 Patent**

Claims 24, 26, 29, 31-33, 38-42, 57-63, 65-75, and 77-81 are rejected under 35 U.S.C. § 103(a) as being unpatentable over the '517 Patent, Davies, the combination taken further in view of U.S. Patent No. 6,281,230 ("'230 Patent"). (Pages 7-8 of the Final Action). Applicant respectfully traverses the rejection.

Again, the Office repeated the same allegation that one of ordinary skilled in the art would have been motivated by the reasonable expectation that lenalidomide effective in decreasing TNF-α would also be effective in the treatment of multiple myeloma, since the decrease in TNF-α of the secondary reference provided the rationale for treating cancers, and the primary reference discloses the cyclical treatment of multiple myeloma. [6] Page 7-8 of the Action. Applicant disagrees.

The '517 Patent and Davies have been discussed above. The '230 Patent is the same family as the '517 Patent, and adds nothing to change the errors in the rejections already pointed out. Therefore, for the same reasons as discussed above, a *prima facie* case of obviousness has not been established and the rejection under 35 U.S.C. § 103(a) be withdrawn.

**Unexpected Results Support the Nonobviousness of the Instant Claims**

Further, even assuming, *arguendo*, a *prima facie* case of obviousness is established by the cited references in combination, Applicant provided evidence of unexpected results of the claimed method sufficient to rebut a *prima facie* case of obviousness. *In re May*, 574 F.2d 1082, 1094 (C.C.P.A. 1978); *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987); *Ortho-Mcneil Pharmaceutical v. Mylan Laboratories*, 348 F.Supp.2d 713, 755 (N.D.W.Va. 2004); and *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991).

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[6] Kyle was not cited as a reference in this rejection; however, page 8 of the Final Action refers to page 587 of the primary reference in alleging that it would have been obvious to adjust the amount of the drug. There is no page 587 in any of the references cited in this rejection. Applicant assumes that the Office refers the '517 Patent as the primary reference, Davies as the secondary reference, and the '230 Patent as the tertiary reference.

The Examiner is required to consider all rebuttal evidence including unexpected results submitted by Applicant. *See In re Sullivan*, 498 F.3d 1345, 1351 (Fed. Cir. 2007), citing *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1369 (Fed. Cir. 2007); MPEP §2145. The previously presented publications support unexpected results that are more than sufficient to rebut any alleged *prima facie* case of obviousness.

**Rajkumar demonstrates Unexpected Results**

The Office alleges that although applicant asserts unexpected results of the combination of LEN/Dex in Rajkumar, (1) there is no Rajkumar cited in IDS, (2) Corral demonstrates lenalidomide is more potent than thalidomide in decreasing TNF-alpha, (3) thus multiple myeloma would be treated more effectively than thalidomide, and (4) it would be expected to have lower toxic effects since less LEN can be used than the less potent thalidomide. (Pages 9-10 of Final Action). Applicant disagrees.

First , Rajkumar was cited in IDS as reference C153 and the Examiner signed the IDS list on December 19, 2007. Another copy of Rajkumar is submitted herewith as Exhibit 2.

Rajkumar reports that the combination of lenalidomide plus dexamethasone resulted in an overall ***91%*** objective response rate in treating multiple myeloma patients (*see* abstract). Indeed, this response rate is much higher than those of single agent thalidomide therapy disclosed in Kyle (response rate %: 32, 25, 24, 43, 65, 25, 54, 27, 70, 78, and 50 %). See page 585, column 2, Table 1 of Kyle.

Also, 91% objective response rate of Rajkumar is much higher than 77 % response rate of thalidomide and dexamethasone combination therapy disclosed in Kyle (page 586, column 1). That is, Rajkumar shows unexpected results over the very art on which the PTO relies. Rajkumar notes that the observed response rate compares favorably with that (Kyle) using Thal/Dex (Rajkumar, page 4053, column 1, lines 20-22).

It is also noted that response criteria of Rajkumar is higher than that of Kyle. In Kyle, for thalidomide and dexamethasone combination therapy, response was defined as a decrease in serum and urine monoclonal protein (M-protein) of 50% or greater (page 585, last line to page 586, first line). In Rajkumar, the objective partial response was defined as (1) at least 50% decrease in serum M-protein, (2) and a reduction in 24 hour urinary M-protein of at least *90%* or to less than 200 mg (page 4051, column 2, lines 1-3). In addition, in Rajkumar, there must be no increase in the number or size of lytic bone lesions or any other evidence of progressive disease by other parameters. (page 4051, column 2, lines 3-5). Further, in Rajkumar, in addition to the criteria required for partial response, the complete

response required complete disappearance of the M-protein in serum and urine. (page 4051, column 2, lines 5-8).

In view of the higher response criteria required in Rajkumar, overall 91% objective response rate of Rajkumar is unexpected over the response rates of thalidomide therapy and over those of thalidomide and dexamethasone combination therapy disclosed in Kyle, the cited art.

Rajkumar also reports that responses were observed even in patients in whom thalidomide had previously failed, and that lenalidomide/dexamethasone combination is a safer and more effective alternative to thalidomide/dexamethasone in newly diagnosed myeloma. Rajkumar at page 4050, column 2, lines 10-13.

Rajkumar further notes an additional unexpected result of lenalidomide/dexamethasone therapy, as compared to thalidomide/dexamethasone therapy, in terms of toxicities. Thalidomide/dexamethasone was found to have significant toxicities. For example, in reporting their thalidomide/dexamethasone studies, Kyle noted: "Major grade 3 or 4 toxicities [with Thal/Dex] included rash in three patients, and sedation, constipation, and myalgias in one patient each." (Kyle, page 586, column 1, lines 13-15). By contrast, lenalidomide/dexamethasone therapy exhibits surprisingly fewer toxicities. Rajkumar, for example, noted: "Unlike thalidomide, side effects such as constipation and neuropathy were uncommon and sedation was not seen; no patient developed grade III or higher neuropathy." (Rajkumar, page 4053, column 1, lines 25-27).

In view of the foregoing, Rajukumar clearly demonstrates unexpected results of the claimed therapy over the cited art using thalidomide or thalidomide plus dexamethasone for multiple myeloma.

Further, the PTO cannot rely on Corral to negate the unexpected results of Rajukumar, because (1) angiogenesis (not TNF-α inhibition) in the cited art provided motivating factor for treating multiple myeloma, (2) mechanisms of actions of multiple myeloma involve many mechanisms, and (3) certain TNF-alpha inhibitors failed against multiple myeloma. Thus, the PTO has erred in ignoring the unexpected results shown in Rajkumar, as lenalidomide plus dexamethasone therapy as claimed is significantly better than thalidomide or thalidomide plus dexamethasone of the cited art.

Furthermore, to further support the unexpected result, Applicant herewith presents Gay (*Blood*, 2010: 115, 1343-1350). [7] Gay did case-control analysis to compare the efficacy and toxicity of lenalidomide plus dexamethasone combination versus thalidomide plus dexamethasone combination for newly diagnosed multiple myeloma patients (page 1343). Gay reports that the study clearly demonstrated that lenalidomide plus dexamethasone is superior to thalidomide plus dexamethasone in treating multiple myeloma, in terms of response rates, survival, and toxicity (page 1349).

In sum, the submitted publications clearly demonstrate the unexpected results of the claimed invention over thalidomide therapy and thalidomide plus dexamethasone combination therapy disclosed in Kyle. The evidence is sufficient to rebut the alleged *prima facie* case of obviousness.

**Unexpected Results from Other Publications**

Next, the Office on page 10 of Final Action alleges that other references mentioned on page 10 of Response do not demonstrate unexpected results for the same reasons as Rajkumar, and none of the references mentioned in Response at page 11 demonstrate a proper side by side comparison of unexpected results. The PTO's reasons are incorrect.

First, the use of lenalidomide for the treatment of multiple myeloma is not disclosed or suggested in Kyle, Davies or any other cited art. Kyle is the only reference that reports on clinical results using thalidomide. Davies studied IMiDs® compounds in multiple myeloma cells and does not specify the structures of any IMiDs® compounds. The '517 patent refers to TNF-α inhibition unlike Davies or Kyle. Thus, the closest art relied upon by the PTO is Kyle, which the PTO alleges teaches thalidomide plus dexamethasone.[8] The unexpected results of the claimed invention over Kyle has been discussed above.

The publications mentioned on pages 10-11 of the Response filed February 27, 2009 further support unexpected results of the claimed invention. For example, Weber, *et al.* (*New England Journal of Medicine*, 357, 2133-42, 2007) reports that the claimed combination of lenalidomide plus dexamethasone had significant clinical activity in increasing response rate, time to progression and overall survival in patients with multiple

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[7] Applicant requests that the references submitted be made of record in the file history of the application and that the Examiner execute the 1449 Form enclosed. To further support the unexpected result, Applicant herewith presents Hideshima (*Theraputics and Clinincal Rick Management*, 2008: 4(1), 129-136), which discusses Rajkumar's results (page 134, column 1) and describes that lenalidomide with dexamethasone is one of the most promising novel treatment options. (page 131, column 2 and page 135, column 1).

[8] As discussed above, Applicant disputes the PTO's allegation.

myeloma, when compared to dexamethasone alone. It reports that the combination was superior even among patients treated previously with thalidomide. Weber at 2139-42.

Dimopoulos, *et al.* (*New England Journal of Medicine*, 357, 2123-32, 2007) reports that dexamethasone plus lenalidomide is more effective than either agent alone (lenalidomide or dexamethasone) in refractory multiple myeloma (page 2124). It notes that lenalidomide is less toxic and more potent than thalidomide, and that lenalidomide in combination with dexamethasone can be administered to patients previously treated with thalidomide without deterioration of thalidomide's side effects (pages 2124 and 2131).

Armoiry, *et al.* (*Journal of Clinical Pharmacy and Therapeutics*, 33, 219-26 2008) reports that lenalidomide, combined with dexamethasone, is superior to dexamethasone alone, in terms of time to progression, response rate and overall survival, in relapsed or refractory multiple myeloma patients (page 219). Armoiry reports that lenalidomide in combination with dexamethasone does not trigger the limiting toxicities of thalidomide. *Id.*

Gareth Morgan, *et al.* (Abstract, European Hematology Association, 13th Cong. June 12-15, 2008) describes that "the significantly better efficacy of Len+Dex" as compared to dexamethasone alone, and concludes that lenalidomide delivers significantly larger survival in this life-limiting orphan disease.

Therefore, all the submitted evidence demonstrates proper showing of unexpected results of the claimed invention over the cited art (thalidomide plus dexamethasone, dexamethasone, thalidomide or lenalidomide).

**Palumbo demonstrates Unexpected Results**

Final Action on page 11 alleges that (1) there was no data in Palumbo showing the 29% response was due to dexamethasone, (2) there was only a comparison of Len/Dex combination to Len alone, not comparison with dexamethasone alone, and (3) Palumbo is not considered unexpected results. Applicant disagrees.

Palumbo clearly demonstrates unexpected results of the claimed invention. Palumbo (*Cancer Treatment Reviews*, 2008, 34, 283-291) reports: "Combined with dexamethasone, oral lenalidomide has proved highly effective in patients whose disease has become resistant to conventional therapy." Palumbo at 283. Palumbo states that, "[i]n patients who failed to respond to lenalidomide monotherapy, after the addition of oral dexamethasone 29% responded." *Id.* at 285. Palumbo also states that "two phase III randomized clinical trials (MM-009 and MM-010) have demonstrated the superiority of lenalidomide plus dexamethasone, compared with dexamethasone alone". *Id.* Palumbo describes that the combination of lenalidomide plus dexamethasone, compared with

dexamethasone alone, delayed time to progression of disease, and improved overall response rate and median overall survival ($p < 0.001$) (page 285). Thus, Palumbo clearly evidences unexpected results of the claimed combination therapy.

Dimopolous (*Leukemia*, pages 1-6, 2009) agrees with Palumbo and reports that the combination of lenalidomide and dexamethasone significantly improved overall response (60.6 vs. 21.9%, $p < 0.001$), complete response rate (15.0 vs. 2.0%, $p < 0.001$), time to progression (median of 13.4 months vs. 4.6 months, $p < 0.001$), and duration of response (median of 15.8 months vs. 7 months, $p < 0.001$), compared to dexamethasone alone in patients with multiple myeloma. *See* page 1, column 1; and page 4, Table 2, a copy submitted herewith. Dimopolous concludes that the results confirm significant response outcomes and significant overall survival benefit with manageable toxicities (page 5, column 1). Dimopolous supports unexpected results of the claimed combination therapy.[9]

Applicant further presents Gandhi (*Current Cancer Drug Targets*, 2010, 10; 1-13) that discusses the synergy of lenalidomide plus dexamethasone in treating multiple myeloma. Gandhi reports that lenalidomide plus dexamethasone synergistically induced expression of the tumor suppressor genes in multiple myeloma cell lines and multiple myeloma patient cells, and that the combination activated caspases, and induced cell cycle arrest and apotosis.

In sum, these publications are sufficient to show that the claimed therapy of the recited compound and dexamethasone significantly increased response rate and survival rate, prolonged time to progression of disease, and reduced toxicity, when compared to thaldidomide/dexamethasone combination, or monotherapy of thaldidomide, lenalidomide or dexamethasone alone, in treating multiple myeloma. The publications also support that the claimed method overcame resistance to thalidomide therapy and conventional chemotherapy in treating multiple myeloma. This evidence as a whole supports unexpected results of the claimed invention. The PTO is invited to carefully review these publications as they are of record or submitted herewith.

For at least the reasons set forth above, Applicant respectfully submits that the instant claims are not obvious, and respectfully request that the rejections under 35 U.S.C. §103 be withdrawn.

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[9] Further, Applicant presents Wang (Blood, 2008, 112; 4445-4451), supporting the unexpected results of the claimed combination therapy in patients with multiple myeloma. Wang reports that lenalidomide plus dexamethasone led to higher overall response rate, longer time to progression, and progression-free survival, compared to dexamethasone alone. (page 4445; and page 4448, Table 3). Wang describes that lenalidomide plus dexamethasone was superior to dexamethasone alone. *Id.*

**Commercial Success Support the Nonobviousness of the Instant Claims**

The Final Action alleges that a sufficient case of commercial success has not been demonstrated and that there is no sufficient connection between the evidence of commercial success and the claimed invention (pages 11-12). Applicant disagrees.

Applicant presents herewith a copy of Press Release of Celgene Corporation, reporting Year 2009 Product Sales (Revlimid® net product sales increased 29 percent to $1.71 billion in 2009) as Exhibit 3. [10] The use of the recited compound in combination with dexamethasone to treat multiple myeloma has been approved in about fifty (50) countries, including in the U.S. in June 2006, in Europe in June 2007, and Australia in December 2007. The sales figures represent the sales of Revlimid® for treating multiple myeloma (in combination with dexamethasone) and for myelodysplastic syndrome (MDS), as these two indications were approved for Revlimid®. *See* Exhibit 4, the tables entitled US Revlimid® Revenue 2009 and ex-US Revlimid® 2009. The tables show that, by far, the greatest sales of Revlimid® are for the treatment of multiple myeloma, and the greatest number of patients treated are multiple myeloma patients (*e.g.*, in the 4$^{th}$ quarter of 2009, 90% of the patients in the US, and 99% of the patients in ex-US). Thus, the sales figures demonstrate the commercial success for the claimed invention of using lenalidomide (Revlimid®) in combination with dexamethasone for the treatment of multiple myeloma.

This commercial success alone supports non-obviousness of the claimed invention. *Pfizer Inc. v. Ranbaxy Labs. Ltd.*, 405 F.Supp.2d 495, 518 (D. Del. 2005), *aff'd & rev'd on other grounds*, 457 F.3d 1284 (Fed. Cir. 2006) (holding that secondary considerations, such as commercial success, support the nonobviousness of the claimed invention); *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 348 F.Supp.2d 713, 755-60 (N.D.W.V. 2004), *aff'd*, 161 Fed. App'x. 944 (Fed. Cir. 2005) (crediting evidence of other secondary considerations, including commercial success, as support for nonobviousness).

In view of the unexpected results and commercial success of the present invention, the presently claimed invention is not obvious. *In re May*, at 1094; *In re Chupp*, at 646; and *Ortho-Mcneil Pharmaceutical v. Mylan Laboratories*, at 755. Therefore, Applicant respectfully requests that the rejections under 35 U.S.C. § 103(a) be withdrawn.

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10 Applicant submitted on Feb. 27, 2009 and March 27, 2008 copies of Press Release, which report on REVLIMID® net product sales increased 71 percent to $1.325 billion in 2008, 141 Percent to $773.9 Million in 2007, compared to $320.6 Million in 2006.

## 6. The Double Patenting Rejections Should Be Withdrawn

Claims 24, 26, 29, 31-33, 38-42, 57-63, 65-75, and 77-81 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over (1) claims 18-26 of the '230 Patent in view of the '517 Patent and Davies; (2) claims 1-17 of the '554 Patent in view of the '517 Patent and Davies; (3) claims 1-7 of U.S. Patent No. 7,119,106 (the '106 Patent) in view of the '517 Patent and Davies; (4) claims 1-34 of U.S. Patent No. 7,189,740 (the '740 Patent) in view of the '517 Patent and Davies; and (5) claims 1-25 of U.S. Patent No. 7,393,862 (the '862 Patent) in view of the '517 Patent and Davies (page 12-15 of Final Action). Applicant respectfully traverses this rejection.

For the obviousness-type double patenting rejections, the Office stated the same reasons as for the rejections under 35 U.S.C. §103(a), by repeating the same phrases of pages 5-8 of Final Action. See pages 12-15 of Final Action. Applicant reiterates that the instant claims are not obvious over the cited Patents in view of the '517 Patent and Davies, for the reasons set forth above in responding to the rejections under 35 U.S.C. §103(a). The Examiner has not established a *prima facie* case for the same reasons as discussed above. Further, the obviousness-type double patenting rejections should be withdrawn in view of the submitted evidence for the unexpected results of the claimed invention.

Further, the claims of the '230 Patent recite methods of treating inflammation, inflammatory disease, autoimmune disease, an oncogenic or cancerous condition, using amino-substituted 1-oxo-2-(2,6-dioxopiperidin-3-yl) isoindolines. The '230 Patent does not disclose or suggest the claimed methods for treating multiple myeloma using the cyclic dosing regimen of about 5-50 mg/day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione and dexamethasone, as recited in the pending claims. The Examiner has made no *prima facie* case that the pending claims are obvious over the claims of the '230 Patent. Further, unexpected results of the claimed method have been established and the rejection should be withdrawn.

The claims of the '554 Patent recite pharmaceutical compositions comprising lenalidomide, in combination with a pharmaceutically suitable carrier, in an amount sufficient to reduce the level of TNFα, improve an oncogenic or cancerous condition, reduce inflammation, or improve autoimmune disease; and methods of reducing undesirable levels of TNFα using amino-substituted 1-oxo-2-(2,6-dioxopiperidin-3-yl) isoindolines.

The '554 Patent does not disclose or suggest the claimed methods of cyclically administering about 5-50 mg/day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione and dexamethasone for treating multiple myeloma, as recited in

the pending claims. The Examiner has made no *prima facie* case that the pending claims are obvious over the claims of the '554 Patent. Further, unexpected results of the claimed invention have been established and the rejection must be withdrawn.

The claims of the '106 Patent recite pharmaceutical compositions comprising an effective amount of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione or acid addition salt thereof, and a pharmaceutically acceptable carrier, diluent or expient. The '106 Patent does not disclose or suggest the claimed methods for treating multiple myeloma using about 5-50 mg/day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione and dexamethasone, as recited in the pending claims. The Examiner has made no *prima facie* case that the pending claims are obvious over the claims of the '106 Patent. Further, unexpected results of the claimed method have been established and the rejection should be withdrawn.

As to the '740 patent, Applicant submitted a terminal disclaimer in the '740 patent over the instant application, on June 23, 2006, in responding to obviousness-type double patenting rejection issued during the prosecution of the '740 patent over the instant application. In view of the terminal disclaimer, the rejection over the '740 patent is moot and should be withdrawn.

As to the '862 patent, Applicant submitted a terminal disclaimer in the '862 patent over the instant application, on Sep. 5, 2006, in responding to obviousness-type double patenting rejection issued during the prosecution of the '862 patent over the instant application. In view of the terminal disclaimer, the rejection over the '862 patent is moot and should be withdrawn.

Thus, all these rejections over the cited Patents under judicially created obviousness-type double patenting are moot and should be withdrawn.

## IV. Conclusion

In view of the foregoing, all the rejections of the claims should be withdrawn. Reconsideration, entry of the above amendment and remarks, and allowance of the pending claims are respectfully requested. Should the Examiner not agree that all claims are allowable, a personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application.

Respectfully submitted,

Date: March 9, 2010

Yeahsil Moon (Reg. No. 52,042)
For Anthony M. Insogna (Reg. No. 35,203)
**JONES DAY**
222 East 41st Street
New York, NY 10017
Tel. (212) 326-3778

**ELECTRONIC FILING**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| Application of: Jerome B. Zeldis | Continuation No.: 4802 |
| Serial No.: 10/438,213 | Group Art Unit: 1612 |
| Filed: May 15, 2003 | Examiner: Simmons, Chris E. |
| For: METHODS FOR TREATMENT OF MULTIPLE MYELOMA USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE (AS AMENDED) | Attorney Docket No.: 9516-074-999 (CAM: 501872-999073) |

**INFORMATION DISCLOSURE STATEMENT**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the duty of disclosure provisions of 37 C.F.R. §1.56, there is hereby provided certain information which the Examiner may consider material to the examination of the subject U.S. patent application. It is requested that the Examiner make this information of record if it is deemed material to the examination of the application.

1. Enclosures accompanying this Information Disclosure Statement are:

1a. ☒ A list of all patents, publications, applications, or other information submitted for consideration by the office.

1b. A legible copy of :

☒ Each publication or that portion which caused it to be listed on the PTO-1449;

☐ For each cited pending unpublished U.S. application, the application specification including the claims, and any drawing of the application, or portion of the application which caused it to be listed on the PTO-1449 including any claims directed to that portion that have been checked to be unavailable at the USPTO's private PAIR system;

☐ An English language copy of search report(s) from a counterpart foreign application or PCT International Search Report;

☐ Explanations of relevancy (ATTACHMENT 1(d), hereto) or English language abstracts of the non-English language publications;

☐ All other information or portion which caused it to be listed on the PTO-1449.

1c. ☐ Pursuant to 37 C.F.R. § 1.98(a)(2)(ii), copies of the cited U.S. patents and U.S. patent application publications are not submitted herewith unless required by the office.

1d. ☐ Pursuant to 1287 OG 163, copies of cited pending unpublished applications that are available at the USPTO's private PAIR system are not submitted herewith.

2. ☒ This Information Disclosure Statement is filed under 37 C.F.R. §1.97(b):

☐ Within three months of the filing date of a national application other than a continued prosecution application under §1.53(d);

☐ Within three months of the date of entry of the national stage as set forth in §1.491 in an international application;

☐ Before the mailing of the first Office action on the merits;

☒ Before the mailing of a first Office action after the filing of a request for continued examination under §1.114.

3. ☐ This Information Disclosure Statement is filed under 37 C.F.R. §1.97(c) after the period specified in 37 C.F.R §1.97(b), but before the mailing date of any of a final action under 37 C.F.R. §1.113, a notice of allowance under 37 C.F.R. §1.311 or an action that otherwise closes prosecution in the application.

*(Check either Item 3a or 3b)*

3a. ☐ The Certification Statement in Item 5 below is applicable. Accordingly, no fee is required.

3b. ☐ The $180.00 fee set forth in 37 C.F.R. §1.17(p) in accordance with 37 C.F.R. §1.97(c) is:

☐ enclosed.
☐ to be charged to Jones Day Deposit Account No. 50-3013.

*(Item 3b to be checked if any reference known for more than 3 months)*

4. ☐ This Information Disclosure Statement is filed under 37 C.F.R. §1.97(d) after the period specified in 37 C.F.R. §1.97(c), but on or before the date of payment of the issue fee.

The Certification Statement in Item 5 below is applicable.

The $180.00 fee set forth in 37 C.F.R. §1.17(p) is:
☐ enclosed.
☐ to be charged to Jones Day Deposit Account No. 50-3013.

5. ☐ Certification Statement (applicable if Item 3a or Item 4 is checked):

*(Check either Item 5a or 5b)*

5a. ☐ In accordance with 37 C.F.R. §1.97(e)(1), it is certified that each item of information contained in this Information Disclosure Statement was first cited in a communication from the Israeli patent office in a counterpart Israeli application not more than three months prior to the filing of this Information Disclosure Statement.

5b. ☐ Each item of information contained in this information disclosure statement was cited in a communication from a foreign patent office in a counterpart application, and the communication was not **received** by any individual designated in 37 C.F.R. §1.56(c) more than thirty days prior to the filing of this information disclosure statement.

5c. ☐ Pursuant to 37 C.F.R. §1.704(d), each item of information contained in this information disclosure statement was cited in a communication from a foreign patent office in a counterpart application, and the communication was not

**received** by any individual designated in 37 C.F.R. §1.56(c) more than thirty days prior to the filing of this information disclosure statement.

6. ☐ This application is a continuation application under 37 C.F.R. §1.53(b) or (d).

*(Check appropriate Items 6a, 6b and/or 6c)*

6a. ☐ A Petition to Withdraw from issue under 37 C.F.R. §1.313(b)(5) is concurrently filed herewith.

6b. ☐ Copies of publications listed on Form PTO-1449 from prior application Serial No. , filed on , of which this application claims priority under 35 U.S.C. §120, are not being submitted pursuant to 37 C.F.R. §1.98(d).

6c. ☐ Copies of the publications listed on Form PTO-1449 were not previously cited in prior application Serial No. , filed on , and are provided herewith.

7. ☒ This is a Supplemental Information Disclosure Statement. (Check Item 7a)

7a. ☒ This Supplemental Information Disclosure Statement under 37 C.F.R. §1.97(f) supplements the Information Disclosure Statement filed on March 9, 2010.

8. ☐ In accordance with 37 C.F.R. §1.98, a concise explanation of what is presently understood to be the relevance of each non-English language publication is:

*( Check Item 8a, 8b, or 8c)*

8a. ☐ Satisfied because all non-English language publications were cited on the enclosed English language copy of the PCT International Search Report or the search report from a counterpart foreign application indicating the degree of relevance found by the foreign office.

8b. ☐ Set forth in the application.

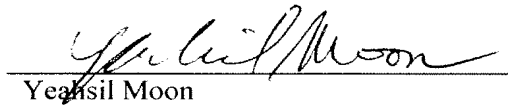
8c. ☐ Enclosed as an attachment hereto.

9. ☒ The Commissioner is authorized to charge any additional fee required or credit any overpayment for this Information Disclosure Statement and/or Petition to Jones Day Deposit Account No. 50-3013.

10. ☒ No admission is made that the information cited in this Statement is, or is considered to be, material to patentability and no representation is made that a search has been made (other than a search report of a foreign counterpart application or PCT International Search Report if submitted herewith). 37 C.F.R. §§1.97(g) and (h).

Respectfully submitted,

Date: June 8, 2010



52,042

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222 East 41st Street
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(212) 326-3939

# LIST OF REFERENCES CITED BY APPLICANT

(Use several sheets if necessary)

| | |
|---|---|
| **Application Number** | 10/438,213 |
| **Filing Date** | May 15, 2003 |
| **First Named Inventor** | Jerome B. Zeldis |
| **Art Unit** | 1612 |
| **Examiner Name** | Chris E. Simmons |
| **Attorney Docket No.** | 9516-074-999 |

## U.S. PATENT DOCUMENTS

| *Examiner Initials | Cite No. | Document Number – Kind Code | Publication Date mm/dd/yyyy | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
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## FOREIGN PATENT DOCUMENTS

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|---|---|---|---|---|---|---|
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## NON PATENT LITERATURE DOCUMENTS

| *Examiner Initials | Cite No. | Include name of the author (in CAPITAL LETTERS), (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T |
|---|---|---|---|
| | C229 | Richardson, P. *et al.*, "Thalidomide in multiple myeloma," *Biomed Pharmacother*, 2002, 56:115-28 | |
| | C230 | Swartz, G. *et al.*, "Pre-clinical evaluation of ENMD-0995: A thalidomide analog with activity against multiple myeloma and solid tumors," *Cell and Tumor Biology*, 2002, 43:181-182, Abstract# 910 | |
| | C231 | Mazucco, R., "Angiogenesis and Anti-angiogenesis Therapeutics," *IDrugs*, 2002, 5(4): 320-322 | |
| | C232 | Worker, C., "JP Morgan Hambrecht & Quist – 20th Annual Healthcare Conference," *IDrugs*, 5(2):113-116 | |
| | C233 | Treston, A. *et al.*, "Pre-Clinical Evaluation of a Thalidomide Analog with Activity Against Multiple Myeloma and Solid Tumors – ENMD-0995 (S-(-)-3-(3-amino-phthalimido)-glutarimide)," *Blood*, 2002, 100(11):816a, Abstract #3225 | |
| | C234 | Mazucco, R. and Williams, L., "Immunotherapy, chemoprevention and angiogenesis," *IDrugs*, 2002, 5(5):408-411 | |
| | C235 | Fernandes, P., "Anti-Cancer Drug Discovery and Development Summit," *IDrugs*, 2002, 5(8):757-764 | |



| EXAMINER SIGNATURE | DATE CONSIDERED |
|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/438,213 | 05/15/2003 | Jerome B. Zeldis | 9516-074-999 | 4802 |

84802 7590 08/03/2010

JONES DAY
222 E. 41ST. STREET
NEW YORK, NY 10017

| EXAMINER | |
|---|---|
| SIMMONS, CHRIS E | |
| ART UNIT | PAPER NUMBER |
| 1612 | |
| MAIL DATE | DELIVERY MODE |
| 08/03/2010 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/438,213 | ZELDIS, JEROME B. | |
| | Examiner | Art Unit | |
| | CHRIS E. SIMMONS | 1612 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *24,26,29,57-63,65-75,77,79 and 80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24,26,29,57-63,65-75,77,79 and 80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/20/2009, 03/09/2010, 06/08/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/09/2010 has been entered.

Applicants' arguments, filed 03/09/2010, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

### *Response to Arguments*

Applicant's arguments, see page 10, lines 7-11 and 26-31, filed 03/09/2010, with respect to the rejections of the claims under 35 USC § 103 have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, new grounds of rejections are made in view of the effects of certain cytokines on the growth and survival of MM cancer cells and the effects of Thal and Thal analogues such as LEN on these cytokines.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 24, 26, 29, 57-63, 65-75, 77, 79 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kyle et al. (cited in 12/31/2007 Office action) in view of Davies et al. (cited in 12/31/2007 Office action), the combination taken in view of Corral et al. (cited in 8/23/2005 IDS) as evidenced by Muller et al. (cited in 8/23/2005 IDS – C15).

Kyle et al. disclose methods for treating multiple myeloma (MM) by cyclically administering thalidomide (Thal) and dexamethasone. Thalidomide was administered in an initial dosage of 200 mg/d for 2 weeks and then increased as tolerated (in 200-mg

increments at 2-week intervals) to a maximum daily dose of 800 mg. Dexamethasone was given orally in a dosage of 40 mg/d on days 1 through 4, 9 through 12, and 17 through 20 in odd cycles and 40 mg/d on days 1 through 4 in even cycles at monthly intervals. Patients with smoldering, indolent and relapsed myeloma showed results for thalidomide treatment. The dosage amounts of Thal had to be adjusted in some patients after signs of toxicity appeared (see first paragraph on page 587). Table 2 at page 586 provides for potential strategies using thalidomide in MM treatment: Thalidomide may be used to treat MM in combination therapy with prednisone, vincristine, doxorubicin, melphalan, biological agents such as alpha-2-interferon. (See abstract). The addition of Dex to Thal may produce a response in patients who are refractory to Thal. Kyle et al. disclose Dex plus Thal produces an objective response in approximately ¾ of previously untreatable MM patients (page 587, first column, top paragraph). Kyle et al. do not expressly teach lenalidomide ("LEN").

Davies et al. discloses that Thal and Thal analogues induce a dose-dependent inhibition of proliferation in MM cell lines and patient MM cells resistant to conventional chemotherapy, and they add to the effect of Dex (See page 210, first column, lines 11-14). Davies et al. discloses that Thal and Thal analogues increase the production of IL-2 and INF-gamma. They suggest that Thal (200-800 mg/day; See page 211, column 2, third paragraph from bottom) and the analogues can treat MM by increasing the killing of the MM cancer cells by natural killer T cells ("NK cells") since the NK cells are modulated by IL-2 and INF-gamma (See page 210, second column, last sentence bridging to page 211, first column, first paragraph; also see page 216 column 1, lines 4-

6 and column 2, lines1-9 and last sentence). Davies et al disclose that Thal and the analogues may also treat MM by inhibiting the growth and survival of MM cells since Thal and the analogues abrogate the up-regulation of IL-6, a major growth factor and survival factor in MM (see page 215, lines 1-12). The analogues are more potent inducers of T-cell proliferation with IFN-gamma and IL-2 secretion (IFN-gamma and IL-2 being modulators of NK cells) and inhibitors of IL-6 secretion from PBMCs (IL-6 being a growth factor for MM cells) (see page 210, column 2, first paragraph, last sentence). The authors concluded that their results show that Thal and its analogues may not only be useful in the treatment of refractory/relapsed disease, but also be effective in the maintenance of minimal residual disease after transplantation by enhancing NK-cell–mediated anti–MM cell immunity (page 216, column 2, last sentence). Davies et al. do not expressly teach lenalidomide ("LEN") as a specific Thal analogue, cyclical treatment thereof, or a dose of 5-50 mg/day.

Corral et al. disclose that analogues of Thal were tested to find more potent agents with decreased teratogenic potential when compared to Thal (see page 383, column 2, first sentence, last paragraph). Corral et al. disclose that compound CI-B (i.e., structure 8a as evidenced at page 1627 of Muller et al., which is the claimed structure for LEN in claim 24; see Corral et al., page 381, column 1, last sentence of first full paragraph) is an immunomodulatory Thal analogue that is a more potent inducer of IL-2 and INF-gamma production (see Fig. 3 at page 383) and an inhibitor of IL-6 production (see page 382, Fig. 1). The reference does not expressly teach the treatment of MM.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the oral treatment of MM with a combination of Thal with Dex as described by Kyle et al. by replacing Thal with LEN. The motivation would have been to take advantage of the increased potency of LEN in inducing IL-2 and INF-gamma production as outlined by Corral et al, since increasing the production of IL-2 and INF-gamma are suggested to be useful to treat MM by increasing the lysis (I.e., killing) of MM cells by NK cells, as it is outlined by Davies et al. The motivation would have also been to take advantage of the inhibitory functions of LEN on the production of IL-6, as described by Corral et al., since IL-6 is a major growth factor and survival factor for MM cells, as outlined by Davies et al. Decrease of IL-6 would deprive the MM cancer cells of a major growth and survival factor.

Because of the increased potency of LEN relative to Thal in inducing IL-2 and INF-gamma production, one of ordinary skill would have been motivated to use LEN at a lower dosage amounts compared to Thal to achieve therapeutic responses with less potential for known side effects caused by Thal. One of ordinary skill in the art would have found it obvious to adjust the amount of the drug depending on its efficacy and side effects. The magnitude of a prophylactic or therapeutic dose of each active ingredient in the acute or chronic management of MM will vary with the specific active ingredients and the severity of disease. The dose, and perhaps the dose frequency, may also vary according to age, body weight, response, and recurrence of symptomology. Accordingly, the differences in claimed amount from the amounts

disclosed in Kyle et al. and Davies et al. will not support the patentability unless there is evidence indicating such amount is critical. See MPEP 2144.05[R-5] II A.

As for the "pharmaceutically acceptable salt" claimed in claim 29, it would have been obvious to use a pharmaceutically acceptable salt form of LEN for treating MM as it is common practice in the pharmaceutical art to provide therapeutic drugs in the form of a pharmaceutically acceptable salt.

As for claim 79, malphalan combined with Thal is expressly disclosed by Kyle et al. at Table 2, page 586, as being suitable as a potential strategy for the treatment of MM. It would have been obvious to add melphalan to the first line therapy of Thal plus Dex disclosed in Kyle et al. at page 585, column 2 to page 586, column 1, in order to achieve at least an additive response since the combination of Dex and Thal as is the combination of melphalan and Thal are individually suggested to be useful in the treatment of MM. As outlined above, it would have been obvious to replace the Thal with LEN to take advantage of LEN's induction of IL-2 and INF-gamma production and inhibition of IL-6 production.

Claim 59 recites well known formulations (.i.e., capsule and tablet forms) used in the pharmaceutical art for oral administration of therapeutic agents and are well within the skill of one of ordinary skill in the art to make. Claim 80 recites well known excipients utilized within the art of oral dosage formulation pharmacology and is well within the skill of the skilled artisan to choose such excipients due to their recognized suitability.

Claims 24, 26, 29, 57-63, 65-75, 77, 79 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,281,230 in view of Kyle et al., Filella et al. (Cancer Detect Prev. 1996;20(1):52-6) and Corral et al.

The disclosures of Kyle et al. and Corral et al. are outlined above. Kyle et al. do not expressly teach LEN. Corral does not expressly teach MM.

'230 relates to substituted 2-(2,6-dioxopiperidin-3-yl)phthalimides and substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolines that are used in methods of treating diseases by reducing levels of TNF-alpha in a mammal through the administration of pharmaceutical compositions containing compounds thereof (column 1, lines 15-21; claim 18). A particularly preferred compound is LEN, which can be in salt form and at an amount ranging from 1-100 mg (claim 2 and 19-26). Decreasing TNF-alpha levels constitutes a valuable therapeutic strategy for the treatment of many inflammatory, infectious, immunological, and malignant diseases, including, *inter alia,* oncogenic and cancerous conditions (column 4, lines 17-25). Prior efforts directed to the suppression of the effects of TNF-alpha have ranged from the utilization of steroids such as dexamethasone and prednisolone to the use of both polyclonal and monoclonal antibodies. (Column 4, lines 31-35). Microcrystalline cellulose may be added (column 8, lines 50-51). The '230 reference does not expressly teach MM.

Filella et al. discloses that serum levels of TNF-alpha and, particularly, IL-6 could be useful in the clinical management of patients with MM. Filella et al. measured serum levels of IL-6, TNF-alpha, soluble sIL-2r, and IL-1alpha in 30 healthy subjects, 22

patients with monoclonal gammopathy of undetermined significance, five patients with smoldering multiple myeloma (SMM), and 46 with MM. Serum levels of IL-6, TNF-alpha, and sIL-2r were significantly increased in patients with active MM when compared with normal controls. Furthermore, MM patients with advanced aggressive disease had significantly higher levels of IL-6, TNF-alpha, and sIL-2r than those with MM in plateau phase. The authors concluded that the data support the involvement of IL-6, TNF-alpha, and sIL-2r in MM. This confirmed in vitro studies suggesting that these cytokines may play a central role in the pathogenesis of MM. The reference does not expressly teach LEN. (See abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the treatment of a oncogenic or cancerous disease using LEN as described in the '230 patent by substituting LEN for Thal in the combined cyclical therapy of Thal plus Dex for treating MM, as Kyle et al. disclose that Thal and Dex are useful for combinatory cyclical treatment of MM. One of ordinary skill would have been motivated by the desire to treat MM by using the anti-TNF-alpha properties of LEN (see '230 patent) in order to decrease the high level of serum TNF-alpha which is suggested as being a useful target in the clinical management of MM patients (see Filella et al.).

One of ordinary skill in the art would have found it obvious to adjust the amount of the drug depending on its efficacy and side effects. The magnitude of a prophylactic or therapeutic dose of each active ingredient in the acute or chronic management of MM will vary with the specific active ingredients and the severity of disease. The dose, and perhaps the dose frequency, may also vary according to age, body weight, response,

and recurrence of symptomology. Accordingly, the differences in claimed amount from the amounts disclosed in Kyle et al. will not support the patentability unless there is evidence indicating such amount is critical. See MPEP 2144.05[R-5] II A.

Claims 24, 26, 29, 57-63, 65-75, 77, 79 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,555,554 in view of Kyle et al., Filella et al. and Corral et al.

'554 relates to substituted 2-(2,6-dioxopiperidin-3-yl)phthalimides and substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolines that are used in methods of treating diseases by reducing undesirable levels of TNF-alpha in a mammal through the oral or intravenous administration of pharmaceutical compositions containing compounds thereof (column 1, lines 15-21; column 2; claim 10-12). A particularly preferred compound is LEN, which can be in salt form, administered in a single or multidose regimen in an amount ranging from 1-100 mg (claim 10-17). Decreasing TNF-alpha levels constitutes a valuable therapeutic strategy for the treatment of many inflammatory, infectious, immunological, and malignant diseases, including, *inter alia,* oncogenic and cancerous conditions (column 4, lines 16-24; claim 1). Prior efforts directed to the suppression of the effects of TNF-alpha have ranged from the utilization of steroids such as dexamethasone and prednisolone to the use of both polyclonal and monoclonal antibodies. (Column 4, lines 30-34). Microcrystalline cellulose may be added (column 8, lines 31-32). The '554 reference does not expressly teach MM.

The disclosures for Kyle et al. and Filella et al are outlined above. The Kyle and Filella references do not expressly teach LEN.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the treatment of a oncogenic or cancerous disease using the TNF-alpha-reducing properties of LEN as described in the '554 patent by substituting LEN for Thal in the combined cyclical therapy of Thal plus Dex for treatment of MM. One of ordinary skill would have been motivated by the desire to treat MM by using the anti-TNF-alpha properties of LEN (see '554 patent) in order to decrease the high level of serum TNF-alpha which is suggested as being a useful target in the clinical management of MM patients (see Filella et al.).

One of ordinary skill in the art would have found it obvious to adjust the amount of the drug depending on its efficacy and side effects. The magnitude of a prophylactic or therapeutic dose of each active ingredient in the acute or chronic management of MM will vary with the specific active ingredients and the severity of disease. The dose, and perhaps the dose frequency, may also vary according to age, body weight, response, and recurrence of symptomology. Accordingly, the differences in claimed amount from the amounts disclosed in Kyle et al. will not support the patentability unless there is evidence indicating such amount is critical. See MPEP 2144.05[R-5] II A.

*Response to unexpected arguments*

Applicant's arguments from page 8 to the middle of page 14 of the response filed 03/09/2010 are found persuasive but are moot due to new rejections being applied.

Regarding the unexpected results, Applicant argues, at page 15, that Rajkumar reports an overall 91% response rate in treating MM with LEN plus Dex which is higher than the response rate of 77% achieved by Kyle et al. when MM was treated with Thal plus Dex instead. Applicant concludes that since 91% of Rajkumar is greater than 77% of Kyle, then this shows treating MM with LEN, instead of Thal, plus Dex demonstrated unexpected results. Applicant further asserts the reduced toxicity observed when LEN plus Dex was used, relative to the combination of Thal plus Dex, also illustrates unexpected results (see page 16 of response). Applicant, at page 17, further cites Gay and asserts that Gay reports superior response rate, survival, and toxicity levels for LEN plus Dex over Thal plus Dex when treating MM subjects.

Examiner does not find these arguments persuasive. The prior art already recognizes that LEN is more potent than Thal at increasing INF-gamma and IL-2 production (see Corral et al., Fig. 3) each disclosed as inducers of NK cell activity and proliferation which ultimately leads to the destruction of MM cancer cells (see Davies et al.). The prior art already discloses that increased TNF-alpha in MM is a potential target for treatment (see Filella et al.) and is inhibited by LEN at a greater rate than Thal (see Corral). It is the examiner's position that treating MM with LEN plus Dex would have been expected to give better response results than Thal plus Dex since LEN is more potent at increasing INF-gamma and IL-2 production and more potent at reducing TNF-alpha. Accordingly, applicant's arguments that the better response rates achieved by LEN/Dex combination compared to a Thal/Dex combination are unexpected are not found to be persuasive.

Applicant also relies on Palumbo et al. to support the argument of attaining unexpected results when MM is treated with LEN plus Dex. Particularly, applicant asserts that unexpected results are demonstrated by Palumbo et al. since in patients who failed to respond to LEN monotherapy, after the addition of DEX, 29% responded. Applicant further recites Palumbo et al. who states that 2 randomized clinical trials have demonstrated the superiority of LEN plus Dex compared with Dex alone. Applicant also asserts Dimopolous agrees with Palumbo. Applicant states that Gandhi discusses the synergy of LEN plus Dex in treating MM. Applicant concludes that the publications are sufficient to show that the claimed therapy of LEN plus Dex significantly increased response rate and survival rate, prolonged time of disease progression and reduced toxicity when compared to Thal plus Dex, monotherapy of LEN, Dex, or Thal alone.

The examiner does not find these arguments persuasive. First, the examiner notes that in making a final determination of patentability, evidence supporting patentability must be weighed against evidence supporting a *prima facie* case of obviousness. The submission of objective evidence of patentability does not mandate a conclusion of patentability in and of itself. *Facts established by rebuttal evidence must be evaluated along with the facts on which the conclusion of a prima facie case was reached, not against the conclusion itself*. (See MPEP Sec. 716.01(d) [R-6]). In the current case, the facts established by the evidence of superior response rates in MM patients receiving combined therapy of LEN plus Dex as compared with Dex alone or LEN alone does not overcome the facts establishing the rationale described in the above rejections as to why one of ordinary skill in the art would substitute Thal in a

composition for treating MM with LEN. The obviousness rejections are based on substituting the Thal in the combined MM therapy of Thal plus Dex with the more potent compound, LEN. The motivation is not based on simply adding LEN to Dex, as such publications demonstrating better results when LEN and Dex are combined as compared to each individually do not sufficiently rebut the reasons one of ordinary skill in the art would *substitute LEN in place of Thal* in the Kyle reference.

Secondly, the prior art already recognizes that Thal and Thal analogues (Davies et al.) adds to the effects of Dex. The prior art also discloses that adding Dex to Thal produces a response in patients who are refractory to Thal. (See Kyle et al.) Accordingly, it would appear then that combinatory therapy of Dex plus either Thal or a Thal analogue would be expected to produce better results than monotherapy would. Accordingly, applicant's evidence of better results when Dex is combined with LEN is not considered to be unexpected.

Applicant also relies on commercial success to over come the *prima facie* case of obviousness. Applicant asserts that the sales figures represent the sales of Revlimid® for treating MM in combination with Dex and for myelodysplastic syndrome (MDS). As an initial matter, it is noted that the Declarations filed on 03/09/2010 does not appear to list revenue data where Dex is in combination with LEN (Revlimid®). In considering evidence of commercial success, care should be taken to determine that the commercial success alleged is directly derived from the invention claimed, in a marketplace where the consumer is free to choose on the basis of objective principles, and that such success is not the result of heavy promotion or advertising, shift in

advertising, consumption by purchasers normally tied to applicant or assignee, or other business events extraneous to the merits of the claimed invention, etc. Conclusory statements or opinions that increased sales were due to the merits of the invention are entitled to little weight. (See MPEP 716.03 R2). The evidence provided is insufficient to allow the examiner to make a determination that the commercial success alleged is directly derived from the claimed invention and that such success is not the result of heavy promotion or advertising, shift in advertising, consumption by purchasers normally tied to applicant or assignee, or other business events extraneous to the merits of the claimed invention.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 24, 26, 29, 57-63, 65-75, 77, 79 and 80 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-7, 11-18 and 22-25 of U.S. Patent No. 7,393,862 in view of Kyle et al.. The patent claims differ from the current claims in so far as the patent claims are directed to treating leukemia instead of MM specifically, however, the specification discloses that MM (i.e., a leukemia) can be treated by compositions containing compounds of the invention. One of ordinary skill in the art would have found it obvious to adjust the amount of the drug depending on its efficacy and side effects. The magnitude of a prophylactic or therapeutic dose of each active ingredient in the acute or chronic management of MM will vary with the specific active ingredients and the severity of disease. The dose, and perhaps the dose frequency, may also vary according to age,

body weight, response, and recurrence of symptomology. Accordingly, the differences in claimed amount and schedule from what is disclosed in Kyle et al. will not support the patentability unless there is evidence indicating such amount is critical. See MPEP 2144.05[R-5] II A.

Claims 24, 26, 29, 57-63, 65-75, 77, 79 and 80 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10-17 of U.S. Patent No. 6,555,554 in view of Kyle et al. and Filella et al. The patent claims differ from the current claims in so far as they are directed to treating undesirable levels of TNF-alpha in a mammal instead of treating MM. It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of reducing undesirable levels of TNF-alpha using LEN as claimed in the '554 patent by adding Thal and Dex to LEN for cyclically treating MM as Kyle et al. disclose that Thal and Dex are useful for combinatory cyclical treatment of MM. One of ordinary skill would have been motivated by the desire to treat MM by using the anti-TNF-alpha properties of LEN (see '554 patent) in order to decrease the high level of serum TNF-alpha which is suggested as being a useful target in the clinical management of MM patients (see Filella et al.). One of ordinary skill in the art would have found it obvious to adjust the amount of the drug depending on its efficacy and side effects. The magnitude of a prophylactic or therapeutic dose of each active ingredient in the acute or chronic management of MM will vary with the specific active ingredients and the severity of disease. The dose, and perhaps the dose frequency, may also vary according to

age, body weight, response, and recurrence of symptomology. Accordingly, the differences in claimed amount and schedule from that disclosed in Kyle et al. will not support the patentability unless there is evidence indicating such amount is critical. See MPEP 2144.05[R-5] II A.

Claims 24, 26, 29, 57-63, 65-75, 77, 79 and 80 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 18-26 of U.S. Patent No. 6,281,230 in view of Kyle et al. and Filella et al. The patent claims differ from the current claims in so far as they are directed to treating an oncogenic or cancerous condition in a mammal instead of treating MM. It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of treating an oncogenic or cancerous condition in a mammal using LEN as claimed in the '230 patent by adding Thal and Dex to LEN for cyclically treating MM as Kyle et al. disclose that Thal and Dex are useful for combinatory cyclical treatment of MM. One of ordinary skill would have been motivated by the desire to treat MM by using the anti-TNF-alpha properties of LEN (see '230 patent) in order to decrease the high level of serum TNF-alpha which is suggested as being a useful target in the clinical management of MM patients (see Filella et al.). One of ordinary skill in the art would have found it obvious to adjust the amount of the drug depending on its efficacy and side effects. The magnitude of a prophylactic or therapeutic dose of each active ingredient in the acute or chronic management of MM will vary with the specific active ingredients and the severity of disease. The dose, and perhaps the dose frequency,

may also vary according to age, body weight, response, and recurrence of symptomology. Accordingly, the differences in claimed amount from the amounts disclosed in Kyle et al. will not support the patentability unless there is evidence indicating such amount is critical. See MPEP 2144.05[R-5] II A.

## *Conclusion*

No claims are allowable at this time.

The following is pertinent art not relied upon as prior art for this Office action:

US 6,077,822 – teaching that it is common practice in the pharmaceutical industry to use salt forms of drugs.

## *Correspondence*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRIS E. SIMMONS whose telephone number is (571)272-9065. The examiner can normally be reached on Monday - Friday from 7:30 - 5:00 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Allison M. Ford/
Primary Examiner, Art Unit 1651

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| Application of: Jerome B. Zeldis | Continuation No.: 4802 |
| Serial No.: 10/438,213 | Group Art Unit: 1612 |
| Filed: May 15, 2003 | Examiner: Simmons, Chris E. |
| For: METHODS FOR TREATMENT OF MULTIPLE MYELOMA USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE (AS AMENDED) | Attorney Docket No.: 9516-074-999 (CAM: 501872-999073) |

## RESPONSE AND STATEMENT OF INTERVIEW SUMMARY

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to Office Action dated August 3, 2010, and further to Examiner interview held on November 29, 2010 and to Interview Summary dated December 1, 2010, Applicant submits the following amendment and remarks for the consideration by the Examiner and entry into the record of the above-captioned application. Submitted herewith is Supplemental Information Disclosure Statement with fee, and Petition for extension of term from November 3, 2010 to and including January 3, 2011 with fee.

**The listing of the claims** begins on page 2 of this paper.

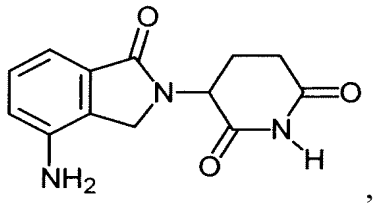
**Remarks** begin on page 4 of this paper.

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of the Claims:**

Claims 1-23. (canceled)

24. (currently amended) A method of treating multiple myeloma, which comprises cyclically administering to a patient having multiple myeloma about 5 to about [[50]] 25 mg per day of a compound of the formula:



or a pharmaceutically acceptable salt thereof, for 21 consecutive days followed by seven consecutive days of rest from administration of said compound during a 28 day cycle, and ~~a therapeutically effective amount of dexamethasone~~ cyclically administering about 40 mg per day of dexamethasone during said 28 day cycle.

25. (canceled)

26. (previously presented) The method of claim 24, wherein the multiple myeloma is smoldering myeloma, indolent myeloma, chemotherapy responsive multiple myeloma, refractory myeloma, relapsed myeloma, or relapsed and refractory Dune-Salmon stage III multiple myeloma.

27-28. (canceled)

29. (previously presented) The method of claim 24, wherein the compound is a pharmaceutically acceptable salt.

30-56. (canceled)

57. (previously presented) The method of claim 24, wherein the multiple myeloma is relapsed, refractory or resistant to conventional therapy.

58. (previously presented) The method of claim 24, wherein the compound and dexamethasone are administered orally.

59. (previously presented) The method of claim 58, wherein the compound is administered in the form of a capsule or tablet.

60. (previously presented) The method of claim 24, wherein the compound is administered in an amount of from about 10 to about 25 mg per day.

61. (currently amended) The method of claim 24, wherein the compound is administered in an amount of about 5, 10, 20, or 25~~, 30, or 50~~ mg per day.

62. (canceled)

63. (previously presented) The method of claim 60, wherein the compound is administered in an amount of about 25 mg per day.

64-70. (canceled)

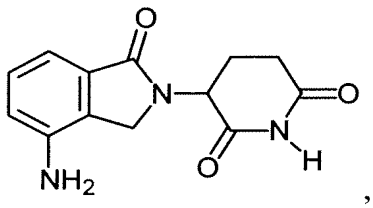
71. (previously presented) The method of claim 24, wherein the compound is administered in an amount of 5 mg per day.

72. (previously presented) The method of claim 60, wherein the compound is administered in an amount of 10 mg per day.

73. (previously presented) The method of claim 24, wherein the compound is administered in a capsule of 5 mg, 10 mg, 15 mg or 25 mg.

74. (canceled)

75. (previously presented) A method of treating multiple myeloma, which comprises administering, on a 28 day cycle, to a patient having multiple myeloma: (a) about 25 mg per day of a compound of the formula:




,

or a pharmaceutically acceptable salt thereof, for 21 consecutive days followed by seven consecutive days of rest from administration of said compound, and; (b) about 40 mg per day of dexamethasone on days 1-4 every 28 days.

76-79. (canceled)

80. (previously presented) The method of claim 73, wherein the capsule comprises the compound, lactose anhydrous, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

81. (canceled)

82. (new) The method of claim 24, wherein said dexamethasone is administered on days 1 to 4.

## REMARKS

### I. Applicant's Statement of the Substance of Interview and Response to the Examiner's Interview Summary of Record

A telephonic interview with Supervisory Patent Examiner Frederick Krass, Patent Examiner Chris E. Simmons, and attorneys for Applicant (Anthony M. Insogna and Yeah-Sil Moon), was held on November 29, 2010. Applicant appreciates the Examiner interview.

During the interview, the Examiners and attorneys for Applicant discussed the amendment to the claims and the pending rejections.

First, the Examiners and attorneys for Applicant discussed claim amendment proposal that was submitted to the PTO by a fax on November 22, 2010. Attorneys for Applicant pointed out that all the obviousness rejections should be withdrawn in view of previous arguments submitted on March 9, 2010, and in view of the further amendments submitted herewith.

In particular, attorneys for Applicant explained that Kyle *et al.* (*Semin. Oncol.*, 2001), Davies *et al.* (*Blood*, 2001) and Corral *et al.* (*Ann. Rheum. Dis.*, 1999), alone or in combination with other cited references, fail to suggest the claimed methods, which require the use of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione and dexamethasone for treating multiple myeloma in specific amounts and specific dosing regimens.

Further, attorneys for Applicant stressed that the obviousness rejections of record also can be overcome by unexpected results of the claimed invention. Attorneys for Applicant discussed articles previously submitted to evidence unexpected results of the claimed invention. *See e.g,* Gay, *Blood*, 2010: 115, 1343-1350, which was filed with March 9, 2010 response. In addition, attorneys for Applicant explained that the claimed method as amended relates to an FDA approved use of lenalidomide (product named Revlimid®) (Exhibit 1 filed with March 9, 2010 response). This method has resulted in one of the newest and most effective treatments available for multiple myeloma. Finally, attorneys for Applicant stated that the commercial success of this approved use supports non-obviousness of the claimed invention (Exhibits 3-4 filed with March 9, 2010 response).

In view of the foregoing, all the outstanding rejections over the cited references are moot and the case should proceed to allowance.

## II. Conclusion

Entry of the above amendment and remarks, and allowance of the pending claims are respectfully requested.

Respectfully submitted,

Date: December 7, 2010

Yeah-Sil Moon (Reg. No. 52,042)
For Anthony M. Insogna (Reg. No. 35,203)
**JONES DAY**
222 East 41st Street
New York, NY 10017
Tel. (212) 326-3778

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| Interview Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/438,213 | ZELDIS, JEROME B. | |
| | Examiner | Art Unit | |
| | CHRIS E. SIMMONS | 1612 | |

All participants (applicant, applicant's representative, PTO personnel):

(1) *CHRIS E. SIMMONS*. (3)_____.

(2) *YEAH-SIL MOON*. (4)_____.

Date of Interview: *01 December 2010*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☐ No.
If Yes, brief description: _____.

Claim(s) discussed: _____.

Identification of prior art discussed: _____.

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Applicant's representative was informed that the examiner intends to issue a notice of allowance for the 11/22/2010 amended claim set*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

| /C. E. S./ Examiner, Art Unit 1612 | |
|---|---|

JONES DAY

# Facsimile Transmission

222 East 41st Street • New York, New York 10017 • (212) 326-3939
Facsimile: (212) 755-7306
ymoon@jonesday.com



December 13, 2010

Please hand deliver the following facsimile to:

Name: **Examiner Chris E. Simmons**

Facsimile No.: **(571) 273-9065**
**(571) 273-8300**

Company: **USPTO (Art Unit: 1612)**

Number of pages (including this page): **1**

Telephone No.: **(571) 272-9065**

From: **Yeah-Sil Moon**

Send Copies To:

Direct Telephone No.: **(212) 326-3778**

JP No.: **JP006595**

☐ **Copies distributed** _____
Operator's Initials

CAM No.: **501872-999073**
(Atty. Docket No.: 9516-074-999)

Re: **U.S. Patent Application No. 10/438,213**



**Message:**

Dear Examiner Simmons,

Further to our call of today, please make the attached Interview Summary of record in PAIR.

Thank you.

Very truly yours,

Yeah-Sil Moon

Please call us immediately if the facsimile you receive is incomplete or illegible. Please ask for the facsimile operator.

**ELECTRONIC FILING**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| Application of: Jerome B. Zeldis | Continuation No.: 4802 |
| Serial No.: 10/438,213 | Group Art Unit: 1612 |
| Filed: May 15, 2003 | Examiner: Simmons, Chris E. |
| For: METHODS FOR TREATMENT OF MULTIPLE MYELOMA USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE (AS AMENDED) | Attorney Docket No.: 9516-074-999 (CAM: 501872-999073) |

**INFORMATION DISCLOSURE STATEMENT**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the duty of disclosure provisions of 37 C.F.R. §1.56, there is hereby provided certain information which the Examiner may consider material to the examination of the subject U.S. patent application. It is requested that the Examiner make this information of record if it is deemed material to the examination of the application.

1. Enclosures accompanying this Information Disclosure Statement are:

1a. ☒ A list of all patents, publications, applications, or other information submitted for consideration by the office.

1b. A legible copy of :

☒ Each publication or that portion which caused it to be listed on the PTO-1449;

☐ For each cited pending unpublished U.S. application, the application specification including the claims, and any drawing of the application, or portion of the application which caused it to be listed on the PTO-1449 including any claims directed to that portion that have been checked to be unavailable at the USPTO's private PAIR system;

☐ An English language copy of search report(s) from a counterpart foreign application or PCT International Search Report;

☐ Explanations of relevancy (ATTACHMENT 1(d), hereto) or English language abstracts of the non-English language publications;

☐ All other information or portion which caused it to be listed on the PTO-1449.

1c. ☐ Pursuant to 37 C.F.R. § 1.98(a)(2)(ii), copies of the cited U.S. patents and U.S. patent application publications are not submitted herewith unless required by the office.

1d. ☐ Pursuant to 1287 OG 163, copies of cited pending unpublished applications that are available at the USPTO's private PAIR system are not submitted herewith.

2. ☐ This Information Disclosure Statement is filed under 37 C.F.R. §1.97(b):

☐ Within three months of the filing date of a national application other than a continued prosecution application under §1.53(d);

☐ Within three months of the date of entry of the national stage as set forth in §1.491 in an international application;

☐ Before the mailing of the first Office action on the merits;

☐ Before the mailing of a first Office action after the filing of a request for continued examination under §1.114.

3. ☒ This Information Disclosure Statement is filed under 37 C.F.R. §1.97(c) after the period specified in 37 C.F.R §1.97(b), but before the mailing date of any of a final action under 37 C.F.R. §1.113, a notice of allowance under 37 C.F.R. §1.311 or an action that otherwise closes prosecution in the application.

*(Check either Item 3a or 3b)*

3a. ☐ The Certification Statement in Item 5 below is applicable. Accordingly, no fee is required.

3b. ☒ The $180.00 fee set forth in 37 C.F.R. §1.17(p) in accordance with 37 C.F.R. §1.97(c) is:

☒ enclosed.
☐ to be charged to Jones Day Deposit Account No. 50-3013.

*(Item 3b to be checked if any reference known for more than 3 months)*

4. ☐ This Information Disclosure Statement is filed under 37 C.F.R. §1.97(d) after the period specified in 37 C.F.R. §1.97(c), but on or before the date of payment of the issue fee.

The Certification Statement in Item 5 below is applicable.

The $180.00 fee set forth in 37 C.F.R. §1.17(p) is:
☐ enclosed.
☐ to be charged to Jones Day Deposit Account No. 50-3013.

5. ☐ Certification Statement (applicable if Item 3a or Item 4 is checked):

*(Check either Item 5a or 5b)*

5a. ☐ In accordance with 37 C.F.R. §1.97(e)(1), it is certified that each item of information contained in this Information Disclosure Statement was first cited in a communication from the Israeli patent office in a counterpart Israeli application not more than three months prior to the filing of this Information Disclosure Statement.

5b. ☐ Each item of information contained in this information disclosure statement was cited in a communication from a foreign patent office in a counterpart application, and the communication was not **received** by any individual designated in 37 C.F.R. §1.56(c) more than thirty days prior to the filing of this information disclosure statement.

5c. ☐ Pursuant to 37 C.F.R. §1.704(d), each item of information contained in this information disclosure statement was cited in a communication from a foreign patent office in a counterpart application, and the communication was not

**received** by any individual designated in 37 C.F.R. §1.56(c) more than thirty days prior to the filing of this information disclosure statement.

6. ☐ This application is a continuation application under 37 C.F.R. §1.53(b) or (d).

*(Check appropriate Items 6a, 6b and/or 6c)*

6a. ☐ A Petition to Withdraw from issue under 37 C.F.R. §1.313(b)(5) is concurrently filed herewith.

6b. ☐ Copies of publications listed on Form PTO-1449 from prior application Serial No. , filed on , of which this application claims priority under 35 U.S.C. §120, are not being submitted pursuant to 37 C.F.R. §1.98(d).

6c. ☐ Copies of the publications listed on Form PTO-1449 were not previously cited in prior application Serial No. , filed on , and are provided herewith.

7. ☒ This is a Supplemental Information Disclosure Statement. (Check Item 7a)

7a. ☒ This Supplemental Information Disclosure Statement under 37 C.F.R. §1.97(f) supplements the Information Disclosure Statement filed on December 7, 2010.

8. ☐ In accordance with 37 C.F.R. §1.98, a concise explanation of what is presently understood to be the relevance of each non-English language publication is:

*( Check Item 8a, 8b, or 8c)*

8a. ☐ Satisfied because all non-English language publications were cited on the enclosed English language copy of the PCT International Search Report or the search report from a counterpart foreign application indicating the degree of relevance found by the foreign office.

8b. ☐ Set forth in the application.

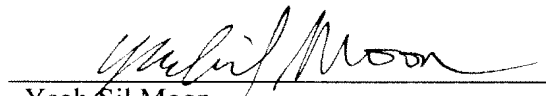
8c. ☐ Enclosed as an attachment hereto.

9. ☒ The Commissioner is authorized to charge any additional fee required or credit any overpayment for this Information Disclosure Statement and/or Petition to Jones Day Deposit Account No. 50-3013.

10. ☒ No admission is made that the information cited in this Statement is, or is considered to be, material to patentability and no representation is made that a search has been made (other than a search report of a foreign counterpart application or PCT International Search Report if submitted herewith). 37 C.F.R. §§1.97(g) and (h).

Respectfully submitted,

Date: December 15, 2010



52,042 (Reg. No.)

Yeah-Sil Moon
JONES DAY
222 East 41st Street
New York, New York 10017-6702
(212) 326-3939

# LIST OF REFERENCES CITED BY APPLICANT

(Use several sheets if necessary)

| | |
|---|---|
| **Application Number** | 10/438,213 |
| **Filing Date** | May 15, 2003 |
| **First Named Inventor** | Jerome B. Zeldis |
| **Art Unit** | 1612 |
| **Examiner Name** | Chris E. Simmons |
| **Attorney Docket No.** | 9516-074-999 |

## U.S. PATENT DOCUMENTS

| *Examiner Initials | Cite No. | Document Number – Kind Code | Publication Date mm/dd/yyyy | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | | | | | |
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## FOREIGN PATENT DOCUMENTS

| *Examiner Initials | Cite No. | Foreign Patent Document Country Code, Number, Kind Code (if known) | Publication Date mm/dd/yyyy | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear | T |
|---|---|---|---|---|---|---|
| | | | | | | |
| | | | | | | |

## NON PATENT LITERATURE DOCUMENTS

| *Examiner Initials | Cite No. | Include name of the author (in CAPITAL LETTERS), (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T |
|---|---|---|---|
| | C249 | Copy of Notice of Opposition to EP 1 505 973 filed by Synthon B.V. on November 30, 2010 | |
| | C250 | Copy of Notice of Opposition to EP 1 505 973 filed by Strawman Limited on December 1, 2010 | |
| | C251 | Samson, D. *et al.*, "Infusion of Vincristine and Doxorubicin with Oral Dexamethasone as First-Line Therapy for Multiple Myeloma," *The Lancet*, 1989, 334(8668):882-885 | |
| | C252 | Barlogie, B. *et al.*, "Effective Treatment of Advanced Multiple Myeloma Refractory to Alkylating Agents," *N. Engl. J. Med.*, 1984, 310(21):1353-1356 | |
| | C253 | Dimopoulos, M. *et al.*, "Thalidomide and dexamethasone combination for refractory multiple myeloma," *Annals of Oncology*, 2001, 12:991-995 | |
| | C254 | Zangari, M., *et al.*, "Thrombogenic activity of doxorubicin in myeloma patients receiving thalidomide: implications for therapy," *Blood*, 2002, 100:1168-1171 | |
| | C255 | List, A. *et al.*, "High Erythropoietic Remitting Activity of the Immunomodulatory Thalidomide Analog, CC5013, in Patients with Myelodysplastic Syndrome (MDS)," Abstract #353, *Blood*, 2002, 100(11):96a | |
| | C256 | Mufti, G. *et al.*, "Myelodysplastic Syndrome," *American Society of Hematology*, 2003, pp. 176-199 | |
| | C257 | Extracts from drug databases: retrieved from http://www.nextbio.com/b/search/ov/IMiD3%20cpd on 11/26/10 and http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=216326 on 11/26/10 | |

NYI-4333948v1

| EXAMINER SIGNATURE | DATE CONSIDERED |
|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

# NOTICE OF ALLOWANCE AND FEE(S) DUE

84802 7590 03/11/2011

JONES DAY
222 E. 41ST. STREET
NEW YORK, NY 10017

| EXAMINER |
|---|
| SIMMONS, CHRIS E |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1612 | |

DATE MAILED: 03/11/2011

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/438,213 | 05/15/2003 | Jerome B. Zeldis | 9516-074-999 | 4802 |

TITLE OF INVENTION: METHOD FOR TREATMENT OF MULTIPLE MYELOMA USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERDINE-2,6-DIONE

| APPLN. TYPE | SMALL ENTITY | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | NO | $1510 | $300 | $0 | $1810 | 06/13/2011 |

**THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.**

**THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.**

**HOW TO REPLY TO THIS NOTICE:**

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

**IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.**

# PART B - FEE(S) TRANSMITTAL

**Complete and send this form, together with applicable fee(s), to: Mail** **Mail Stop ISSUE FEE**
**Commissioner for Patents**
**P.O. Box 1450**
**Alexandria, Virginia 22313-1450**
**or Fax (571)-273-2885**

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

84802 7590 03/11/2011

JONES DAY
222 E. 41ST. STREET
NEW YORK, NY 10017

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

**Certificate of Mailing or Transmission**

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

| |
|---|
| (Depositor's name) |
| (Signature) |
| (Date) |

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/438,213 | 05/15/2003 | Jerome B. Zeldis | 9516-074-999 | 4802 |

TITLE OF INVENTION: METHOD FOR TREATMENT OF MULTIPLE MYELOMA USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERDINE-2,6-DIONE

| APPLN. TYPE | SMALL ENTITY | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | NO | $1510 | $300 | $0 | $1810 | 06/13/2011 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| SIMMONS, CHRIS E | 1612 | 514-323000 |

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

| Notice of Allowability | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/438,213 | ZELDIS, JEROME B. | |
| | Examiner | Art Unit | |
| | CHRIS E. SIMMONS | 1612 | |

***-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--***

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the 12/07/2010 amendment*.

2. ☒ The allowed claim(s) is/are *24,26,29,57-61,63,71-73,75,80 and 82*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE**.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS ( as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review ( PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   **Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

**Attachment(s)**

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 12/7/2010, 12/15/2010, 02/24/2011
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

| | |
|---|---|
| /C. E. S./<br>Examiner, Art Unit 1612 | /Frederick Krass/<br>Supervisory Patent Examiner, Art Unit 1612 |

## EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Yeah-Sil Moon on 12/13/2010.

The application has been amended as follows:

1) The title of the application has been changed to:

--- METHODS FOR TREATMENT OF MULTIPLE MYELOMA USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE ---

2) Claim 24, last three lines, the entire passage "and … 28 day cycle" has been deleted and replaced with --- in combination with 40 mg per day dexamethasone ---

3) Claim 57, line 2, "conventional" has been deleted and --- previous --- inserted in its place.

4) Claim 75, penultimate line, “about” has been deleted.

5) Claim 82, “on days 1 to 4” has been deleted and replaced with --- orally ---

***Correspondence***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRIS E. SIMMONS whose telephone number is (571)272-9065. The examiner can normally be reached on Monday - Friday from 7:30 - 5:00 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/C. E. S./
Examiner, Art Unit 1612

/Frederick Krass/

Supervisory Patent Examiner, Art Unit 1612

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | ISSUE DATE | PATENT NO. | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/438,213 | 06/28/2011 | 7968569 | 9516-074-999 | 4802 |

84802 7590 06/08/2011

JONES DAY
222 E. 41ST. STREET
NEW YORK, NY 10017

# ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

**Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)**
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 145 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Jerome B. Zeldis, Princeton, NJ;

**ELECTRONIC FILING**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent of: Jerome B. Zeldis

Patent No.: 7,968,569 B2

Application No.: 10/438,213

Filed: May 15, 2003

For: METHODS FOR TREATMENT OF MULTIPLE MYELOMA USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE

Issued on: June 28, 2011

Confirmation No.: 4802

Group Art Unit: 1612

Examiner : Simmons, Chris E.

Attorney Docket No.: 9516-074-999
CAM: 501872-999073

**REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 C.F.R. § 1.322**

Attn: Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

The Patentee hereby respectfully requests the issuance of a Certificate of Correction in connection with the above-identified patent. The correction is listed on the attached Form PTO/SB/44, which is submitted herewith. The errors to be corrected are as follows:

**In claim 1**, at column 39, line 11, after "followed by seven", insert -- consecutive days of rest from administration of said compound during a 28 day cycle, --

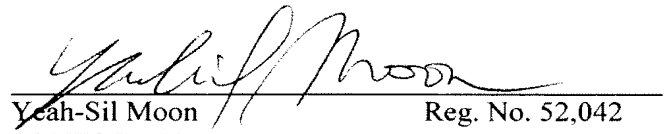
**In claim 1**, at column 39, line 12, between "day" and "dexamethasone", insert -- of --

**In claim 15**, at column 40, line 30, after "administered", insert -- orally ---

The mistakes were incurred through the fault of the Office, which mistakes are clearly disclosed in the records of the Office. See MPEP §1480 and Examiner's Amendment dated March 11, 2011. Thus, Patentee believes that no fee is due with this request. However, in case that any fees are due, the Commissioner is authorized to charge any required fee to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: July 1, 2011



Yeah-Sil Moon Reg. No. 52,042
**JONES DAY**
222 East 41st Street
New York, New York 10017-6702
(212) 326-3939

*Enclosure*

NYI-4383147v1

PTO/SB/44 (09-07)
Approved for use through 08/31/2013. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

# UNITED STATES PATENT AND TRADEMARK OFFICE
## CERTIFICATE OF CORRECTION



PATENT NO. : 7,968,569 B2

APPLICATION NO.: 10/438,213

ISSUE DATE : June 28, 2011

INVENTOR(S) : Jerome B. Zeldis

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In claim 1, at column 39, line 11, after "followed by seven", insert -- consecutive days of rest from administration of said compound during a 28 day cycle, --

In claim 1, at column 39, line 12, between "day" and "dexamethasone", insert -- of --

In claim 15, at column 40, line 30, after "administered", insert -- orally --

MAILING ADDRESS OF SENDER (Please do not use customer number below):

Jones Day
222 E. 41st Street
New York, NY 10017-6702

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION



PATENT NO. : 7,968,569 B2
APPLICATION NO. : 10/438213
DATED : June 28, 2011
INVENTOR(S) : Jerome B. Zeldis

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In claim 1, at column 39, line 11, after "followed by seven", insert -- consecutive days of rest from administration of said compound during a 28 day cycle, --

In claim 1, at column 39, line 12, between "day" and "dexamethasone", insert -- of --

In claim 15, at column 40, line 30, after "administered", insert -- orally --

Signed and Sealed this
Ninth Day of August, 2011

David J. Kappos

David J. Kappos
*Director of the United States Patent and Trademark Office*