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Sir:

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(c).

Docket Number	9516-062-888	Type a plus sign (+) inside this box →	+

INVENTOR(s) APPLICANT(s)

LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)

TITLE OF THE INVENTION (280 characters max)

METHODS OF USING SMALL AND LARGE MOLECULES FOR THE TREATMENT AND MANAGEMENT OF CANCER, AND COMPOSITIONS AND KITS USEFUL THEREIN

CORRESPONDENCE ADDRESS: **PENNIE & EDMONDS LLP** 20582

ENCLOSED APPLICATION PARTS (*check all that apply*)

☒ Specification, Claims and Abstract	*Number of Pages*	43	☐ Applicant claims small entity status, see 37 CFR §1 27
☐ Drawing(s)s	*Number of Sheets*		☐ Other (specify)

METHOD OF PAYMENT (*check one*)

☐ A check or money order is enclosed to cover the Provisional filing fees	ESTIMATED PROVISIONAL FILING FEE AMOUNT ☒ $160 ☐ $80
☒ The Commissioner is hereby authorized to charge the required filing fee to Deposit Account Number 16-1150	

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government
☒ No. ☐ Yes, the name of the U.S Government agency and the Government contract number are: _____

Respectfully submitted,

Signature Max Bachrach
Max Bachrach
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REGISTRATION NO. (*if appropriate*) 45,479

Date May 17, 2002

☐ Additional inventors are being named on separately numbered sheets attached hereto.

Total number of cover sheet pages 1

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METHODS OF USING SMALL AND LARGE MOLECULES FOR THE TREATMENT AND MANAGEMENT OF CANCER, AND COMPOSITIONS AND KITS USEFUL THEREIN

1. FIELD OF THE INVENTION

This invention relates to methods of treating and/or managing cancer using the combined administration of a small molecule-based active agent, such as a derivative or analogue of thalidomide, or a pharmaceutically acceptable salt, solvate, hydrate, clathrate, or prodrug thereof and a large molecule-based active agent. Examples of large molecule-based active agents include, but are not limited to, proteins such as IL-2, IL-10, IL-12, IL-18, G-CSF, GM-CSF, and EPO. The invention further relates to pharmaceutical compositions, single unit dosage forms, and kits suitable for use in methods of treating and/or managing cancer.

2. BACKGROUND OF THE INVENTION

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) grow. A tremendous demand therefore exists for new methods and compositions that can be used to treat patients with cancer.

2.1. PATHOBIOLOGY OF CANCER

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.

Pre-malignant abnormal cell growth is exemplified by hyperplasia, metaplasia, or most particularly, dysplasia (for review of such abnormal growth conditions, see Robbins and Angell, 1976, *Basic Pathology*, 2d Ed., W.B. Saunders Co., Philadelphia, pp. 68-79). Hyperplasia is a form of controlled cell proliferation involving an increase in cell number in a tissue or organ, without significant alteration in structure or function. As but one example, endometrial hyperplasia often precedes endometrial cancer. Metaplasia is a form of controlled cell growth in which one type of adult or fully differentiated cell substitutes for another type of adult cell. Metaplasia can occur in epithelial or connective tissue cells. Atypical metaplasia involves a somewhat disorderly metaplastic epithelium. Dysplasia is frequently a forerunner of cancer, and is found mainly in the epithelia; it is the most disorderly form of non-neoplastic cell growth, involving a loss in individual cell uniformity

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and in the architectural orientation of cells. Dysplastic cells often have abnormally large, deeply stained nuclei, and exhibit pleomorphism. Dysplasia characteristically occurs where there exists chronic irritation or inflammation, and is often found in the cervix, respiratory passages, oral cavity, and gall bladder.

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: 1993).

2.2. TYPES OF CANCERS

There is an enormous variety of cancers which are described in detail in the medical literature. Examples of some are discussed below.

2.2.1. AIDS-RELATED NON-HODGKIN'S LYMPHOMA

AIDS has been closely associated with a variety of cancers. Further, the types of malignancies and their incidence rates are increasing as the development of effective antiretroviral therapies and prophylaxis against opportunistic infections leads to prolonged survival in the immunodeficient state for AIDS patients. Karp and Broder, *Cancer Res.* 51:4747-4756 (1991). AIDS-related non-Hodgkin's lymphoma is a very aggressive disease with a very high incidence of central nervous system involvement. Since its discovery in 1981, the incidence of AIDS-related non-Hodgkin's lymphoma has reportedly increased. One reason for such an observation is that patients infected with the AIDS virus now live longer than they used to.

2.2.2. PRIMARY AND METASTATIC CNS TUMORS

The incidence of primary and metastatic brain tumors is also increasing in the United States. Unfortunately, the arsenal of chemotherapeutics for these types of cancers is minimal, while the need for such therapeutics is high.

Glioblastoma multiform and other primary and metastatic central nervous system tumors are devastating malignancies. The treatment of these tumors include surgery, radiation therapy and treatment with agents such as the nitrosourea BCNU. Other chemotherapeutic agents utilized include procarbazine, vincristine, hydroxyurea and cisplatin. But even when all three modalities (surgery, radiation therapy and chemotherapy) are utilized, the average survival of patients with central nervous system malignancies is only about 57 weeks. Clearly, new treatment approaches are needed both for patients with newly diagnosed primary and metastatic central nervous system tumors, as well as for patients with such tumors which are refractory to the above modalities.

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2.2.3. BREAST, LUNG, BLADDER AND PROSTATE CANCERS

In the United States, the cumulative risk of developing breast cancer is reportedly about 10.2 percent. *The Merck Manual* 1815 (16th ed. 1992). The treatment for early breast cancer is surgery, with or without radiation therapy, or surgery, with or without radiation therapy, plus chemotherapy and/or hormonal therapy. Current chemotherapy for patients with primary or metastatic breast cancer includes treatment with cyclophosphamide, methotrexate, doxorubicin, 5-fluorouracil, cisplatin, vinblastine, taxol, taxotere, mitomycin C and occasionally other agents. Unfortunately, even with these agents, almost all women who develop metastatic breast cancer succumb to their disease. One particular place that metastatic breast cancer does metastasize to is the central nervous system. When central nervous system metastases do occur, the usual treatment is surgery (for a solitary metastasis) or radiation, or surgery plus radiation therapy.

Lung cancer is reportedly the leading cause of cancer death in men and women. *The Merck Manual* 731 (16th ed. 1992). A variety of causes exist, but cigarette smoking accounts for greater than 90 percent of reported cases in men and greater than 70 percent of reported cases in women. *Id.*

Most patients with lung cancer present a tumor that has already metastasized to a variety of organs, including lung, liver, adrenal gland and other organs. Treatment of metastatic lung cancer is not yet standardized. Ihde, D.C., *The New England Journal of Medicine* 327:1434-1441 (1992). However, chemotherapy regimens that are utilized include treatment with cisplatin plus etoposide, combinations of cyclophosphamide plus doxorubicin plus cisplatin, and single agents alone or in combination, including ifosfamide, teniposide, vindesine, carboplatin, vincristine, taxol, nitrogen mustard, methotrexate, hexamethylmelamine and others. Despite these chemotherapeutic regimens the average patient with metastatic lung cancer still only survives 7-12 months. One particular troublesome place for metastases of lung cancer is the central nervous system. The treatment for central nervous system metastases includes surgery (to remove a solitary lesion), radiation therapy, or a combination of both.

Each year about 50,000 new cases of bladder cancer are reported in the United States. *The Merck Manual* 1749 (16th ed. 1992). Although at presentation the disease is usually localized, most patients develop distant metastatic disease. The most recent advances have been in the area of chemotherapy for patients with such metastatic disease. One effective regimen is called the MVAC regimen. It consists of treatment with methotrexate plus vinblastine plus adriamycin (doxorubicin) plus cisplatin. Although the response rate is high to this chemotherapeutic regimen, medical oncologists are noting that one place the patients fail is with metastases to the central nervous system.

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It is estimated that more than 120,000 men will be diagnosed with prostate cancer this year. *The Merck Manual* 1750 (16th ed. 1992). The most common sites of metastases in patients with prostate cancer are the bone and lymph nodes. The bone metastases are particularly bothersome in that they can create intense pain for the patient. The current treatment for metastatic prostate cancer includes treatment with flutamide, leuprolide, diethylstilbestrol, and other hormonal manipulations, as well as chemotherapy (doxorubicin, estramustine phosphate, vinblastine, suramin, cisplatin, and others). Unfortunately, none of these agents are consistently helpful in the disease. In addition, as patients with prostate cancer live longer with their malignancy, they will most likely develop a higher incidence of metastases to the central nervous system (including the spinal cord).

2.2.4. ESOPHAGEAL CANCER

Several years ago, carcinoma of the esophagus reportedly represented only about six percent of all cancers of the gastrointestinal tract; however, it reportedly caused a disproportionate number of cancer deaths. Boring, C.C., *et al., CA Cancer J. Clin.* 43:7 (1993). These cancers usually arise from the epithelial layer of the esophagus and are either squamous cell carcinomas or adenocarcinomas. Overall, the 5 year survival is about five percent.

2.2.5. LEUKEMIA

Leukemia refers to malignant neoplasms of the blood-forming tissues. Although viruses reportedly cause several forms of leukemia in animals, causes of leukemia in humans are to a large extend unknown. *The Merck Manual* 1233 (16th ed. 1992). Transformation to malignancy typically occurs in a single cell through two or more steps with subsequent proliferation and clonal expansion. In some leukemias, specific chromosomal translocations have been identified with consistent leukemic cell morphology and special clinical features (*e.g.*, translocations of 9 and 22 in chronic myelocytic leukemia, and of 15 and 17 in acute promyelocytic leukemia). Acute leukemias are predominantly undifferentiated cell populations and chronic leukemias more mature cell forms.

Acute leukemias are divided into lymphoblastic (ALL) and non-lymphoblastic (ANLL) types. They may be further subdivided by their morphologic and cytochemical appearance according to the French-American-British (FAB) classification or according to their type and degree of differentiation. The use of specific B- and T-cell and myeloid-antigen monoclonal antibodies are most helpful for classification. ALL is predominantly a childhood disease which is established by laboratory findings and bone marrow examination. ANLL, also known as acute myeloblastic leukemia (AML), occurs at all ages

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