

7. Clinical development of SelCID analogues
8. Clinical development of IMiD analogues
9. Expert opinion

Ashley Publications  
www.ashley-pub.com



derivatives fall into at least two categories; selective (SelCID), which are phosphodiesterase Type 4 (PDE4) modulatory drugs (IMiD), similar to thalidomide mechanism(s). These compounds are in the process of laboratory studies and are also now being assessed in clinical studies. In this review we will highlight the novel classes of compound in terms of their effects on immunological and non-immunological systems *in vitro*. We will discuss how these studies are enabling the characterisation and development of these compounds into clinically relevant drugs in widely varied indications. We will describe the various clinical studies of these compounds, their progress and speculate as to the potential and future of these exciting compounds.

**Keywords:** anti-TNF- $\alpha$ , antitumour, immunotherapy, PDE4, TNF- $\alpha$  analogues

*Expert Opin. Biol. Ther.* (2001) 1(4):675-682

## 1. History of thalidomide use

Thalidomide ( $\alpha$ -N-phthalimidoglutarimide) is a synthetic sedative acid designed and synthesised by the German company Chemie Grünenthal in the mid-1950s. Thalidomide was marketed as a non-habit forming sedative in Europe, New Zealand, Australia and Canada. It led to the drug's popularity as a sleeping aid. However, it was not given FDA approval in the United States at this time due to concerns associated with the drug's use. However, early in 1960 a link between thalidomide was associated with neuropathies [1] and by 1961 it was taken off the market thalidomide had been taken off the market. Women to counter the effects of morning sickness resulted in children being born with thalidomide type birth defects.

Forty years later, thalidomide is now established as a sedative, anti-inflammatory drug [3-5]. In fact, for many years it was the World Health Organization (WHO) drug of choice.

**DR. REDDY'S LABS., INC. EX. 1**

ical conditions for which there is little other treatment option. In particular, thalidomide has shown potential for the treatment of a range of conditions, including rheumatoid arthritis (RA) [10], the inflammatory and wasting effects of chronic tuberculosis [11], Behcet's disease [12] and Crohn's disease [13-15]. Thalidomide is also effective in the treatment of aphthous ulcers [16-18] and cachexia (wasting) associated with HIV infection [19,20] and AIDS related Kaposi's sarcoma [21]. In 1998, it was reported by researchers at the University of Arkansas that thalidomide was an effective treatment for refractory multiple myeloma with positive effects being observed in approximately 30% of the patients [22]. There is an increasing body of evidence from larger scale studies showing the effectiveness of thalidomide in the treatment of patients with multiple myeloma [22-25] and also in the treatment of patients with a number of other tumours [26-29].

The obvious clinical benefits associated with thalidomide treatment in acute ENL led to thalidomide (THALOMID<sup>®</sup>) being given FDA approval for treatment of this condition in 1998. However, this was necessarily subject to very strict controls. These include a distribution program, developed and patented by Celgene Corporation, called STEPS. (System for Thalidomide Education and Prescribing Safety) which involves comprehensive patient counselling, a cautionary message from thalidomide victims, a detailed consent form and a mandatory thalidomide survey form [30]. In Britain, the drug remains unlicensed and is only available on a named patient basis although there have been a number of clinical studies in HIV infected patients and end stage cancer patients.

## 2. Mechanisms of thalidomide activity

It is only in the last ten years that information concerning

promotion of tumour growth and may support a possible role for thalidomide in the treatment of cancers. Indeed, it has been proposed that thalidomide may suppress the growth of tumours arise in sites of chronic inflammation. In this respect it is also worth noting that thalidomide has been shown to upregulate endothelial integrins which is crucial for new vessel formation [36].

More recently, thalidomide has been shown to have immunomodulatory activity; on the one hand it suppresses type immunity [37] and inhibiting the proliferation of mononuclear cells [38] and on the other hand it sends activation signals to T-cells stimulated in the presence of inflammatory signals [39]. These activities may explain thalidomide's diverse effects; for example, it has been shown to suppress some autoimmune conditions associated with humoral type cellular immunity as well as promote the promotion of T-cell responses. The mechanisms for these activities remain unclear, but they may also explain the bidirectional effect of thalidomide on TNF- $\alpha$  production *in vitro* which is TNF- $\alpha$  dependent.

The side effect profile (that includes peripheral neuropathy), the low aqueous solubility and the stability of thalidomide may impose limitations on its use. It can be tolerated. Thalidomide continues to be used clinically as a result of its efficacy. Reports in the literature have suggested that the side effects may only be associated with thalidomide. To get around this problem it has been proposed that the administration of a single thalidomide enantiomer or a racemic mixture present in non-toxic doses may improve the side effect profile. However, it has been reported that thalidomide rapidly undergoes racemization under both *in vitro* and *in vivo* conditions.

seem likely that novel compounds designed using thalidomide structure as a lead would allow optimisation of its immunological and anticancer properties while decreasing its side effects (Figure 1).

Celgene Corporation initiated a medicinal chemistry program to design and prepare thalidomide analogues. Initial focus of this program was on improving thalidomide's anti-TNF- $\alpha$  properties [42,43]. Primary screening is based on the ability of these compounds to inhibit the TNF- $\alpha$  production by activated human PBMC. Subsequent *in vitro* assays include testing for TNF- $\alpha$  inhibition in activated human and rat whole blood. A primary *in vivo* assay for potent TNF- $\alpha$  inhibitors is to test the analogues for their ability to decrease TNF- $\alpha$  levels in LPS treated mice. More recently the emphasis has changed to focus not only on anti-inflammatory properties but also anticancer properties.

#### 4. Characterisation of thalidomide analogues

Thalidomide analogues are presently being assessed in laboratory studies and several reports into their activity have been published. During the characterisation of these compounds it has become apparent that there are at least two distinct classes of thalidomide analogues. These have been termed SelCIDs™ consisting of PDE4 inhibitors and IMiDs™ which do not inhibit PDE4 and act *via* an unknown mechanism(s) [42-46]. Both groups of compounds are potent TNF- $\alpha$  inhibitors, although T-cell co-stimulatory activity is limited to the latter group [39,46].

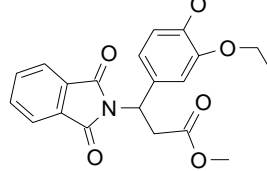
##### 4.1 SelCID analogues

Information on the characterisation of SelCID analogues, a number of which contain the phthalimide moiety of thalido-

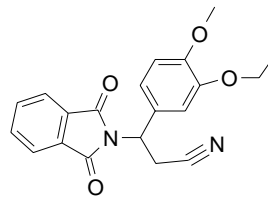
the S-enantiomer of one IMiD fold more potent against TNF-mide [48]. Thalidomide was originally a TNF- $\alpha$  inhibitor, although more recently it has also been reported [38]. Interferon- $\gamma$  is a thalidomide analogue with only minimal activity. Other thalidomide analogues with only minimal activity are also potent inhibitors of LPS stimulated hPBMC [46,49].

#### 5. Differential effects of thalidomide analogues on cytokine production

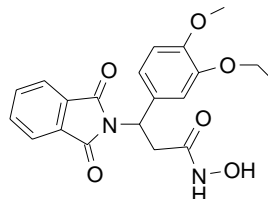
The SelCID and IMiD analogues have different effects on cytokine production by monocytes or T-cells. During LPS treatment it was shown that in addition to inhibiting TNF- $\alpha$ , IMiDs potently inhibit IL-1 $\beta$ , IL-6 production and upregulation of CD11b. In contrast, SelCIDs weakly inhibit TNF- $\alpha$  and have a more modest effect on IL-10 stimulation of IL-6. During T-cell co-stimulation of PBMC by IMiDs there is strong inhibition of  $\gamma$  associated with increased TNF- $\alpha$  production. In contrast, more, during T-cell co-stimulation with SelCIDs TNF- $\alpha$  and soluble IL-2 receptor expression in an IL-2 dependent manner. These effects are observed as decreased T-cell surface expression of CD137 (see observations). These effects are also observed in cocultures of PBMC cultures. The effects are similarly highlighted by the bidirectional regulation of IL-12 production; decreased production while increased production of T-cell activation.



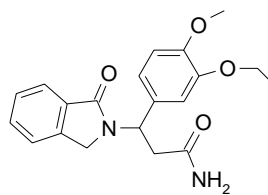
0.12



0.115



4.3



## 6. Other *in vitro* characterisation

A number of laboratories have recently published other *in vitro* data that highlights the potential of these compounds for future clinical use. For example, one group has shown that thalidomide analogues are more effective than thalidomide in the inhibition of HIV replication in human macrophages [50]. Furthermore, this activity appears to be due to inhibition of transcription factor NF- $\kappa$ B-binding activity. Another group has shown that the previously characterised [51] SelCID analogue, CC-3052, was able to inhibit HIV replication in chronically and acutely infected monocytes and T-cells [52]. This activity was attributed to its inhibitory effect on TNF- $\alpha$  production by both cell types since NF- $\kappa$ B is unaffected by this analogue [51].

Thalidomide analogues also clearly possess enhanced activity over the parent compound in their relative effects on the growth inhibition of chemoresistant human myeloma cells [25]. IMiD analogues were far more effective than both thalidomide and SelCID analogues with IC<sub>50</sub> values of 0.1 - 1.0  $\mu$ M. Furthermore, their effect appeared to be IL-6 dependent. Subsequently at least one subgroup of SelCID analogues possess potent antimyeloma activity and this appears to be IL-6 independent (unpublished results). This activity is also observed in a range of solid tumour types and is currently under investigation. Furthermore, unpublished preliminary studies suggest that both SelCID and IMiD analogues demonstrate improved anti-angiogenic activity in both rat and human *in vitro* systems and this is clearly an area of considerable interest.

safety and pharmacokinetics [54] were observed in this trial. CDC-501 was evaluated in a Phase II double-blind trial for the treatment of moderate to severe rheumatoid arthritis at a number of sites. A drop of 70% in disease activity index (CDAI) will be compared to placebo. The trial was expanded in late 2000 to include a longer treatment period and should be completed by early 2001.

Celgene has also begun clinical trials with SelCID, CDC-998. CDC-998 is a more potent than thalidomide inhibitor of TNF- $\alpha$  stimulated human PBMC. CDC-998 is a PDE4 inhibitor with a PDE4 IC<sub>50</sub> of 0.1  $\mu$ M. CDC-998 shows minimal inhibition of PDGF-stimulated T-cell proliferation. One of the major side effects of thalidomide evaluated in the clinic has been peripheral neuropathy. Studies conducted in dogs and studies to assess the emetic effects of CDC-998 have shown no emetic effects. CDC-998 has completed initial Phase I clinical trial and has now moved forward into a Phase II trial. A Phase II trial was initiated in the UK at the end of 2000.

## 8. Clinical development of IMiDs

The clinical development of the IMiDs was initiated in 2000. The IMiDs are a class of compounds that potently inhibit TNF- $\alpha$  and have been shown to inhibit proliferation in LPS stimulated human T-cells. IMiDs stimulate T-cell proliferation in animal models to a greater extent than thalidomide. IMiD (CC-501) completed a Phase I clinical trial in 2000. It was found to be safe and well tolerated and CDC-501 was therefore advanced to a Phase I/II clinical trial in relapsed and refractory multiple myeloma at the Dana-Farber Cancer Institute and the Arkansas Medical Centre. These studies are ongoing.

Expert Opin. Biol. Ther. (2001) 1(4)

DR. REDDY'S LABS., INC. EX. 1

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.