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derivatives fall into at least two categories; selectiv
(SelCID), which are phosphodiesterase Type 4 (PI
nomodulatory drugs (IMiD), similar to thalidomi
mechanism(s). These compounds are in the proces
laboratory studies and are also now being assess
clinical studies. In this review we will highlight th
novel classes of compound in terms of their effe
and non-immunological systems *in vitro*. We wi
studies are enabling the characterisation and de
pounds into clinically relevant drugs in widely va
we will describe the various clinical studies of le
progress and speculate as to the potential and fu
exciting compounds.

Keywords: anti-TNF-α, antitumour, immunotherapy, PDE4, T
analogues

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1. History of thalidomide use

Thalidomide (α-*N*-phthalimidoglutarimide) is a syn
acid designed and synthesised by the German compan
in the mid-1950s. Thalidomide was marketed as a non
urates in Europe, New Zealand, Australia and Canada
led to the drug's popularity as a sleeping aid. However
FDA approval in the United States at this time due to
ciated with the drug's use. However, early in 1960 ala
thalidomide was associated with neuropathies [1] and b
was taken off the market thalidomide had been take
women to counter the effects of morning sickness re
children being born with thalidomide type birth defect

Forty years later, thalidomide is now established as
tory and anti-inflammatory drug [3-5]. In fact, for man
the World Health Organization (WHO) drug of cho

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®) 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 tha
of cancers. Indeed, it has been p
tumours arise in sites of chronic i
respect it is also worth noting that
upregulation of endothelial integrin
is crucial for new vessel formation [3

More recently, thalidomide has be
nomodulatory activity; on the one
type immunity [37] and inhibiting th
mononuclear cells [38] and on the oth
tion signals to T-cells stimulated in
tory signals [39]. These activitie
thalidomide's diverse effects; for exa
some autoimmune conditions asso
type cellular immunity as well as po
the promotion of T-cell responses
mechanisms for these activities rem
they may also explain the bidirecti
on TNF-α production *in vitro* w
dependent.

The side effect profile (that in
neuropathy), the low aqueous solub
stability of thalidomide may impos
can be tolerated. Thalidomide cont
has always been used clinically as a
reports in the literature have sugg
effects may only be associated with t
get around this problem it has been
istration of a single thalidomide en
racemic mixture present in nor
improve the side effect profile. How
reported that thalidomide rapidly
under both *in vitro* and *in vivo* cond

seem likely that novel compounds designed using thalidomides 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-α properties [42,43]. Primary screening is based on the ability of these compounds to inhibit the TNF-α production by activated human PBMC. Subsequent *in vitro* assays include testing for TNF-α inhibition in activated human and rat whole blood. A primary *in vivo* assay for potent TNF-α inhibitors is to test the analogues for their ability to decrease TNF-α 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

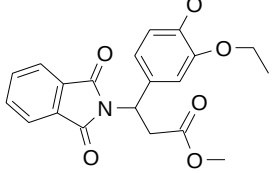
Thalidomide analogues are presently being assessed in laboratory studies and several reports into their activity have been published. During the characterisation of these compounds it has become apparent that there are at least two distinct classes of thalidomide analogues. These have been termed SelCIDs™ 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-α inhibitors, although T-cell co-stimulatory activity is limited to the latter group [39,46].

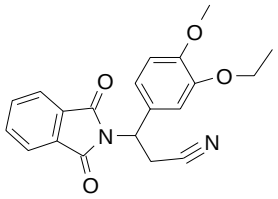
4.1 SelCID analogues

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

5. Differential effects of
logues on cytokine prod

The SelCID and IMiD analogu
effects on cytokine productio
monocytes or T-cells. During L
was shown that in addition to i
IMiDs potently inhibit IL-1β,
IL-6 production and upregula
contrast, SelCIDs weakly inhib
more modest effect on IL-10 sti
on IL-6. During T-cell co-stim
PBMC by IMiDs there is strong
γ associated with increased T
more, during T-cell co-stimulat
TNF-α and soluble IL-2 recept
an IL-2 dependent manner. Th
decreased T-cell surface expressi
observations). These effects are
lation of PBMC cultures. The i
similarly highlighted by the bid
IL-12 production; decreased pr
lation while increased producti
T-cell activation.





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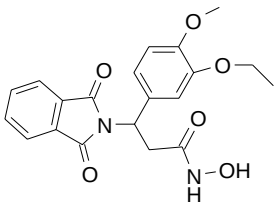

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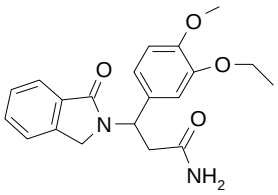

4.3

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-κB-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-α production by both cell types since NF-κB 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_{50} values of 0.1 - 1.0 μM. 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
ated in a Phase II double-blinde
trial for the treatment of modera
a number of sites. A drop of 70
activity index (CDAI) will be co
was expanded in late 2000 to inc
and treatment period and should

Celgene has also begun clini
SelCID, CDC-998. CDC-998
more potent than thalidomide i
stimulated human PBMC. CD
inhibitor with a PDE4 IC_{50} o
shows minimal inhibition of PD
One of the major side effects o
evaluated in the clinic has been e
uated in dogs and studies to ass
have shown no emetic effects
CDC-998 has completed initial
has now moved forward into a
was initiated in the UK at the en

8. Clinical development o

The clinical development of the I
initiated in 2000. The IMiDs are a
that potently inhibit TNF-α and
mation in LPS stimulated human
stimulate T-cell proliferation in ar
to a greater extent than thalidomi
501) completed a Phase I clinical
2000. It was found to be safe an
tested and CDC-501 was therefo
Phase I/II clinical trial in relapsed
loma at the Dana-Farber Cancer
Arkansas Medical Centre. These st

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