Discovery Technology

HDAC Inhibitors: New Promise in the Treatment of Immune and Inflammatory Disease

The development of HDAC inhibitors (HDAC-Is) has emerged as an important strategy in the design of new drugs to treat cancer, but more recently they have also found application in the treatment of immune and inflammatory diseases.

Histone proteins and DNA collectively constitute the nucleosomes, the structural units of chromatin that are essential for DNA packaging in eukaryotic cells. Histone deacetylases (HDACs) are enzymes that deacetylate lysines in the tail regions of histones. Through this mechanism, HDACs play a critical role in the modulation of chromatin architecture, and govern the expression of oncogenes, tumour suppressor genes and inflammatory genes (1).

The development of histone deacetylase inhibitors (HDAC-Is) has, until recently, been principally driven by their potential as anticancer agents; however, there is emerging evidence that they could also have utility as therapeutics in the treatment of chronic immune and inflammatory disorders such as rheumatoid arthritis, psoriasis, inflammatory bowel disease (IBD), multiple sclerosis and systemic lupus erythematosus (SLE).

The HDAC enzyme family consists of four subclasses. Class I HDACs are nuclear proteins whose tissue expression is ubiquitous. By comparison, Class II and IV HDACs are found in both the nucleus and the cytoplasm, and exhibit greater tissue-specific expression. Class I, II and IV HDACs are all zinc-dependent enzymes and are the exclusive focus of this article; the class III HDACs – or sirtuins – constitute a structurally distinct subfamily of NAD-dependent enzymes and are not discussed here.

CANCER THERAPY

HDAC inhibitors developed to date fall into four main structural classes: carboxylates, hydroxamates, benzamides, and cyclic peptides. All of these HDAC-Is contain common structural features, including a zinc-binding group, a linker that occupies the channel leading to the HDACs’ active site and a surface recognition ‘cap’. Representative examples of each structural type, some of which have been the subject of extensive clinical development, are listed in Table 1 (2). All of these compounds – which were originally developed as anticancer agents – exhibit distinct patterns of HDAC sub-type selectivity, the therapeutic significance of which remains the source of considerable discussion (3).

Over the past decade, several HDAC-Is have been evaluated in cancer patients, with the greatest success found in the treatment of haematological malignancies such as T-cell lymphoma (4). In 2006, SAHA (vorinostat, Zolinza®) became the first HDAC-I to be approved for cancer (advanced cutaneous T-cell lymphoma) (5). More recently, the development of HDAC-Is for the treatment of patients with solid tumours has begun to gain momentum, and is indeed a cornerstone of our HDAC oncology programme at Karus (6). At the time of writing, there is one approved HDAC-I and a further nine under evaluation in efficacy trials in cancer. Further, in light of the potent anti-tumour synergy observed with HDAC-Is and molecular-targeted cytostatic and cytotoxic agents (7), more than 70 co-agent combination therapy trials are currently in progress (8).

POTENTIAL IN IMMUNE AND INFLAMMATORY DISORDERS

To date, the overwhelming majority of drug development in the HDAC-I arena has focused on the treatment of cancer. However, a number of HDAC-Is have emerged as promising anti-inflammatory agents (9). Recently, studies to elucidate the precise immunomodulatory mechanisms of action of these molecules and the assessment of their in vivo efficacy in a diverse range of animal disease models have been reported (10), with the greatest level of activity being in a rheumatoid arthritis (RA) setting (11).

Rheumatoid Arthritis

On a broad level, it has been shown that HDAC-Is confer their anti-inflammatory properties through the inhibition of nuclear factor-kappa B (NF-kB) transcriptional activity, the suppression of a spectrum of pro-inflammatory cytokines and matrix metalloproteases (MMPs), and the inhibition of rheumatoid arthritis.

Table 1: Representative examples of each structural type of HDAC-inhibitor

<table>
<thead>
<tr>
<th>Class</th>
<th>Representative Examples</th>
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<tbody>
<tr>
<td>Carboxylates</td>
<td>butyrate, sodium butyrate, sodium valproate (VP-101)*, phenylbutyrate</td>
</tr>
<tr>
<td>Hydroxamates</td>
<td>trichostatin-A, vorinostat (SAHA)<em>, belinostat (PXD101)</em>, panobinostat (LBH589)*, JNJ-26481585, ITF-2357, SB-939</td>
</tr>
<tr>
<td>Benzamides</td>
<td>CRA-024781, mocetinostat (MGCD0103)<em>, entinostat (SNX-275)</em>, CI-944</td>
</tr>
<tr>
<td>Cyclic Peptides</td>
<td>romidepsin (FK228)*</td>
</tr>
</tbody>
</table>

*In Phase II trials or beyond for cancer (1 February 2009)
In addition to RA, it has been shown that HDAC-Is have great promise in the treatment of several other immune/inflammatory diseases.

In a rat adjuvant-induced arthritis model, phenylbutyrate and trichostatin-A were seen to induce expression of p16 and p21 in RASFs, resulting in suppression of pannus formation, reduced joint swelling, and the prevention of cartilage and bone destruction (15). Additionally, trichostatin-A has been reported to sensitize RASFs for TRAIL-induced apoptosis (16) and, in combination with ultrasound, induce apoptosis of RASFs (17).

In other reports, vorinostat was seen, in vivo, to reduce the expression of pro-inflammatory cytokines (18), including TNF-α, IL-1β and IFN-γ; also, in preclinical rodent models of type-II collagen-induced arthritis, vorinostat and entinostat attenuated paw swelling and decreased bone erosion and bone resorption – key hallmarks of the disease (19). In a mouse autoantibody-induced arthritis model, romidepsin suppressed joint swelling, synovial inflammation and bone and cartilage destruction (20). Romidepsin also significantly decreased TNFα and IL-1 levels in synovial tissues, again through induction of p16 and p21 expression, and was seen to inhibit angiogenesis (21). Similar observations have been made with ITF-2357 (22).

**OTHER IMMUNE/INFLAMMATORY DISEASES**

In addition to RA, it has been shown that HDAC-Is have great promise in the treatment of several other immune and inflammatory disorders.

The clinical efficacy of HDAC-Is in inflammatory bowel diseases (IBD) has been disclosed. Local administration of butyrate was seen to be efficacious in the treatment of ulcerative colitis, one major form of IBD (23,24), exerting its activity through inhibition of NF-κB activation in macrophages. In addition, vorinostat and valproate have been shown to ameliorate colitis in preclinical mouse disease models, with a marked suppression of colonic pro-inflammatory cytokines being observed (25).

HDAC-Is have been shown to confer efficacy in preclinical models of systemic lupus erythematosus (SLE), an autoimmune disease characterised by elevated levels of cytokines, dysregulated autoantibody production, and renal inflammation. Both trichostatin-A and vorinostat were seen to reduce proteinuria, glomerulonephritis and spleen weight in mouse disease models (26); additionally, suppression of pro-inflammatory cytokines and reduction of autoantibodies associated with anti-SLE efficacy were observed.

Trichostatin-A has been seen to attenuate ovalbumin-induced airway inflammation in a mouse allergic asthma model, suggesting the potential of HDAC-Is in the treatment of respiratory diseases (27). Additionally, HDAC-Is exhibit potent in vivo activity in models of multiple sclerosis (MS): trichostatin-A diminished spinal cord inflammation and neuronal and axonal loss, and ameliorated disability in the relapsing phase of experimental autoimmune encephalomyelitis (EAE), a widely-employed rodent model of MS (28,29).

Finally, there is emerging potential for HDAC-Is in the treatment of psoriasis, with HDAC1 having been reported to be over-expressed in psoriatic skin (30).

**NOVEL ANTI-INFLAMMATORY HDAC-Is**

At Karus, our R&D activities in the HDAC area have largely focused on the development of a novel class of cyclic peptides to treat both cancer and inflammatory diseases. These compounds exhibit best-in-class biochemical and cellular activity, and exert a unique, highly potent and sustained pharmacodynamic marker modulatory profile. With our partner, EOS SpA (Milan, Italy), we are currently planning our first cancer clinical trials. However, in addition to our cancer programme, we have designed and developed a sub-series of HDAC-Is that exhibit highly potent anti-inflammatory activity. Together with our oncology programme, we have active HDAC R&D projects in both psoriasis and rheumatoid arthritis, and will be initiating clinically tracked activities in the coming months.

An example of representative preclinical RA efficacy data obtained for an early lead compound is shown in Figure 1. This early lead was dosed in a prophylactic mouse model of type II collagen-induced arthritis, and was seen to significantly ameliorate the disease, suppressing pannus formation, bone resorption and cartilage damage by...
approximately 60 per cent at very low, intermittent doses (1mg/kg every four days). The efficacy of this early lead is comparable with literature data for vorinostat administered 50mg/kg daily (19) and the biological TNFα inhibitor, Enbrel (etanercept), administered 30mg/kg daily. We have subsequently optimised the potency and the physiochemical and pharmacokinetic properties of this early lead, and will shortly nominate a preclinical development candidate that we believe will represent the first of an exciting class of novel HDAC-I therapeutics for the treatment of rheumatoid arthritis.

CONCLUSION

HDAC-IIs represent a class of promising agents for the treatment of immune and inflammatory disorders such as RA, IBD, MS, SLE, psoriasis and asthma – as well as transplant rejection, endotoxaemia and hepatic injury – by simultaneously, synergistically or epigenetically modulating multiple targets in the pathogenesis of these diseases. We anticipate that, over the coming years, there will be an increase in clinical activity in these therapeutic areas using HDAC-IIs, and that the agents will have great potential as new anti-inflammatory therapies.

References

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