OVERVIEW

• Low nM HDAC2/3 inhibitors developed with >250 fold selectivity over other HDAC’s

• Potential utility in N-CoR/SMRT driven leukaemias such as AML and DLBCL

• Potent activity (100-500nM GI50) in NCI60 cell panel against several tumour types

• In vitro ADME and in vivo PK data available

THE OPPORTUNITY

HDAC inhibitors (HDI) are effective inducers of apoptosis, cell cycle arrest and/or differentiation in malignant cells. Most available HDIs are pan inhibitors with poor isoform selectivity and high toxicity. The field currently needs HDI that will target specific enzymes known to play a central role in disease leading to improved efficacy, reduced toxicity and improved clinical utility.

Novel and selective compounds with HDAC2/3 inhibitory activity have been rationally designed under funding from Cancer Research UK. CRT is now seeking a co-development (or licensing) partner for the further development of these novel inhibitors.

BACKGROUND AND RATIONALE

HDAC-3 activity has been shown to be tightly linked to N-CoR/SMRT repressor complexes (1). HDAC-3 selective inhibitors are therefore expected to have therapeutic activity in N-CoR/SMRT-mediated cancers e.g. AML, Diffuse Large B-cell Lymphoma (DLBCL) and some types of breast and endometrial cancers. Moreover, siRNA-mediated knock-down of HDAC-3 has been shown to be sufficient to decrease proliferation, survival and/or migration in ovarian, colon, cervical and synovial carcinoma cell lines (2-4). Thus, selective inhibition of HDAC-3 is likely to be an effective strategy for the treatment of various cancer types.
The AML-associated PML-RARα fusion protein silences expression of genes normally required for myeloid cell differentiation by binding to retinoic acid response elements (RaRE) in the promoter of RARα target genes and recruitment of SMRT/N-CoR corepressor complexes. In addition to HDAC3, the other “core” components of SMRT/N-CoR corepressor complexes are GPs2, TBL1 and TBL1R. Recruitment of HDAC3 leads to repression of target gene transcription. Inhibition of HDAC3 activity (by small chemical compounds or siRNA) prevents PML-RARα mediated repression leading to induction of RARα target gene expression and results in differentiation, cell cycle arrest and/or apoptosis in leukaemic cells. The model is based on PML-RARα positive APL but N-CoR/SMRT complexes are also involved in transcriptional repression mediated by other leukaemic fusion proteins and BCL-6 (in this case the complex is termed B-CoR).

HDACs BEYOND CANCER

Although, the development of HDAC inhibitors has principally been driven by their potential as anti-cancer agents, there is emerging evidence that HDAC inhibitors could have utility in the treatment of chronic immune and inflammatory disorders, including rheumatoid arthritis (RA) (5). In collaboration with Michael McDermott’s group in Leeds it has been demonstrated that HDIs represent a novel approach for RA therapy and selective inhibition of HDAC-2/3 may improve therapeutic margin as compared to pan HDAC inhibition (6).

POTENT AND SELECTIVE HDAC-3 INHIBITORS

• The lead compound has low nanomolar potency against HDAC-2 and 3 in biochemical assays and selectivity over the majority of other HDAC family members.
• The lead compound showed significant growth inhibition in a number of cell lines in the NCI-60 panel with GI50 of 100–200nm in leukaemia cell lines and <500nM in most of breast, colon, melanoma and ovarian cell lines tested (7).
• The current lead compound promotes growth inhibition apoptosis and differentiation in AML cells (7).
• The current lead compound shows good drug like properties and desirable in vitro ADME profile (low molecular weight, microsomal stability, low CYP450 inhibition).
• In vivo PK suggests good oral bioavailability of ~30% and sustained exposure above required cellular GI50 concentrations.
• A patent application was filed on the lead series in July 2011.

Table: Selectivity vs. HDAC3 (fold)

<table>
<thead>
<tr>
<th>HDAC</th>
<th>Selectivity vs. HDAC3 (fold)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDAC1</td>
<td>&gt;250</td>
</tr>
<tr>
<td>HDAC2</td>
<td>1.9</td>
</tr>
<tr>
<td>HDAC3</td>
<td>1</td>
</tr>
<tr>
<td>HDAC4</td>
<td>&gt;250</td>
</tr>
<tr>
<td>HDAC6</td>
<td>&gt;1000</td>
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<tr>
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<td>&gt;250</td>
</tr>
<tr>
<td>HDAC8</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>HDAC10</td>
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</table>

FUTURE DEVELOPMENT PLANS

Further assessment of this compound series is currently ongoing within CRT and in vivo proof of efficacy studies are underway.

ORIGINATING INSTITUTE

This programme was developed at the University of Leeds under the direction of Professor Ron Grigg.

REFERENCES


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