

CRT Licensing Opportunity



Novel Histone Deacetylase (HDAC) – 2 and 3 Selective Inhibitors

- Isoform selective HDAC-3 inhibitors are being rationally designed for the treatment of AML and other N-CoR/SMRT related malignancies
- The lead series has low nM biochemical potency
- The lead series has <math><500\text{nM}</math> - Desirable *in vitro* ADME and *in vivo* PK properties have been demonstrated

SMALL MOLECULES | Hit-to-Lead

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Commercial Opportunity

Novel compounds with HDAC-3 inhibitory activity have been rationally designed under funding from Cancer Research UK. HDAC-3 activity has been shown to be tightly linked to N-CoR/SMRT repressor complexes (1). Therefore these inhibitors are expected to have therapeutic activity in N-CoR/SMRT-mediated cancers like Acute Myeloid leukaemia (AML). CRT is now seeking a co-development (or licensing) partner for the further development of these novel inhibitors. Data available under confidentiality includes biochemical in vitro ADME profiles, *in vivo* PK, phenotypic efficacy studies and *in vitro* PD biomarker activity.

Background and Rationale

HDAC inhibitors (HDI) are effective inducers of apoptosis, cell cycle arrest and/or differentiation in malignant cells, with selectivity versus normal 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 specific diseases leading to improved efficacy and tolerability.

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 B-cell Lymphoma (DBCL) 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.

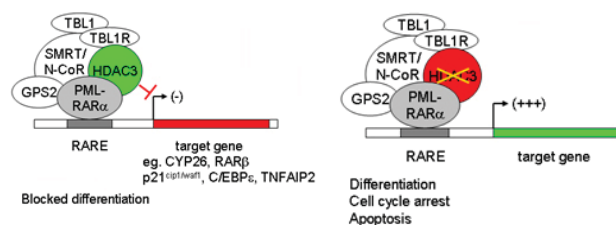


Figure 1. HDAC3-mediated transcriptional repression in APL.

The AML-associated PML-RAR α fusion protein silences expression of genes normally required for myeloid cell differentiation by binding to retinoic acid response elements (RARE) in the promoter of RAR α 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-RAR α mediated repression leading to induction of RAR α target gene expression and results in differentiation, cell cycle arrest and/or apoptosis in leukaemic cells. The model is based on PML-RAR α 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).

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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.

Potent and Selective HDAC-3 Inhibitors

- The series of inhibitors has been developed with the benefit of extensive CADD and predictive modelling expertise.
- 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, as shown below.

	Selectivity vs. HDAC3 (fold)
HDAC1	>250
HDAC2	1.9
HDAC3	1
HDAC4	>250
HDAC6	>1000
HDAC7	>250
HDAC8	>1000
HDAC10	>250

Table 1. HDAC selectivity of lead compound

- The current lead compound promotes growth inhibition and differentiation in AML cells with <500nM IC₅₀
- The current lead compound shows good drug like properties and desirable *in vitro* ADME profile (low molecular weight, microsomal stability, low CYP450 inhibition) and favourable *in vivo* PK properties.
- The lead compound showed significant growth inhibition in a number of cell lines in the NCI-60 panel with GI₅₀ of <100nm in all leukaemia cell lines tested and <500nM in most of breast, colon, melanoma and ovarian cell lines tested.
- Preliminary PK suggests good oral bioavailability.
- A patent application currently being filed on the lead series.

Future Development Plans

The development of this compound series is currently ongoing within CRT. Biomarker development and *in vivo* proof of efficacy studies are key future development milestones.

Originating Institute

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

References

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