Towards new drugs for trypanosomatid diseases based on specific high-affinity inhibitors for RNA editing ligase 1

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Abstract:

Messenger RNA editing by uridylyl insertion/deletion is a unique process in kinetoplastid mitochondria and therefore a potential drug target (Read, Lukeš and Hashimi, 2016). We previously showed that knock-down of RNA editing ligase 1 (REL1), an essential component of ~20S editosome, is lethal in *Trypanosoma brucei* (Schnaufer *et al.*, 2001). REL1 is highly conserved throughout trypanosomatids, which, together with what is known about mitochondrial biology in these organisms, suggests an essential function in other pathogens like *T. vivax*, *T. congolense*, *T. cruzi* and *Leishmania spp.* as well. The crystal structure of the catalytic domain of *Tb*REL1 (Deng *et al.*, 2004) shows a unique active centre with a well-defined ATP binding site. Together with the low sequence and structural similarity between REL1 and DNA ligases (which represent the closest mammalian homologs), this suggests the feasibility of developing highly specific REL1 inhibitors with little side effects. Recently, we developed a new REL1 activity assay suitable for high-throughput screening (HTS) and a proof-of-concept screen against the LOPAC library resulted in a hit rate of 1.7% and identified interesting REL1 inhibitors such as suramin and the flavonoid myricetin (Zimmermann *et al.*, 2015).

Here we report results from HTS screening campaigns of diversity and kinase inhibitor-focused compound libraries at the Dundee Drug Discovery Unit and the European Screening Centre Newhouse and subsequent hit optimisation efforts that led to the identification of several promising compound series with potency up to an IC_{50} of 20 nM. Furthermore, we have expressed REL1 orthologs from four kinetoplastid parasites, *T. cruzi*, *T. congolense*, *T. vivax* and *L. donovani*, in *Escherichia coli* cells and purified all proteins in soluble form. REL1 enzymes from *T. cruzi*, *T. vivax* and *L. donovani* are functional in the HTS activity assay and some *Tb*REL1 inhibitors show similar potency against these orthologs. Aided by the orthologous proteins we are continuing the lead development of the initial hits and analogues

and will present findings on structure-activity relationships, biophysical characterization by Differential Scanning Fluorimetry and Microscale Thermophoresis, and activity against parasites.

Bibliography:

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