Chemistry

Non-confidential summary

DUB*target*™-001: The first compound library comprising novel small molecules designed to target deubiquitylase enzymes

Summary

Ubiquigent Ltd and The Drug Discovery Unit at the University of Dundee have jointly developed one of the first commercially available compound libraries designed to target deubiquitylase (DUB) enzymes, DUB*target*™-001.

The library has been screened against USP2 (a key target opportunity in cancer) employing Ubiquigent's DUB*profiler*™ – DUB affinity and selectivity profiling – platform. This data as well as the physical library is now available to access, along with the option to screen the library against any of the other 40 DUB enzymes available as part of DUB*profiler*™ to help inform starting points for drug development programmes.

Ubiquigent is now offering parties access to the library, associated data and further characterisation of the compound set using DUB*profiler*™ to support their ubiquitin-system drug discovery programmes.

Ubiquigent is a unique enabler of ubiquitin-system targeted drug discovery.

We provide access to the necessary expertise, Drug Discovery Services, high quality Research Tools and Chemistry required to support our commercial and academic partners in pursuing ubiquitin system-focused drug discovery programmes, and in undertaking basic research.

Library Design

The library has been screened against USP2 (a key target opportunity in cancer) employing Ubiquigent's DUB*profiler*™ – DUB affinity and selectivity profiling – platform. This data as well as the physical library is now available to access, along with the option to screen the library against any of the other 40 DUB enzymes available as part of DUB*profiler*™ to help inform starting points for drug development programmes.

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We generated a virtual library by combining chosen warheads with monomers selected to produce lead-like structures. The virtual library was then docked into a published structural model of USP2 (PDB 2IBI). Monomers were then prioritised if they gave positive results in the model to generate a partially targeted library suitable for hit identification against any DUB target.

The compound physical properties were calculated and monomers selected in order to generate a lead-like library design. Using this filtering approach the DUB*target*™-001 library was synthesised.

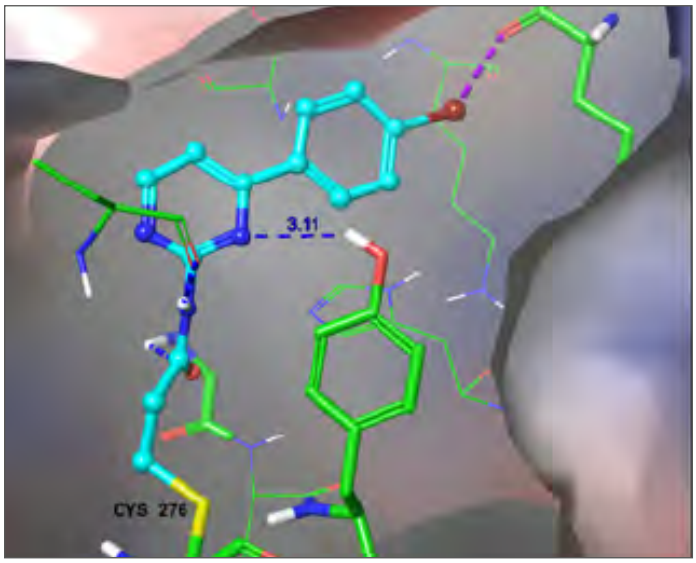

Figure 1:
Depicting the docking pose of a covalently bound compound (cyan, ball and stick) with Cysteine 276 in the USP2 active site. The binding mode was generated using the covalent docking protocol of Schrodinger's modelling suite. The important active site residues involved in polar interactions with the ligand are depicted as sticks and key interactions are highlighted as dotted lines (hydrogen bonding blue, polar in purple).

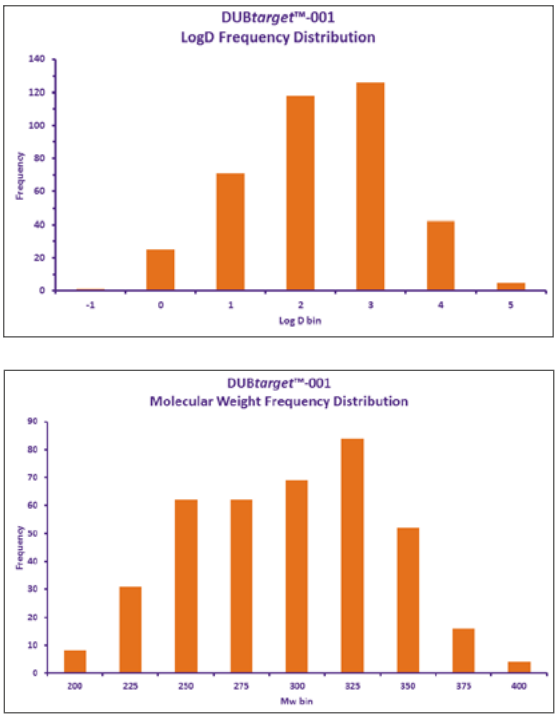

Figure 2:
Calculated properties of the DUB*target*™-001 library

Library Characterisation

DUB*target*™-001 was screened (N=2) in single point mode (at 100µM) against USP2 using the DUB*profiler*™ platform. 'Hits' were determined where the single point compound inhibition assay data sits outside 3x the standard deviation of the positive (non-inhibited) DUB control data in both experiments (Figure 3) where the assay Z' for the two screening assays were 0.67 and 0.74.

The data demonstrates a hit rate of 9.3% for the DUB*target*™-001 library in this USP2 screen. The hits are structurally diverse.

DUB*profiler*™ is a DUB assay platform that has been developed by Ubiquigent that measures the cleavage – and thus de-quenching – of rhodamine (110)-glycine from the substrate ubiquitin-rhodamine (110)-glycine. The platform allows any number of compounds to be rapidly screened for inhibitor activity across up to 40 individual DUB targets chosen to be representative of all the five DUB families. Compounds may be screened initially in single concentration then in IC_{50} mode.

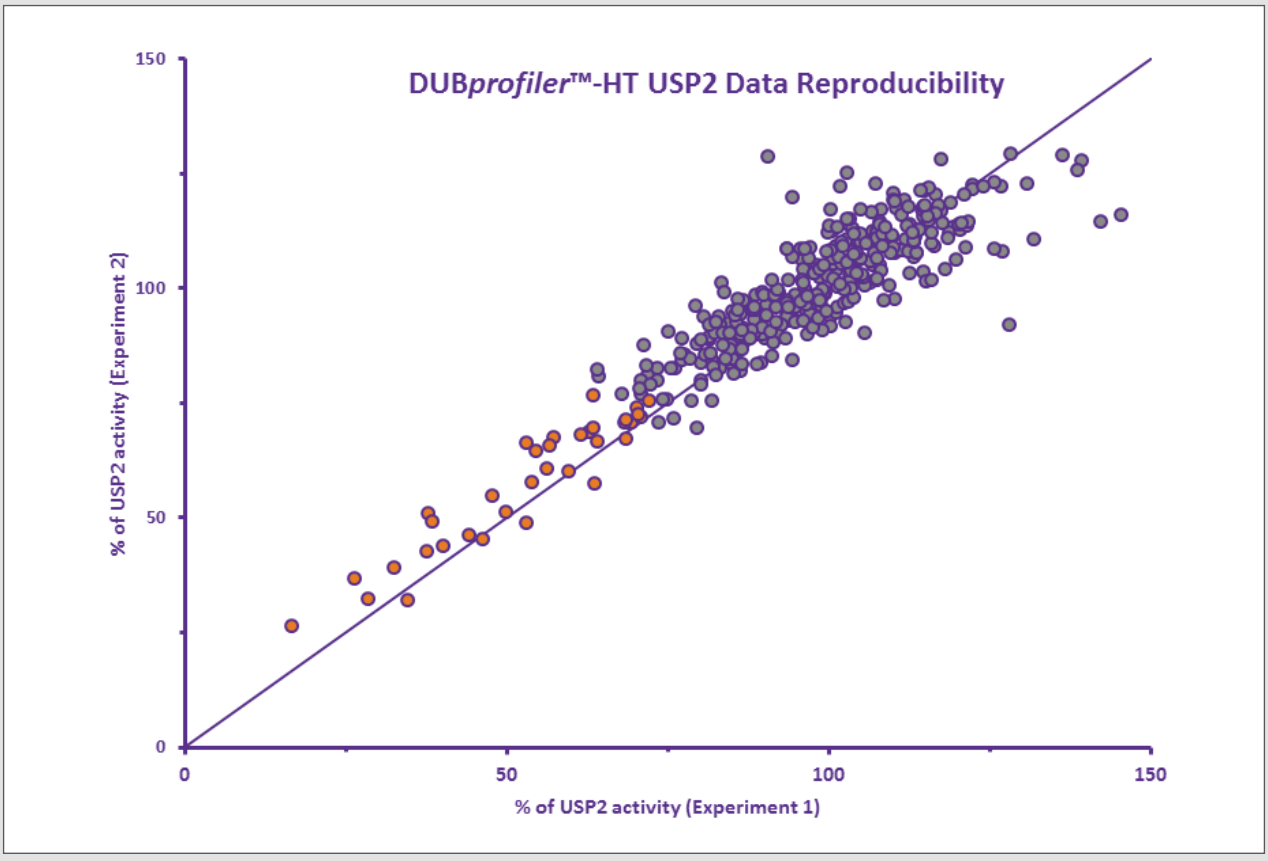

Figure 3:
Reproducibility plot: Screening of DUB*target*™-001 (N=2) in single point mode (at 100µM) against USP2. Inhibitors identified as orange filled circles sit outside of three times the standard deviation of the positive enzyme control data. Screening data has been compound autofluorescent signal corrected.

Background

Ubiquitylation, like phosphorylation, describes a reversible post-translational protein modification. Ubiquitylation or 'ubiquitination' may control the protein substrate's destiny – in respect of its turnover – or its signalling functionality. It is a process that refers to the covalent attachment of a small, 76 amino acid protein called ubiquitin to the epsilon-amino group of a lysine residue residing within a substrate protein – which may also be another ubiquitin molecule: This results in either mono- or poly-ubiquitylation of the substrate; the latter being where chains of ubiquitin are attached to the substrate protein. The structure of the chain determines how ubiquitylation regulates protein degradation – in a proteasomal or lysosomal dependent manner, coordinates cellular localisation, activates or inactivates proteins, and can modulate protein-protein interactions. Mono-ubiquitylated proteins may be further ubiquitylated to form substrate attached polyubiquitin chains.

Deubiquitylating enzymes (DUBs) are a family of proteases that reverse the above described process of ubiquitylation by cleaving ubiquitin from substrate proteins or reducing ubiquitin chains to their constituent monomers. In humans there are nearly 100 genes coding for DUBs, which can be classified into two main classes; cysteine proteases (the largest class) and metalloproteases which all together span across five DUB sub-groups. Targeting ubiquitin system family proteins and more specifically the DUBs has been recognised as offering significant new drug discovery opportunities across a range of therapeutic areas.

Despite considerable efforts few well validated small molecule modulators of DUBs have been described in the literature to date, and many of those which are known have a low potency and/or lack specificity; many of these would also be considered to possess non-drug-like structures. That said, more recently the small molecule 'tractability' of DUBs is now being demonstrated by a cadre of commercial and academic drug discovery entities who are reporting success in developing selective and high affinity inhibitors of this enzyme class.

Commercial Offering

Ubiquigent is now seeking partners interested in gaining access to DUB*target*™-001.
The library is available to be accessed in a number of ways, including:

- In its physical form for those wishing to screen it using their in house-assay platforms
- In a virtual form along with the screening data generated against USP2
- In a virtual form along with screening data generated against any other DUB enzyme(s) from the DUB*profiler*™ panel. In this case the data will be generated upon request

If you're interested in exploring how you can access the DUB*target*™-001 DUB targeted library please contact us directly.

For further information please contact:

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