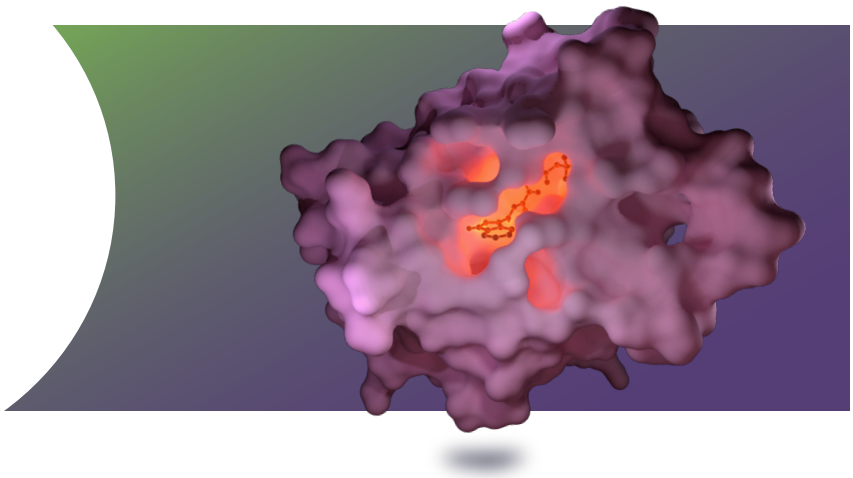
CASE STUDY

CYCLICA

Anticipating Drug-Drug Contraindications with Ligand Express™



Proteome-wide screening provides plausible mechanism for observed drug intolerances

PROBLEM
Drug-drug contraindications can contribute to the costly abandonment of assets in late clinical trials, as was likely the case for the rheumatoid arthritis drug decernotinib.

TECHNOLOGY
Ligand Express™ tools:
$PROBE_X$ Proteome Docking,
$SWITCH_X$ Ligand Effect Prediction,
$DIVE_X$ Systems Biology Discovery Platform

SOLUTION
$PROBE_X$ proteome-wide screening predicts likely drug-protein interactions. Analysis using $DIVE_X$ and $SWITCH_X$ highlighted interactions that may contribute to poor drug tolerance.

INTRODUCTION

Drug molecules are designed to perform a specific function within the body and will do so through an interaction with a target biomolecule, usually a protein. Chemists will optimize a drug's affinity for a desirable target in order to increase its effectiveness in eliciting the desired effect while limiting its proclivity for other biomolecules. Drugs are often evaluated for selectivity towards a target protein compared to other off-target proteins; however, these evaluations are limited in scope to either highly-related proteins or other high-priority targets, meaning that the full landscape of the human proteome is overlooked. Off-target interactions within the body are inevitable, with an interacting protein's exact biological role determining whether an interaction with a drug is benign or harmful. In some cases, non-specific interactions have little consequence when a drug is used independently of other treatments, but can represent a substantial health risk when used with other agents in combination. Instances in which two or more drugs are incompatible due to the harmful adverse effects they cause are called drug-drug contraindications, with this incompatability oftentimes derailing a promising therapeutic. Finding drug-drug contraindications prior to the clinic is challenging given the breadth of proteins to explore and the interconnected nature of biological signalling.

Anticipating possible drug-drug contraindications may have prevented decernotinib's (**Figure 1**) abandonment as a rheumatoid arthritis drug. Decernotinib disrupts the pro-inflammatory protein Janus Kinase 3 (JAK3) that demonstrated poor drug-tolerability when used in combination with other mainstay steroid-based arthritic drugs, namely methylprednisolone (MPL). Application of decernotinib led to over a four-fold increase of MPL within blood plasma which represented an unsafe accumulation of the circulating drug[1]. Exploration of decernotinib's polypharmacological profile using Cyclica's Ligand Express™ revealed potential explanations for its incompatibility with MPL-based treatments. Having these hypotheses earlier in the design process would allow scientists to address these concerns prior to clinical trials and improve an agent's potential for success.

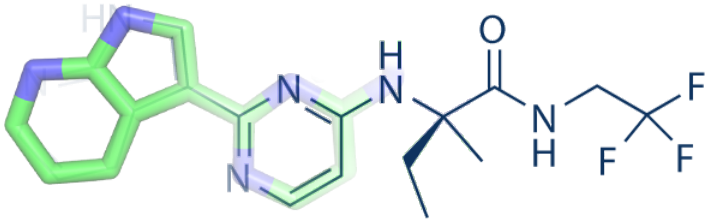


Figure 1. A fused 3D-2D Structure of decernotinib.

METHODOLOGY

Using Ligand Express™ $PROBE_X$ proteome-wide screening technology, Cyclica scientists generated an exhaustive list of putative decernotinib-protein interactions. Next, Cyclica's systems biology tool, $DIVE_X$, was used to explore the biological consequences associated with the predicted interactions. Cognizant of MPL's increased plasma concentrations, $DIVE_X$ was used to focus analysis towards proteins linked to drug metabolism, and specifically explored proteins that would impact steroid-based therapeutics either through direct modification or indirectly though related pathways. Lastly, $SWITCH_X$ was used to determine the exact modulatory effect decernotinib would have on off-target proteins of significance, leading to a comprehensive assessment of their biological impact.

RESULTS

Decernotinib's known target, JAK3, was identified as a leading human hit in the PROBE$_X$ proteome-wide screening procedure (**Figure 2**). JAK1 and JAK2 isoforms were also detected as potential interaction partners; however, they were found at a lower docking scores (representing a lower likelihood of interaction, in agreement with their lower *in vitro* affinities).

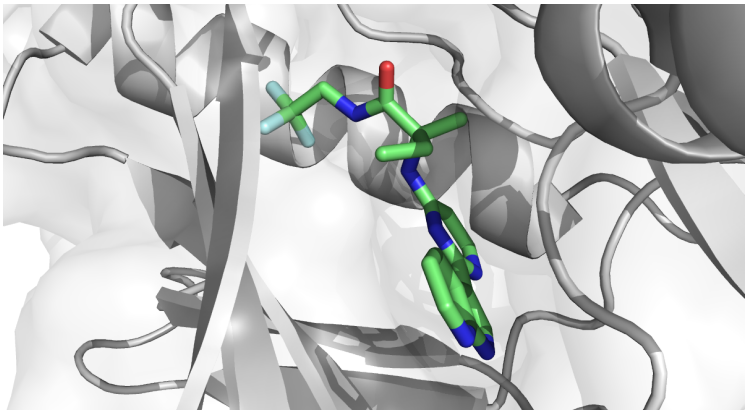


Figure 2. Decernotinib (green) shown in the active site of JAK3 protein (grey).

Besides its top ranking true molecular target, PROBE$_X$ identified several drug-metabolizing cytochrome proteins, including Cytochrome P450 isoforms 2B6 and 7A1, which could influence the metabolism of steroidal medications. A key steroid metabolizing protein is CYP3A4 and has been implicated in many drug-drug contraindications. Human liver microsome assays which explored the inhibition of CYP3A4 with decernotinib demonstrated no discernable interaction between the drug-protein pair, which was in agreement with the PROBE$_X$ results. A follow-up study showed that a metabolite of decernotinib could inhibit CYP3A4 and contributes to the accumulation of MPL[2].

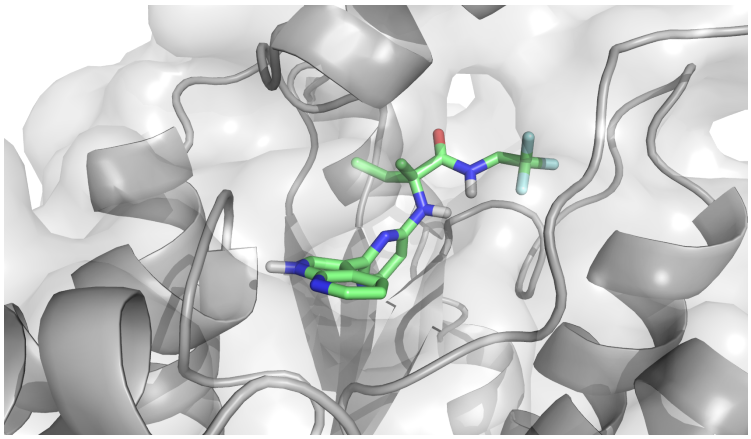


Figure 3. A novel interaction between decernotinib (green) and 11β-hydroxysteroid dehydrogenase 1 (grey) was predited during PROBE$_X$ screening.

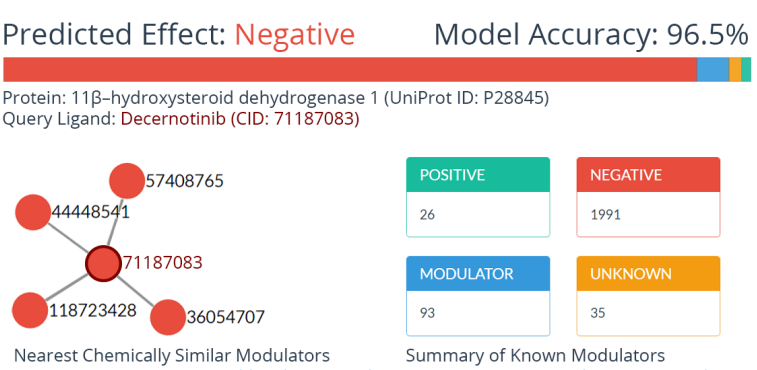


Figure 4. Output generated by the Ligand Express™ SWITCH$_X$ tool. Decernotinib was predicted to inhibit (Negative modulator) 11β-hydroxysteroid dehydrogenase 1.

In addition, the protein 11β–hydroxysteroid dehydrogenase 1 (11 β-HSD) was detected in the screen and represents a promising candidate for further exploration (**Figure 3**). 11β-HSD is a steroid metabolizing enzyme that has been linked to increased levels of the highly-related steroid prednisolone when inhibited[3]. SWITCH$_X$ analysis of decernotinib's inhibitory effect on 11β-HSD predicts inhibition of the protein with 96.5% model accuracy (**Figure 4**).

SUMMARY

Ligand Express™ takes a holistic view of a drug's polypharmacological profile, providing insights into a compound's off-target interactions. Decernotinib's proteome-wide profile was analyzed both naively and with therapeutics likely to be co-treated with decernotinib in mind, which allowed for a general overview of off-target interactions with notable biological consequences and a targeted look at possible drug-drug contraindications. SWITCH$_X$ and DIVE$_X$ analyses identified a possible inhibitory interaction with 11β–HSD, which has previously been linked to increased concentrations of prednisolone. Ligand Express™ is uniquely capable of identifying potential contraindications due to the breadth of proteins it analyses. Additionally, proteome-wide screening and systems biology analysis has utility in elucidating the mechanism-of-action when unanticipated and undesirable side effects are encountered. Together, these functions along with other Ligand Express™ applications, help drive the discovery of safer drugs.

RESOURCES

1. Huang, J. et al. THU0135 Evaluation of Drug-Drug Interactions of VX-509 (Decernotinib), an Oral Selective Janus Kinase 3 Inhibitor, in Healthy Human Volunteers. *Ann. Rheum. Dis.* **73**, 225–226 (2014).

2. Zetterberg, C. et al. VX-509 (Decernotinib)-Mediated CYP3A Time-Dependent Inhibition: An Aldehyde Oxidase Metabolite as a Perpetrator of Drug-Drug Interactions. *Drug Metab. Dispos.* **44**, 1286-1295 (2016).

3. Escher, G. et al. 11β-Hydroxysteroid Dehydrogenase Accounts for Low Prednisolone/Prednisone Ratios in the Kidney. *Endocrinology.* **135**, 101-106 (1994).

CYCLICA INC.
18 King St East, Suite 801
Toronto, Ontario, M5H 1A1, Canada
1-416-304-9201