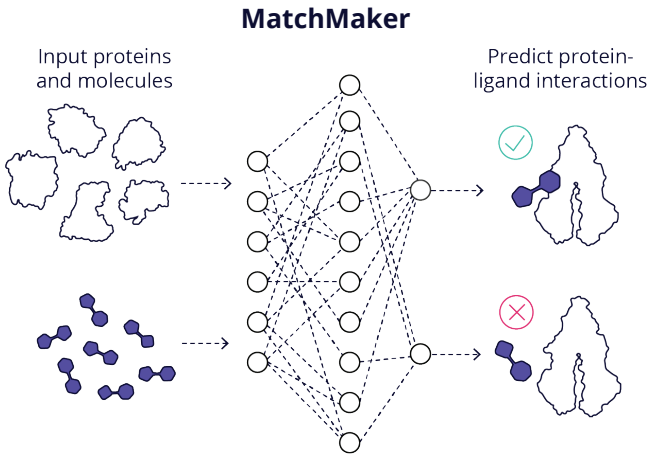
CASE STUDY

Cyclica's Ligand Design platform identifies active molecules for repurposing which can be used to treat Parkinson's

Overview

- Cyclica partnered with Kalia labs from the Krembil Brain Institute at University Health Network to accelerate the discovery of critical medicines for patients suffering from neurodegenerative diseases.
- Powered by MatchMaker, a deep learning engine for the prediction of drug-target interactions, Cyclica's Ligand Design platform enables large-scale library screening to identify compounds predicted to bind to protein targets of interest while avoiding anti-targets.
- In this study Ligand Design was employed to find molecules capable of preventing alpha-synuclein oligomerization.
- Experimental validation demonstrated that three (3) out of nineteen compounds tested from the top twenty-five led to a reduction of alpha-synuclein oligomers independent of cell viability reduction. Compounds that reduce alpha-synuclein oligomers may be disease-modifying treatments for Parkinson's disease.

Ligand Design is Cyclica's holistic platform for discovering biologically active molecules for a range of applications. Powered by Cyclica's MatchMaker deep learning engine, Ligand Design was deployed in its Library Screening mode in this study to evaluate a custom library of 572 small molecules already in clinical use to treat conditions other than Parkinson's disease. MatchMaker, a deep-learning methodology, predicts binding of small molecules across the structurally characterised human proteome (8642 proteins) to generate a molecule's polypharmacological profile, enabling rapid identification of unintended off-target interactions that may contribute to a molecule's physiological effect. Further, by evaluating predictions in the context of the proteome, one can prioritize compounds based on the attractiveness of their polypharmacological profiles, reducing the probability of downstream attrition. In this application, our partner identified a single protein of interest linked to both alpha-synuclein aggregation and Parkinson's disease. Of the 572 small molecules assessed by Ligand Design, 19 compounds from the top 25 compounds (i.e. yielded the highest rank percentiles for the protein target) were selected for experimental validation.



Experimental validation of 19 repurposing drugs identifies 7 that reduce alpha-synuclein oligomers

Targeting alpha-synuclein oligomerization is a proposed therapeutic strategy for Parkinson's disease. Protein-fragment complementation is a reliable approach for measuring alpha-synuclein oligomer formation. This approach uses cells expressing alpha-synuclein tagged with the N- or C-terminal of luciferase[1]. In this assay, as the alpha-synuclein monomers interact, two halves of a luciferase construct come into close proximity to form a functional enzyme. Enzymatic activity, in the form of bioluminescence, quantitatively reports levels of alpha-synuclein oligomers. Of the 19 small molecules tested *in vitro*, seven demonstrated a

reduction in alpha-synuclein oligomers. Of the seven actives, three affected alpha-synuclein oligomer reduction independent of cell viability reduction, which would also show a decrease in luciferase reporting. Furthermore, these three molecules did not affect the activity of luciferase alone, confirming that the reduction in bioluminescence was due to reduced alpha-synuclein oligomer levels. Critical next steps will include assessing the ability of these active compounds to reduce alpha-synuclein oligomerization in animal models.

This study demonstrates that Ligand Design, a purely *in-silico* approach, provides useful insights through Library Screening by predicting interaction with a specific protein target against the background of the entire proteome, which can aid in expediting the hit identification phase of drug discovery.

References

1. Moussaud S, et al. Targeting alpha-synuclein oligomers by protein-fragment complementation for drug discovery in synucleinopathies. Expert Opin Ther Targets. 19(5): 589-603 (2015)