THE USE OF AI AND ADVANCED COMPUTER SYSTEMS TO DEVELOP DRUGS AGAINST NEW EMERGING THREATS

Fung-AI: AI/ML-driven Antifungal Discovery

Laura Dunphy JHU/APL **Daniel Berman** JHU/APL **Diego Luna** JHU/APL **Libby Lewis** JHU/APL **Tom Curtis** JHU/APL **Rickey Egan** JHU/APL

For the past many decades, fungal disease research has been chronically underfunded, resulting in an overall lack of novel antifungal countermeasures1. As a result, emerging fungal pathogens represent a concerning threat to both global health and US Biosecurity. In this study, we aimed to address the nation's vulnerability to fungal pathogens through the development of AI/ML-driven pipelines for antifungal discovery. Separate approaches were explored for the discovery of 1) antifungal small molecules and 2) antifungal peptides. For the task of small molecule antifungal discovery, we leveraged the publicly available directed-message passing neural network (DMPNN), Chemprop2. Chemprop was previously used in literature for the task of antibiotic discovery3. Here, Chemprop was retrained to predict compound antifungal activity using publicly available antifungal screening data. Trained models were then used to virtually screen >75 million molecules for the potential to be repurposed as antifungal agents. High probability hits are in the process of being further down-selected for experimental validation.

In parallel to the small molecule virtual screen, a generative adversarial network (GAN) was trained on a balanced dataset of antifungal and non-antifungal peptides. Rather than classifying the antifungal activity of known peptides, the GAN generates new peptide sequences that appear "antifungal-like," thus providing novel potential antifungal peptide designs. A collection of ~10k candidate peptides each ranging from ~10-30 amino acids in length were generated by the GAN. To demonstrate proof-of-concept, five peptides that exhibited physical properties comparable to known antifungals (e.g., charge, % hydrophobicity, etc.) and that were predicted to be non-hemolytic were prioritized for synthesis and experimental susceptibility testing.
Immediate next steps include the analysis and down-selection of predicted small molecule hits as well as experimental validation of candidate antifungals against relevant fungal species. If successful, this effort has the potential to be applied to countermeasure development against a range of biological threats.

References:
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