An improved bioinformatics/cheminformatics drug repurposing pipeline to identify novel anti-schistosomal compounds

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Introduction

- *Ab initio*, whole-organism screening of druggable gene sets for early anti-schistosomal leads using high-throughput *ex vivo* techniques is expensive, laborious, and time-consuming.
- This study fills this gap by developing a bioinformatics/cheminformatics pipeline that can identify hit to lead compounds based on prioritized schistosome targets using ChEMBL and other drug databases

Aims

- (1) Develop a pipeline that can identify and prioritize *Schistosoma mansoni* drug targets
- (2) Categorize, prioritize and rank chemical matter that have the probability of inhibiting the targets from Aim 1 using ChEMBL and other databases
- (3) Validate activities of compounds recovered in Aim 2 using *in vitro* and *in vivo* techniques

Approach

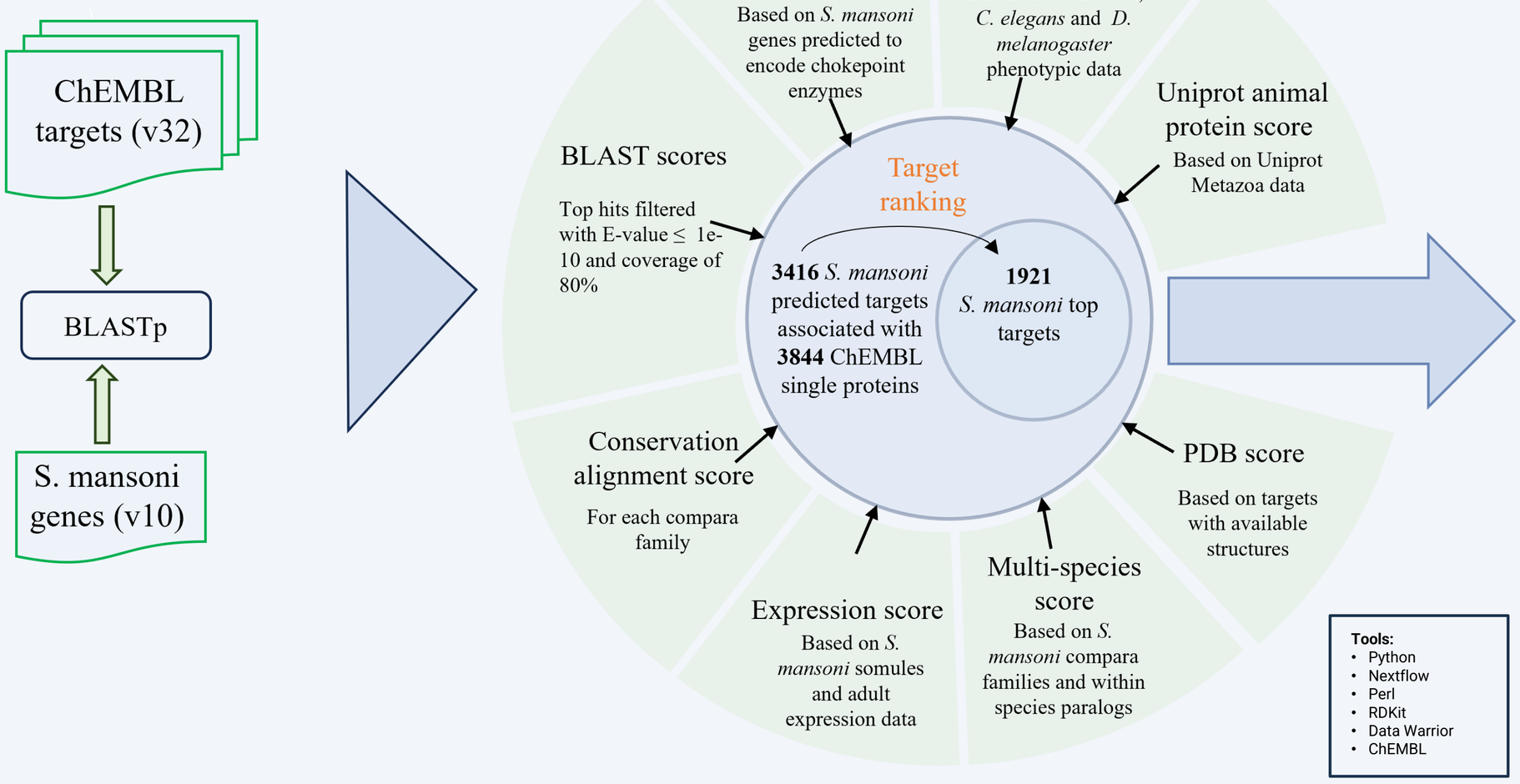

Figure 1: An integrated bioinformatics/cheminformatics pipeline for the discovery of early stage antischistosomal lead compounds

Results

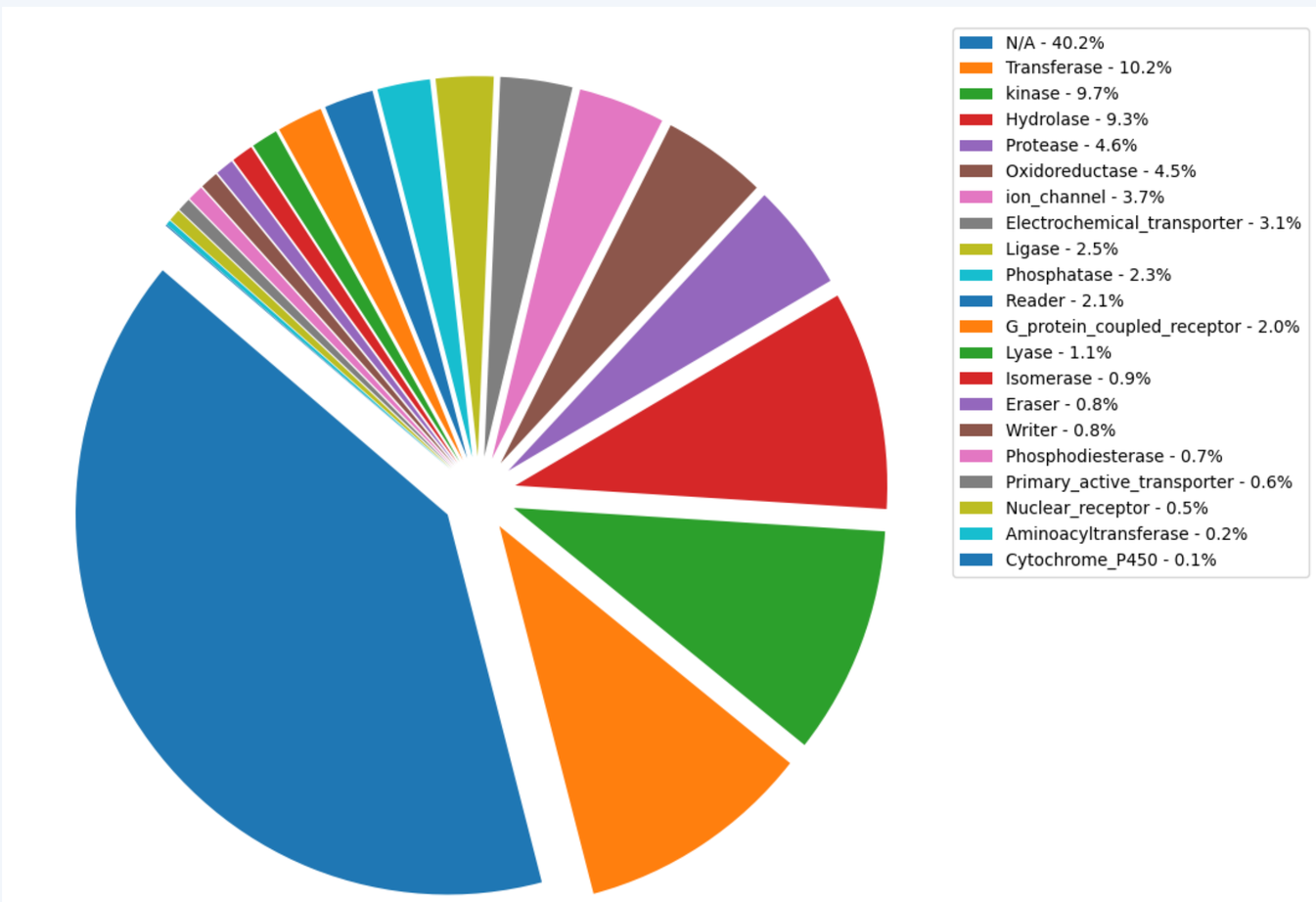

Figure 2: Protein class distribution of 1921 potential *S. mansoni* targets generated from the pipeline (N/A : proteins with no identified class)

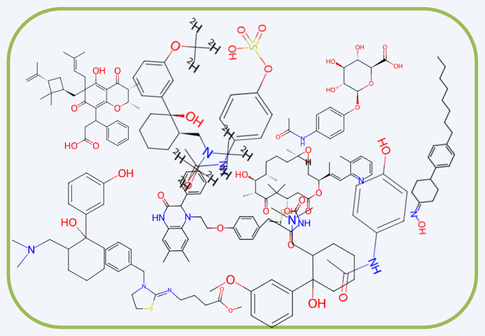

Figure 3: **1796** library of prioritized compounds generated from the pipeline

- **180 compounds** from the prioritized library were found to show strong similarities (>90%) with existing anthelmintic compounds
- **1796** of **4916** were prioritized as the final library list
- Final prioritization were based on:
  - Availability
  - Eliminating already screened compounds either from literature and inhouse
  - Within library similarity clustering by removing analogues of compounds which share >90% similarity
  - Cost Analysis

Conclusion

This study generated an automated pipeline for the identification of drug targets and associated lead compounds at an advanced stage in the development of anti-schistosomal drugs. While this pipeline is being built around *S. mansoni,* there is the possibility of applying it to other helminth parasites of humans, animals and plants.

References

- Berriman, M., Coghlan, A., Mutowo, P., O'Boyle, N., Lomax, J., & Leach, A. R. (2018). Creating a screening set of potential anthelmintic compounds using ChEMBL.
- Coghlan, A., Tyagi, R., Cotton, J. A., Holroyd, N., Rosa, B. A., Tsai, I. J., Laetsch, D. R., Beech, R. N., Day, T. A., Hallsworth-Pepin, K., Ke, H. M., Kuo, T. H., Lee, T. J., Martin, J., Maizels, R. M., Mutowo, P., Ozersky, P., Parkinson, J., Reid, A. J., … Berriman, M. (2019). Comparative genomics of the major parasitic worms. Nature Genetics, 51(1), 163–174. https://doi.org/10.1038/s41588-018-0262-1
- Padalino, G., Coghlan, A., Pagliuca, G., Forde-Thomas, J. E., Berriman, M., & Hoffmann, K. F. (2023). Using ChEMBL to complement schistosome drug discovery. Pharmaceutics, 15(5), 1359.

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