Universitat Pompeu Fabra Barcelona | Master in Bioinformatics for Health Sciences

Master project 2024-2025

Personal Information

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Project

Pharmacoinformatics & systems pharmacology

Project Title:

Predicting small-molecule drug metabolites to de-risk drug discovery

Keywords:

drug metabolism, preclinical safety, machine learning

Summary:

The metabolic system evolved as a line of defence against external substances, including small-molecule drugs, and transforms them into readily excretable metabolites [1]. These metabolites are important for drug development as they can have different biological activity than the parent drug and influence clinical efficacy, as we have recently demonstrated for the cancer drug rucaparib [2]. Moreover, drug metabolism can also lead to unanticipated toxicities that endanger the development of new drugs [3]. It is therefore essential to predict them accurately. Current metabolite prediction models mainly rely on rule-based methods and machine learning approaches, most of which produce a large number of false positives, probably because of limitations on available training data [4]. In this respect, public databases on drug metabolites are scarce because, although data on the structures and properties of drug metabolites exist, they are printed in scholarly articles waiting from someone to collect them. A while ago, Chemotargets collected a drug metabolite database that has been used internally to construct a metabolite prediction model available to CLARITY users [5]. The main objective of this project is to comprehensively harness drug metabolism data and explore available methods, including rule-based, machine, and deep learning approaches, to improve metabolite prediction. The project is a collaboration between the Medicinal Chemistry & Drug Design group at Bellvitge Biomedical Research Institute (IDIBELL) and the Catalan Institute of Oncology (Dr. Albert A Antolín) and the Translational Research group at the biotechnology company Chemotargets (Dr. Jordi Mestres), both in Barcelona.

References:

[1] Kirchmair, J., Göller, A., Lang, D. et al. Predicting drug metabolism: experiment and/or computation?. Nat Rev Drug Discov 14, 387–404 (2015). [2] Hu H, Serra C, Zhang W, Scrivo A, Fernández-Carasa I, Consiglio A, Aytes A, Pujana MA, Llebaria A, Antolin AA. Identification of differential biological activity and synergy between the PARP inhibitor rucaparib and its major metabolite. Cell Chem Biol. 2024 Feb 6:S2451-9456(24)00043-6. [3] Gray B, et al. Rare Variation in Drug Metabolism and Long QT Genes and the Genetic Susceptibility to Acquired Long QT Syndrome. Circ Genom Precis Med. 2022 Feb;15(1): e003391. [4] Litsa EE, Das P, Kavraki LE. Machine learning models in the prediction of drug metabolism: challenges and future perspectives. Expert Opin Drug Metab Toxicol. 2021 Nov;17(11):1245-1247. [5] Ackerson T, Amberg A, Atzrodt J, Arabeyre C, Defossa E, Dorau M, Dudda A, Dwyer J, Holla W, Kissner T, Kohlmann M, Kürzel U, Pánczél J, Rajanna S, Riedel J, Schmidt F, Wäse K, Weitz D, Derdau V. Mechanistic investigations of the liver toxicity of the free fatty acid receptor 1 agonist fasiglifam (TAK875) and its primary metabolites. J. Biochem Mol Toxicol. 2019; 33(8): e22345.

Expected skills:

Good scripting and programming skills are required. Some experience in data management and machine learning will be valued. A decent level of English is also assumed.

Possibility of funding:

Yes

Possible continuity with PhD:

Yes