Unravelling the Structure and Function of Promiscuous Drug Transporters

**SLC22 Family**

The absorption, distribution, and excretion of drugs and metabolites depends on membrane-bound proteins to transport small molecules across the cell membrane. The SLC22 family of organic anion and cation transporters are involved in the regulation of chemical signals in metabolism and physiology, uptake of nutrients into the blood or tissue, and renal/hepatic excretion of drugs and their metabolites.

SLC22 transporters are capable of transporting a variety of molecules with varying chemical structures. However, this promiscuity can lead to unintended competitive drug-drug or drug-metabolite interactions at SLC22 transporters, altering drug effectiveness and toxicity. Consequently, regulatory agencies such as the FDA require preclinical testing of drug-SLC22 interactions for all new compounds entering clinical trials. A number of existing drugs can also inhibit SLC22 function, including morphine (analgesic), metformin (anti-diabetic), and imatinib (anti-cancer), resulting in possible off-target effects especially with an increase in patients with comorbidities.

**Projects on SLC22 members**

The Stewart Lab is involved in characterising the specificity and selectivity of SLC22 members at a molecular level using structural and pharmacological methods. Our work will lead towards understanding the structural mechanism of drug uptake, re-evaluating the effect of existing drugs against SLC22 members, and developing tools to aid drug discovery and toxicity screening for new novel drug entities.

Our projects include:
- Structural characterisation of organic cation and anion transporters involved in drug transport
- Pharmacological evaluation of drug specificity and selectivity in SLC22 transporters
- Computational modelling of drug binding at organic cation and anion transporters

**Stewart Lab @ VCCRI**

We use a diverse set of chemistry, molecular biology and pharmacology tools to understand drug transporters. In our lab:

- You will be trained in large-scale expression of membrane proteins in bacteria, yeast, insect and mammalian cells. You will learn how to isolate and purify target proteins from host cells to be used for structural and functional studies.
- You will learn how to use X-ray crystallography or cryo-electron microscopy to obtain 3D models of membrane proteins to atomic resolutions. These structures will be used in computational models to learn more about protein conformational changes and ligand-binding interactions.
- You will also perform pharmacological assays to evaluate the functional effects of drugs and/or sequence mutations on transport activity which is combined with our structural models to understand drug specificity and selectivity of membrane transporters.

**Contact us**

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