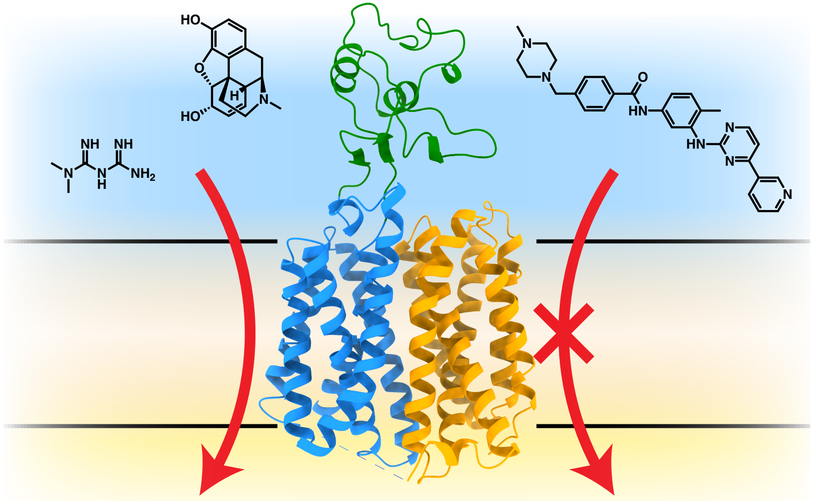
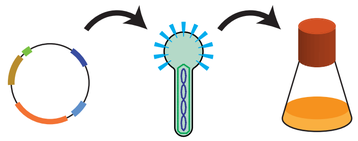
Unravelling the Structure and Function of Promiscuous Drug Transporters

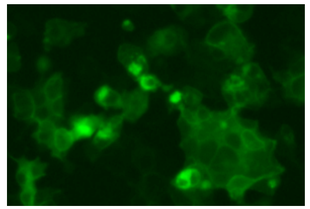
SLC22 Family

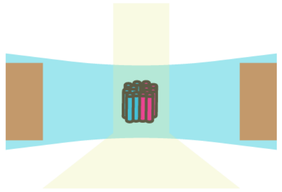
The **absorption, distribution, and excretion of drugs and metabolites depends on membrane-bound proteins** to transport small molecules across the cell membrane. The **SLC22 family** of organic anion and cation transporters are involved in the **regulation of chemical signals** in metabolism and physiology,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

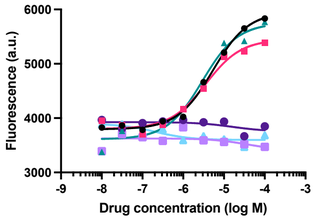
SLC22 transporters are capable of **transporting a variety of molecules** with varying chemical structures. However, this promiscuity can lead to **unintended competitive drug-drug or drug-metabolite interactions** at SLC22 transporters, **altering drug effectiveness and toxicity**. Consequently, regulatory agencies such as the FDA require preclinical testing of drug-SLC22 interactions for all new compounds entering clincal 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.

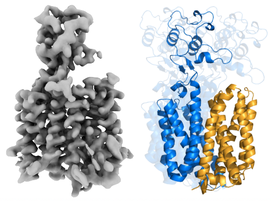


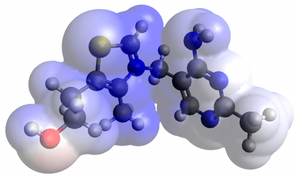












Stewart Lab @ VCCRI

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.

Projects on SLC22 members

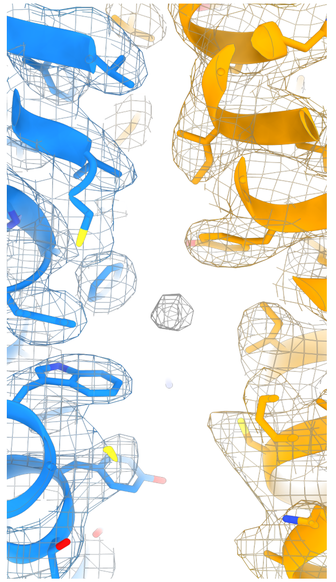
The Stewart Lab is involved in **characterising the specificity and selectivity of SLC22 members** at a molecular level using **structural and pharmacological methods**. Our work will lead towards understanding the **structural mechanism of drug uptake**, re-evaluating the **effect of existing drugs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

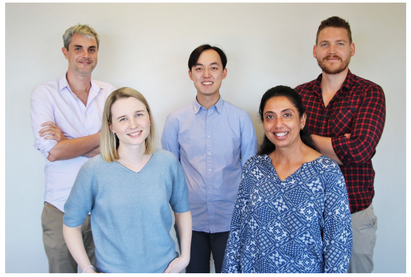
Our projects include:

- 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





Contact us

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