Movement of both endogenous and foreign molecules across cellular membranes is an essential cellular function and many diseases are associated with, or caused by, impaired transport processes. A/Prof Richard Callaghan’s research interests involve the direct examination of membrane transport proteins to ascertain how impairment of function leads to disease. The primary approach is to generate a molecular understanding of their often complex translocation mechanisms using structural and biochemical strategies. Once the process of translocation has been elucidated, the information may be used to restore normal activity in diseased tissues. Typically this involves pharmacological modulation of transporter activity directly, or via regulatory proteins. Investigations from my laboratory span molecular, cellular and tissue based systems and a wide range of investigative systems that we have developed or pioneered.

His four main streams of research are:

- Contributions of ABC transporters (P-glycoprotein and ABCG2) to chemotherapy resistance in cancer.
- Does faulty retinoid transport (by ABCA4) underpin several visual disorders?
- Malarial resistance to chemotherapy and drug translocation.
- Adaptive changes to bioenergetic metabolism and nutrient utilisation in solid tumours.
P-glycoprotein (P-gp) gained notoriety for its role in conferring drug resistance to an astonishing number of cytotoxic drugs used in oncology. The protein is able to confer resistance by preventing sufficient accumulation of chemotherapy drugs within cancer cells and there is no clinical strategy to overcome this activity. P-gp is one of three multidrug efflux pumps in humans and their actions have been the focus of considerable research. Moreover, P-gp can be considered a paradigm for drug efflux pumps, which are involved in numerous diseases and found throughout biology. Recently, an x-ray crystallography based structure has been presented for P-gp. The widely anticipated structure has long been touted as the “missing piece in the puzzle” to generate a mechanistic understanding of this complex protein. Has this been achieved yet and is there any worth to continuing with biochemical studies of the protein?

It has long been established that P-gp uses the energy from ATP hydrolysis to power drug transport against considerable concentration gradients. However, its ability to transport such an array of chemically unrelated compounds remains a truly enigmatic property. The presence of multiple pharmacologically distinct binding sites for drugs has been demonstrated and the site(s) are located within the transmembrane domains (TMDs). A more precise location has not been elucidated nor has the spatial relationship between the pharmacological sites. Drug transport by P-gp is a coupled process since transported substrates are able to accelerate the rate of ATP hydrolysis. The regions of protein involved in the process of coupling drug binding to ATP hydrolysis are likely to involve those located at domain interfaces. Structural biology can provide information on protein regions that comprise the interfaces; however dynamic data will be required to reveal their movements during translocation.

Our continuing research focus is to provide a dynamic molecular understanding of the complex drug translocation process of P-gp. In particular, we aim to locate the drug binding site(s) on the protein and describe the communication process between the NBDs and TMDs during bio-energetic coupling. This information will be used to describe the precise steps involved in multidrug transport at a molecular level. Ultimately, information from such studies may be utilised to design modulators or inhibitors of P-gp in order to overcome its unwanted actions in cancer.