Advances in drug discovery for aquaporin channels

A.J. Yool, Discipline of Physiology, University of Adelaide, Adelaide, SA 5005, Australia.

Fluid homeostasis in the body is known to be regulated by ion channels and transporters, but the co-expressed classes of aquaporin (AQP) water channels are equally important. Mammalian AQPs 0 to 12 are expressed in tissue-specific patterns in the body, and are essential for regulating the movement of fluid across barrier membranes, governing cell volume, producing cerebral spinal fluid, counteracting oedema, controlling fluid pressures, facilitating transporter activity, and more. Developing a pharmacological portfolio for aquaporins could benefit basic research and promote new therapeutic strategies in many conditions involving aquaporins in the symptoms or disease process. The first drug-like agent for aquaporins (AQPs) 1 and 4 was an arylsulfonamide compound AqB013 developed by our research team (Migliati *et al.*, 2009), which blocks by occluding the water pore at the internal vestibule. We also developed the first AQP agonist agent, AqF026, which potentiates water channel activity (Yool *et al.*, 2013). One of the goals of our ongoing drug discovery work is to test the hypothesis that natural medicinal plants which are traditionally used to influence body fluid homeostasis contain chemical components which act differentially as agonists or antagonists of aquaporin channels.

Botanical compounds over many centuries have been an important source of useful drugs. Our preliminary studies provide evidence for the presence of potent, distinctive, subtype-specific, dose-dependent modulators of AQP water channel activity. Using quantitative imaging assays of *Xenopus* oocytes expressing cloned mammalian aquaporin channels, we are identifying novel chemical modulators, defining pharmacological properties and mechanisms of action, determining dose-response relationships and analysing the molecular sites of action on the AQP protein with in silico docking and site directed mutagenesis, and biological assays of osmotic water flux rates. Traditional remedies that are used for treating conditions (such as kidney and gastrointestinal disorders, swelling, brain edema, and inflammation) which logically could benefit from a possible alternative medicine-induced alteration in AQP water channel activity. These findings could open novel strategies for clinical interventions in brain oedema; glioblastoma and other cancers; bowel and renal disorders; and other diseases.

Migliati E, Meurice N, DuBois P, Fang JS, Somasekharan S, Beckett E, Flynn G & Yool AJ. (2009) *Molecular Pharmacology* **76:**105-112.

Yool AJ, Morelle J, Cnops Y, Verbavatz JM, Campbell EM, Beckett EA, Booker GW, Flynn G & Devuyst O. (2013) *Journal of the American Society of Nephrology* **24:** 1045-52.