

Identification of Small Molecules to Modulate Membrane Transport

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The identification of small-molecule modulators of membrane transporters, such as chloride transport inhibitors, is being done extensively in pharmaceutical companies and more recently, in academic labs. In general, drug discovery involves target validation, lead identification by high-throughput screening, and lead optimization by medicinal chemistry (1). Followup preclinical evaluation includes analysis in animal models of compound efficacy and pharmacology (ADME: administration, distribution, metabolism, and elimination); and studies of toxicology, specificity, and drug interactions. The key to successful small molecule discovery is a robust assay suitable for high-throughput screening, so that hundreds of thousands of chemically diverse, drug-like, small molecules can be tested. For identification of modulators of chloride transporters, our lab has developed halide-sensing green fluorescent proteins whose fluorescence is reduced by halides. These indicators are stably expressed in cell cytoplasm, allowing continuous fluorescence readout of halide influx across the cell plasma membrane (2). Examples of chloride channel modulators identified by high-throughput screening will be presented, including CFTR inhibitors for therapy of secretory diarrheas and polycystic kidney disease, $\Delta F508$ -CFTR activators for therapy of cystic fibrosis, and calcium-activated chloride channel inhibitors. Challenges and possible approaches for discovery of oxalate transport modulators will be considered.

References:

1. Verkman AS. Drug discovery in academia. *Am. J. Physiol.* 2004;286:C465-74.
2. Verkman AS and Galiotta LJ. Chloride channels as drug targets. *Nature Rev. Drug Discovery* (In press, 2009).