Human cytosolic sulfotransferases (SULTs) transfer the sulfuryl-moiety (-SO₃) from PAPS (3-phosphoadenosine 5′-phosphosulfate) to the hydroxyls and amines of hundreds, perhaps thousands of metabolites, including many drugs and signaling small molecules... estrogens, androgens, thyroid hormones, hydroxysterols, catecholamine neurotransmitters — the target interactions of these metabolites are altered dramatically via sulfonation, which, when imbalanced, leads to disease. Thirteen SULT isoforms are encoded in the human genome. Each isoform operates in a separate metabolic domain and offers a unique means of controlling the domain-linked biological processes. Our structural and dynamics descriptions of SULT molecular behavior are revealing, for the first time, how these catalysts can be controlled in vivo. New isoform-specific allosteric-binding pockets are bringing to light a deeper metabolic dialogue, and the pocket structures are providing templates for the design of novel first-generation therapeutics, which we are synthesizing and testing in vivo. Finally, our studies of SULT ligand-recognition principles reveal how molecules/drugs can be designed to escape sulfonation without affecting their target interactions or inhibiting SULTs — a strategy which we have used to enhance the in vivo efficacy of dopamine and nuclear-receptor agonists 10²- to 10⁵-fold.

Wednesday, November 15, 2017 at 3:00 PM
Communicore Building, Room C1-15