Chemical & Physical Sciences
UNIVERSITY OF TORONTO
MISSISSAUGA

Colloquium Seminar Series
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3:15PM in CC3150

featuring

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NATIVE NANODISC DESIGN AND NEW CONCEPTS FOR MEMBRANE-TARGETED DRUG DISCOVERY BASED ON THE PROTEOLIPID CODE

Proteins including GPCRs are controlled by a proteolipid code that extends from the genetic code to determine spatial and temporal organization in cells. This involves surfaces that recognize of sets of co-localized lipids or “lipidons” that specify context-specific activation. Lipidon complexes are being resolved with technologies including situ cryo-electron imaging and membrane-active polymers, revealing a the catalogue of unique bar codes for plasma membrane zones and subcellular organelles. Tools being developed include next-generation styrene maleic acid (SMA)-based copolymers for the study of native membrane protein assemblies. Amine oxide derivatized alternating and intrinsically fluorescent SMA spontaneously convert biological membranes into nanodiscs with diameters of 15-25 nm that can be resolved by dynamic light scattering and electron microscopy. These zwitterionic polymers are useful in a broad range of pH (4-10), are tolerant of high levels of divalent cations (>200 mM calcium) and are designed to reduce undesirable nonspecific interactions. Their native nanodiscs are shown to accommodate the PagP palmitoyltransferase expressed in Escherichia coli outer membranes and the human adenosine A2A receptor expressed into Pichia pastoris membranes, resulting in readily purified proteins that are less likely to be perturbed by polymer charge or hydrophobicity. Applications include the discovery of sites and lead candidates specific for therapeutic target states that depend on their native membrane environments.