UNIVERSITY of GUELPH

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FACULTY CANDIDATE

Biochemistry

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Breaking the Barrier: Integrative Structural and Functional Studies of Molecular Machines at One Mega-Dalton and Beyond

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2:30p.m.
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Cells employ macromolecular assemblies, so-called molecular machines, to perform a myriad of biological tasks. Gaining an atomic-level understanding of the *modus operandi* of these machines and their structure: dynamics: function relationship represents the "holy grail" of modern structural biology. Unfortunately, there is no single technique that gives us all the information that we need. X-ray crystallography and cryo-electron microscopy (cryo-EM) provide valuable data about protein structure, but leave out important insights about dynamics. Nuclear magnetic resonance (NMR) is an excellent high resolution method for studying protein dynamics, but needs large quantities of isotopically labeled material and is low throughput. A number of mass spectrometry (MS)-based methods report on both structure and dynamics of low abundance proteins, but deliver only medium-resolution data. In addition, high-molecular weight proteins often are not amenable to one method or another, forming barriers in our understanding of these systems.

This lecture will draw examples from past and present research to illustrate how a combined and integrative approach can provide a detailed characterization of mega-Dalton sized molecular machines implicated in human health. Fundamentals of MS-based methods including covalent labeling, native electrospray, and hydrogen/deuterium exchange (HDX) will be discussed, with a focus on the investigation of FoF1 ATP synthase in natural membrane vesicles. This will be followed up by a brief introduction of methyl-transverse relaxation-optimized spectroscopy (TROSY) NMR and cryo-electron microscopy and their application to study the conformational dynamics of the ClpXP protein degradation machinery from *Mycobacterium tuberculosis*. It will be shown that this powerful combination of methods can be used to identify allosteric drug binding sites for inhibition, and crucial insights into the structure-function relationship of molecular machines. I will chart how my future research program can thrive in the ever-shifting landscape of structural biology: away from a single-perspective view of proteins and towards an integrative and comprehensive exploration of the molecular players involved in mitochondrial homeostasis that affect acute myeloid leukemia patients.

Search Committee: Marc Coppolino, Chair; John Dawson; Steffen Graether; Ian Tetlow; Melissa Perreault; Morgan Stykel, Graduate Student; Todd Gillis, CBS Dean's Office