



Donnelly Centre
for Cellular + Biomolecular Research
UNIVERSITY OF TORONTO



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“Small-molecule and biotherapeutic strategies for treating human disease”



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The Donnelly Centre

James Friesen | Cecil Yip Red Seminar Room

Abstract:

Conserved longevity pathways capable of regulating the lifespan of organisms such as yeast, worms, and flies have recently been discovered. Remarkably, these same pathways are implicated in multiple age-related diseases in mammals such as cancer, Alzheimer's disease, and diabetes. Identifying small molecules that target these pathways could potentially prevent dozens of diseases simultaneously. In 2003, a high-throughput chemical screen identified small-molecule activators of SIRT1, a conserved longevity gene that mediates several effects of caloric restriction. Despite reports showing beneficial effects of SIRT1 activators in numerous human disease models, controversy erupted surrounded the biochemical mechanism by which these compounds work. In the first part of my seminar, I will discuss a series of biochemical, biophysical, structural, and cellular experiments performed during my graduate studies that resulted in the formation of a new model for SIRT1 activation by allosteric activators. Furthermore, several complimentary small-molecule approaches for activating SIRT1 and related pathways in cells will be presented.

Small-molecule drugs to effectively treat monogenic loss-of-function diseases such as cystic fibrosis and hemophilia remain elusive. However, recent developments in the areas of gene therapy, biotherapeutics, and genome engineering offer new hope to potentially cure these diseases. Transcription activator-like effectors (TALEs), originally identified as plant pathogens secreted by *Xanthomonas*, are DNA-binding proteins that can be programmed to bind to a specific sequence. Moreover, these proteins can be functionalized via attachment to gene activation or repression domains to produce synthetic regulatory elements, or fused to nuclease domains to perform site-specific genome editing. In the second part of my seminar, I will discuss the development of a generalized DNA-binding protein selection platform for phage-assisted continuous evolution (PACE), and discuss my efforts to improve both sequence targeting and specificity of TALE arrays using this new technology. Finally, future experiments aimed at applying these tools to the treatment of human disease will be outlined.

Host: Igor Stagljar