Supervisor/Project Information Form

Due February 6, 2020 by email to crems.programs@utoronto.ca

Supervisor Name: Dr. Robert Hamilton, Dr. Linda Penn

Project Title: Maximizing statin efficacy in prostate cancer by interrogating and attacking feedback mechanisms

Hospital/Research Institution: Princess Margaret Cancer Centre, University Health Network

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Field of Research (2 keywords):
Prostate cancer, chemoprevention

Department:
Surgical Oncology/Urology

School of Graduate Studies Appointment (IMS, LMP, IHPME etc)? Yes/No: If YES, please name: No
Brief Project Description (<300 words):

There is an unmet need for safe and effective therapies to treat Prostate Cancer (PCa) and delay disease progression. Statins inhibit HMGCR, the rate-limiting enzyme of the metabolic mevalonate pathway, which are clinically-approved agents that are commonly prescribed for the management of high cholesterol. We and others have shown elevated mevalonate pathway activity is associated with PCa progression and statins possess anti-PCa activity, suggesting that PCa patients may benefit from the addition of statins to their treatment regimen. We've recently shown that blocking the statin-induced restorative feedback response potentiates the pro-apoptotic activity of statins (Longo et al.). To identify agents that block this feedback response to maximize statin efficacy, we recently completed a screen of 1,500 FDA-approved compounds to identify agents that potentiate the pro-apoptotic activity of statins. We conducted high-content image-based analysis of two PCa cell lines, LNCap and PC3 cells, which do and do not possess a feedback response to statin exposure, respectively. The CREMS summer student would analyze these data remotely to distinguish drugs that on their own had no effect, but in combination with a sub-lethal dose of statin, triggered PCa cell death. This will be accomplished using remote VPN access to the captured image-based data using established Columbus software. This would be a significant contribution and mark a key advance. The CREMS student would then analyze the hits for pathway analysis (GO, String) as well as chemical structure analysis and prioritize these hits for further wet-lab validation. Validation and mechanism will be determined once we are back in the lab.