DEPARTMENTAL SEMINAR

Molecular Genetics
UNIVERSITY OF TORONTO

Temerty Medicine

Saturation variant-to-function mapping across DNA repair pathways

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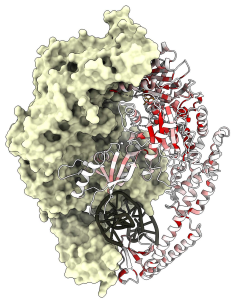
Understanding how individual variants impact gene function and contribute to disease risk is a central challenge in human genetics, even for the most intensively studied genes. To address this challenge, we employ high-throughput mutagenic screens to exhaustively test all possible coding variants in clinically impactful human disease genes. I will describe scaling these approaches across the entire DNA mismatch repair (MMR) pathway, a frequent mutational target in sporadic cancers as well Lynch Syndrome, an inherited colorectal and endometrial cancer risk syndrome which affects ~1:300 individuals worldwide. We have measured the functional status of >98% of the possible missense variants across four key MMR genes (MSH2, MLH1, MSH6, and PMS2), and observe near-perfect concordance with existing clinical interpretations and previous functional studies. We identify several variants for which discordance between clinical interpretation and our functional measurement can be explained by the presence of a second variant in affected families. These exceptions underscore the importance of genetic context, and motivate ongoing combinatorial mutagenesis screens. Our variant-to-function maps have enabled the resolution of thousands of standing variants of uncertain significance (VUS) and are now assisting clinical variant interpretation in practice. Finally, I will share how we are extending these approaches to other key DNA repair pathways.



Host: Dr. Fritz Roth

Date: September 16th, 2024
Time: 2:30 PM
Location: Red Room, Donnelly Centre