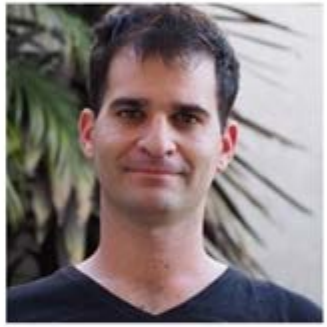
SickKids RESEARCH INSTITUTE

2018
Faculty Candidate Seminar
Rare Disease Genetics and Genomics

Identification of Druggable and Redox Vulnerabilities in a Genetically Defined Cancer



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4 PM
Robert B Salter Auditorium
Peter Gilgan Centre for Research and Learning
686 Bay St

The transcription factor NRF2 is a master regulator of the cellular antioxidant response and is often genetically activated in Non-Small Cell Lung Cancers (NSCLCs) by, for instance, mutations in the interacting protein KEAP1. While direct pharmacological inhibition of NRF2 has proven challenging, its aberrant activation rewires biochemical networks in cancer cells that may create special vulnerabilities. Here, we use chemical proteomics to map druggable proteins that are selectively expressed in KEAP1-mutant NSCLC cells. Principal among these was NR0B1, an atypical orphan nuclear receptor that we show engages in a multimeric protein complex to regulate the transcriptional output of KEAP1-mutant NSCLC cells. We further identify small molecules that covalently target a conserved cysteine within the NR0B1 protein interaction domain and demonstrate that these compounds disrupt NR0B1 complexes and impair the anchorage-independent growth of KEAP1-mutant cancer cells. Our findings designate NR0B1 as a druggable, transcriptional regulator that supports NRF2-dependent lung cancers.