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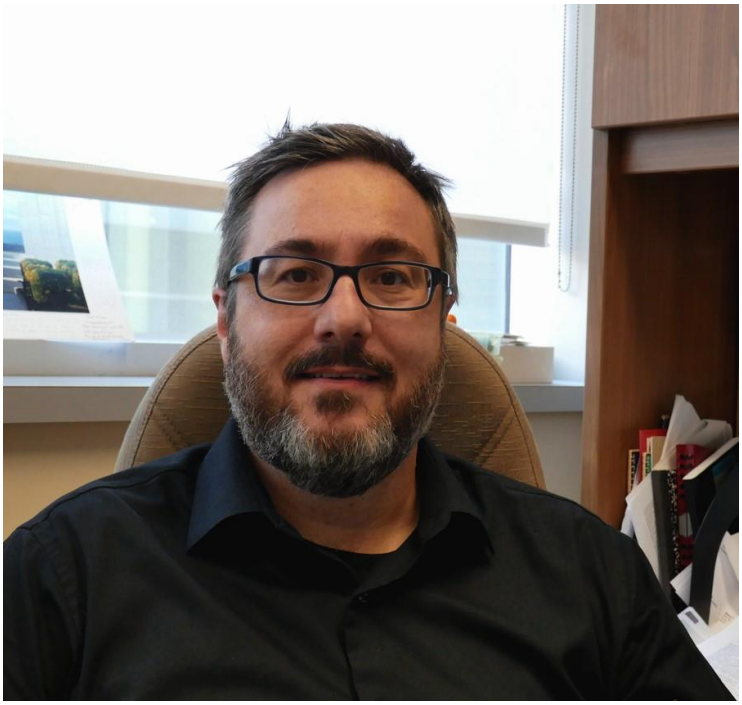
Focus on Faculty #23
Michael Witcher



Dr. Michael Witcher is an Associate Professor in the Gerald Bronfman Department of Oncology and a member of the Lady Davis Institute and Segal Cancer Centre of the Jewish General Hospital. He is a FRQS Scholar (Junior 1).

Dr. Witcher began his research career as an undergraduate in the Department of Biochemistry at Memorial University of Newfoundland where he spent many hours purifying carcinogenic fungal toxins. After experiencing a frightening spill involving these toxins he decided to switch to a less dangerous field for his MSc degree (also at Memorial) where he studied the regulation of nuclear hormone receptors in cancer. From there, he went on to McGill for his PhD in the laboratory of Dr. Wilson Miller and subsequently pursued postdoctoral work at the Salk Institute in La Jolla, California under the tutelage of Dr. Beverly Emerson. During his PhD, Dr. Witcher became interested in understanding mechanisms whereby transcription is deregulated in cancer and how to utilize this information to identify new therapeutic approaches to treat cancer. He further explored this concept during his postdoctoral fellowship where he incorporated epigenetic processes into his models of transcriptional deregulation. His postdoctoral work was the first to identify chromatin boundaries as key regulators of tumour suppressor genes.

Since starting his own research program in 2010, Dr. Witcher's work has been focused on two major research themes. First, his laboratory studies transcription and epigenetic programs governed by the "master epigenetic regulatory protein" CTCF. CTCF is deregulated through deletion, mutation, and loss of post-translational modifications in multiple cancers, but to date, the impact on neoplastic growth and oncogenic progression remain obscure. His laboratory has

uncovered that disruption of CTCF function in cancer plays important roles in promoting genomic instability, tumour invasion and predicts sensitivity to chemotherapy.

Second, Dr. Witcher's laboratory aims to optimize the use of inhibitors targeting poly (ADP-ribose) polymerases (PARPs) and related pathways in breast and ovarian cancer. As a part of this program, his laboratory has defined a new role for the enzyme poly (ADP-ribose) glycohydrolase (known as PARG) as an oncogene and therapeutic target. PARG initiates the catabolism of an expansive protein post-translational modification termed poly (ADP-ribose), primarily placed by PARP-1. Dr. Witcher's laboratory has now demonstrated that PARG is elevated in many cancers, acts as a potent oncogene and its knockdown prohibits tumour growth and metastasis *in vivo*. Currently, Dr. Witcher is cooperating with industry to develop novel inhibitors of PARG that he hopes will display anti-tumour activity.

While Dr. Witcher has attempted to focus these research themes on exploring mechanisms whereby PARG and CTCF regulate transcriptional and epigenetic processes, this work has broadened into the fascinating, albeit confusing, areas of DNA damage repair and bioenergetics. Fortunately, he is surrounded by supportive colleagues with considerable expertise in these fields and additional collaborators who have helped transition his work to incorporate *in vivo* models.

We asked Dr. Witcher to list a few of his articles whose work he is particularly proud or enjoyed the most. This is what he provided:

Hilmi K, Jangal M, Marques M, Zhao T, Saad A, Zhang C, Luo VM, Syme A, Rejon C, Yu Z, Krum A, Fabian MR, Richard S, Alaoui-Jamali M, Orthwein A, McCaffrey L and **Witcher M**. CTCF facilitates DNA double-strand break repair by enhancing homologous recombination repair. Science Advances (In Press).

Peña-Hernández R, Marques M, Hilmi K, Zhao T, Saad A, Alaoui-Jamali MA, Del Rincon SV, Ashworth T, Roy AL, Emerson BM, **Witcher M**. Genome-wide targeting of the epigenetic regulatory protein CTCF to gene promoters by the transcription factor TFII-I. Proc Natl Acad Sci USA. 2015 Feb 17;112(7):E677-86.

Marques M, Beauchamp MC, Laskov I, Qiang S, Gotlieb WH and **Witcher M**. Chemotherapy depletes PARP1 protein in ovarian cancer tumors: Implications for future clinical trials involving PARP inhibitors. BMC Medicine. 2015 Sep 9;13(1):217.

Witcher M, Emerson BM. Epigenetic silencing of the p16(INK4a) tumor suppressor is associated with loss of CTCF binding and a chromatin boundary. Mol Cell. 2009 May 15;34(3):271-84.