PROFESSOR JEAN-JACQUES LEBRUN
Professor of Medicine, McGill University Health Center | Cancer Research Program | Molecular and Translational Oncology, Crisperized Medicine for Precision Oncology
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PRESENTATION TITLE: Crisperized Medicine for Precision Oncology

ABSTRACT: Cancer is a multifactorial disease and while the number of clinical trials based on combination therapies is rising, efficient strategies to identify relevant targets are lacking. Triple negative breast cancer (TNBC) patients exhibit the poorest survival outcome of all breast cancers and lack effective targeted therapies. We performed an unbiased in vivo genome-wide CRISPR screen to interrogate cancer vulnerabilities in TNBC and identified novel interplay between oncogenic and tumor suppressor pathways. We discovered novel tumorigenic functions for essential components of mTORC2 (RICTOR) and the amino acid-sensing arm of mTORC1 (Sestrin3/GATOR2/WDR59) as well as the oncoprotein YAP and the Hippo members (SAV1 and FRMD6). Furthermore, using in vitro drug matrix synergy models and in vivo patient-derived xenograft, we exploited these cancer vulnerabilities and discovered a targeted combination therapy that efficiently blocked mTORC1/2 (torin1) and YAP (verteporfin) tumor promoting effects in TNBC. At the molecular level, we found that while verteporfin-induced YAP inhibition led to apoptosis, torin1-mediated mTORC1/2 inhibition promoted macropinocytosis. Torin1-induced macropinocytosis further facilitated the verteporfin uptake, thereby greatly enhancing its pro-apoptotic effects in cancer cells. Overall, our study underscores the power and robustness of in vivo CRISPR genome-wide screens in identifying clinically relevant and innovative targeted combinational therapies against cancer.

BIOGRAPHY: Dr. Jean-Jacques Lebrun is an expert in synthetic biology and drug discovery whose breakthrough was elected the “Discovery of the year” by the public and celebrated by the Ministry of Health of Canada

Dr. Lebrun’s research aims at understanding of the molecular mechanisms underlying cancer initiation, metastasis, stemness and drug resistance, all of which considered as major challenges in the management of cancer patients with the long-term goal of advancing and accelerating the translation of basic laboratory discoveries into new cancer therapeutics. Using state of the art technologies, gene editing (CRISPR), genome-wide molecular approaches and preclinical models, Dr Lebrun lab has developed a cutting edge “Crisperized Precision Medicine” cancer research program to offer cancer patients rationalized, rapid and personalized drug response profiling, neoadjuvant solutions and therapeutic options. For this, the Lebrun lab developed molecular systems (in vitro), genome-wide and customized CRISPR libraries, patient-derived organoids (ex-vivo) and xenografts (in vivo), bioinformatics and patient data mining analysis (in silico). Dr. Lebrun expertise in the field of cancer research and international recognition by his peers are probably best reflected by his publication track record, presentations worldwide, awards, press releases and his activities as Associate Dean, promoting University professional activities and research across and abroad.

This research was generated over the years by highly qualified personnel who trained in Dr. Lebrun lab and who have now successfully established themselves in the industry or academy in Canada and abroad. Dr. Lebrun is very well funded and his work is being published top-level peer-reviewed journals. As a leader, Dr. Lebrun served as an executive board member and president of the Club de Recherches Cliniques du Quebec, an organization that regroups all Universities from Quebec. He established and served as Director of the Hormones and Cancer Research Unit, recruited and mentored high-profile young investigators at McGill.

Dr Lebrun lab unveiled novel functions for TGFβ signaling and microRNAs in regulating tumorigenesis and metastasis. He developed a decision tree classifier that predicts for early breast cancer recurrence and as part of a multi-university team effort, he developed new approaches to modify the genetic material of cancer stem cells, using femtosecond laser and nanoparticle technologies. The Lebrun lab made important inroads into understanding cancer stem cells biology and uncovered novel functions for the cyclin-dependent kinases CDK4/6 in regulating metastasis. Using a CRISPR-based in vivo gene therapy system, they showed that CDK6 genomic deletion blocks tumorigenesis. Expanding on this, they developed new small molecules CDK4/6-PLK1 inhibitors and are in discussion with pharmaceuticals to promote their development and further transition to Phase I clinical trials. Using genome wide in vivo CRISPR screen to identify cancer vulnerabilities, the Lebrun lab made recent breakthrough discoveries, uncovering a novel targeted combination therapy that efficiently reduced tumor growth in metastatic breast cancer.