



Team Progress Updates

SU2C Canada Cancer Stem Cell Dream Team: “Targeting Brain Tumour Stem Cell Epigenetic and Molecular Networks”

Malignant brain tumors remain deadly and incurable. This Dream Team is focusing on glioblastomas in adults and children and on posterior fossa ependymomas in infants. Treatment options for both tumor types are limited, leaving a dismal outlook for these patients.

Researchers previously discovered that at the root of these tumors lies a relatively small population of cells known as brain tumor cancer stem cells (BTSCs). These cells are resistant to known forms of therapy. When patients undergo treatment, these cells survive and regrow the whole tumor, causing a relapse.

To better understand these cells, the team is taking a three-tiered approach: 1) analyzing BTSCs from 70 patients using cutting-edge technology to reveal their full biological profile; 2) testing a panel of drugs on these tumors to find promising candidates; and 3) performing tests on these promising drugs in preclinical mouse models to predict efficacy in human patients.

Taking a multidisciplinary approach, the team is providing new insights into BTSC biology, offering a promising avenue by which to solve a long-standing problem.

In progress to date, the team has:

June 2018

- The team has completed its targeted sequencing of genomes and transcriptomes of 70 brain tumor samples.
- Team members have optimized a technique that will help them evaluate individual cells within a tumor. This will aid in understanding how different cell types vary and influence one another.
- The team has utilized 21 brain tumor stem cell cultures to try to identify genes important for glioblastoma survival. It has submitted a manuscript for publication focused on one of the newly discovered genes.
- In the quest for novel drug candidates, the team has screened 10 glioblastoma samples with an expanded drug library and has found some candidates that merit further study.
- Among these candidates is an epigenetic drug, Panobinostat, that has been approved for treating multiple myeloma and is already being used in clinical trials to treat pediatric brain tumor patients. This could be a potential drug to treat adult glioblastoma in the near future.



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December 2017

- Identified two new drugs that can target brain tumor stem cells. One blocks a protein called glutaminase. Another is an inhibitor for a protein called glucose transporter.
- Shown that blocking a protein called PRMT5 keeps brain tumor stem cells from multiplying, and therefore, can keep cancer from growing. They are now testing a drug that can block PRMT5 in mice.

June 2017

- Found a common characteristic in the way the DNA of brain tumor stem cells are organized. This commonality can be used to kill these cells even if the cells have different mutations.
- Developed software that can combine all the data from the DNA sequencing and drug testing. This software called netDx can be used to identify ways to predict favorable drug response from a patient's DNA characteristics.
- Identified numerous drug candidates and shown that the clinical drug EPZ5676 was effective against glioblastoma brain tumor stem cells.

December 2016:

- Begun rigorous analysis of the first cohort of 20 patient samples. The genomic analysis thus far confirms that the majority of the tumor tissue and the stem cell compartments do not have the same genetic profile.
- Identified a unique metabolite from the first few samples of their project, which may serve as a biomarker for a subset of tumors.
- Tested the two leading targets in several cell culture systems and moved them into preclinical studies.

June 2016:

- Nominated the first 20 of 70 patient tumors to undergo all brain tumor stem cell characterization to investigate the genetic and functional characteristics of these cells across tumors.
- Identified two promising drugs and begun studies by Team members in unique experimental models.