Scientific Abstract

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

[This abstract was provided by the scientists when their application was accepted.]

Brain tumours remain largely incurable diseases. To address the poor outcome of these tumours, we have formed a Pan-Canadian Dream Team. Our goal is to focus our attention on the worst prognosis brain tumours, glioblastoma (GBM) of adults and children, and posterior fossa subtype A (PFA) ependymomas of infants, with a goal of finding new treatments. We, and others, have shown that these tumours contain subpopulations of cells, brain tumour stem cells (BTSCs), that drive disease relapse and resistance to therapy.

The central hypothesis is that: Human glial tumours are driven by disturbances in epigenetic and related metabolic/neural signaling processes that are common across heterogeneous genetic subtypes. In order to gain clinically relevant insights into the complementary and compensatory networks that drive brain tumour growth, these processes cannot be studied in isolation but need an integrated approach.

We propose three integrated specific aims:

1. Conduct a comprehensive investigation of genomic, epigenomic and metabolomic profiles of BTSCs to define networks of self-renewal, therapeutic resistance and targetable vulnerabilities. We propose to define and target the aberrant epigenetic and related metabolic/neurochemical processes which fuel the maintenance of the BTSC reservoir. We will perform detailed experimental characterization of the genomic, epigenomic, metabolomic, proteomic, and neurobiologic profiles of BTSCs.

2. Identify targets whose pharmacological inhibition is efficacious on BTSCs from GBM and PFA ependymoma. We propose to integrate testing of chemical probes and promising drugs, with the BTSC biological readouts and phenotypes, towards developing the necessary understanding of clinical successes and setbacks. We will particularly pay attention to the (epi)genomic mechanisms that are vulnerable, and under which circumstances combination therapies might be utilized. The best targets (as defined by experienced Pharma advisors) will be tested in pre-clinical models of BTSC function in vivo.

3. Pre-clinically test five targets to accelerate translation to the clinic. We have data that points to blocking epigenetic or abnormal metabolism in BTSCs as potential therapeutic strategies. In parallel to our BTSC 'omics, we will accelerate pre-clinical testing of several strong target hypotheses at the outset of funding. We will use best-in-practice in vivo assays of tumourigenicity using orthotopic

transplantation, with emphasis on assays that test whether target inhibition reduces or eliminates self-renewal properties.

We believe that integrating the testing of chemical probes and preclinical/approved drugs whose target inhibition and selectivity are well documented, with the critical BTSC biologic readouts, is necessary for understanding the reasons for both success and failure. Our ultimate goal is to demonstrate proof of concept for new BTSC targets in human clinical trials for adult and childhood GBM and PFA ependymoma.