SUMARRY

One of the key hurdles in developing therapies for brain tumor patients is the limited understanding of transformation between normal neuronal cells and cancer cells, and what is the role of different molecules (including non-protein coding genes) in this process. Recently, unprecedented progress has been made in understanding the function of small and long non-coding RNAs (microRNAs and lncRNAs), which constitute a vast majority of the human transcriptome, but their role in the pathobiology of glioblastoma (GBM) remains unknown. These tumors are genetically and phenotypically heterogeneous, with GBM stem-like cells (GSCs) belonging to subtypes defined by transcriptome analysis, that adapt to the brain tumor microenvironment.

Our proposal aims to elucidate the mechanisms of neuronal specific, non-protein coding factors in cancer initiation and progression. Overall, our proposed studies will reveal a facet of brain cancer biology that is virtually unknown and has great potential to change the way we think about, and treat, brain cancers.

The loss of a cell's ability to terminally differentiate is a pivotal event during tumorigenesis and occurs during a pro-mesenchymal transition. Recent transcriptome-wide studies have unveiled the complexity of glioma heterogeneity and intratumoral transitions, and provided new insights into both: protein coding and non-protein coding transcriptional landscape.

We identified non-coding RNA (ncRNA) – *miR-128* that is lost in particularly aggressive mesenchymal glioma. Its re-introduction to mesenchymal glioma stem–like cells (MGSCs) was associated with substantial de-repression of neuronal genes, including long non-coding RNA MEG3 (*lncMEG3*). This brings us to the study of stem cells and the neurogenic niche that lies at the intersection between brain development and gliomagenesis. We hypothesize that loss of expression of these two ncRNAs that are dynamically regulated during neurogenesis and downregulated in glioma impairs terminal differentiation and collaboratively promotes tumorigenesis. Using patient-derived adjacent and glioma tissue, as well as GSCs and non-malignant neuronal progenitors we characterized the intricacies of *miR-128* and *lncMEG3* expression. Identification of BRAF35 (that inhibits neuronal differentiation) as an interaction partner of *lncMEG3* provided rationale for studying the role of *miR-128-lncMEG3* ncRNAs network in loss of terminal differentiation capacity in neural and glioma stem cells.

We propose to achieve this by validation of *lncMEG3* protein interactome in normal and cancer stem cells (Aim 1); by defining whether loss of *miR-128*/*lncMEG3* cooperation drives tumor initiation and progression (Aim 2); and by evaluation of the effect of *lncMEG3* expression as a therapeutic replacement (Aim 3).

The study of biology of cancer stem cells and their role in brain tumor initiation from neural stem cells that undergo a defective process of differentiation might permit the development of novel treatment strategies targeting cancer stem cells. This model would provide the evidence that de-regulated function of ncRNAs impairs differentiation and is therefore an important target in early gliomagenesis.