Title: Constructing the in-brain transcriptional landscape of transplanted stem cells during rescue of cognitive impairment due to Radiotherapy damage. Professor Charles Limoli and Professor Robert Spitale.

Abstract

Radiotherapy remains a frontline treatment for primary and metastatic brain cancers, along with surgery and chemotherapy. Numerous clinical studies have characterized debilitating cognitive side effects of cranial radiotherapy. The Limoli lab, and others, have shown that transplantation of human neuronal Stem Cells (hnSCs) into the brain of mice after radiation rescues cognitive defects, yet there remains much room for improvement. The Limoli lab has shown that cranial transplantation of hnSCs can reduce inflammation, preserve dendritic complexity, spine density and the integrity of the microvasculature. These nhSCs are able to differentiate and survive in the brain for many months.

Despite these exciting observations it is still largely unknown how these cells are remodeled or what gene expression programs they utilize to differentiate. This knowledge gap continues to be a major hurdle limiting the design and efficacy of highly efficient cellular therapies to treat cognitive dysfunction and other neuronal challenges.

The major goal of my proposal is to surmount such a barrier through the systematic development of chemical and genomic tools, so as to better understand the gene expression programs responsible for nhSC differentiation within the living brain. Toward this goal, the Spitale lab has developed a novel method for cell-specific tracking of nascent RNA expression. We will utilize this method for elucidating the gene expression program of transplanted hnSCs during their differentiation in the brain. Such analysis will provide novel insight into their therapeutic mechanisms and provide a roadmap for future cell engineering for enhanced therapeutics. Our ultimate goal is to use these findings as a stable base for extramural funding. We anticipate our findings will have far-reaching impact on the fields of stem cell transplantation as it will be the first to understand cellular differentiation of transplanted cells within their transplanted environment.