Injury to the human brain—as a result of stroke, traumatic injury, or neurodegenerative disease—is typically irreversible. While stem cell treatments show promise for patients with brain or spinal cord injuries, it is likely that transplant of stem cells or differentiated stem cell progeny will be insufficient to recapitulate the cellular diversity, connectivity, and patterning of human brain tissue. Therefore, there is a ***critical need*** to develop and explore models that reveal how pluripotent stem cells reconstitute neural tissue, particularly the brain, *in vivo* with high fidelity and functionality. Though most traditional model organisms regenerate brain tissue poorly, freshwater flatworms called planarians are capable of *perfect, complete* brain regeneration after nearly any injury. Therefore, study of planarian regeneration can reveal *fundamental principles of successful neural repair and can reveal specific molecules or pathways with critical roles in promoting brain regeneration*.

Planarians have been studied for the past several decades for their regenerative prowess. Planarians possess pluripotent adult stem cells that give rise to all the diverse cell types of the planarian body during homeostasis and after injury, including neurons. More than fifty distinct planarian neural subtypes utilize neuropeptides and conserved neurotransmitters (dopamine, serotonin, GABA, glutamate, acetylcholine, etc.). Planarian neurons are arranged in highly organized patterns and in predictable ratios, so we can study regeneration of nervous tissue with appropriate structure, cellular diversity, and connectivity. We also previously discovered that planarians possess glia and we have published work characterizing these novel cells. Planarian nervous systems regulate behaviors that include movement in response to stimuli, mating, rest, and predation. The strengths of the planarian as a model and the track record of the Roberts-Galbraith laboratory in exploring regenerative neurobiology position us uniquely to investigate mechanisms that underlie successful regeneration of complex neural structures. Our *long-term goal* is to use planarians to understand the cellular and molecular basis of successful brain regeneration. By furthering a foundational understanding of neural and glial regeneration from pluripotent stem cells *in vivo*, we hope to *identify mechanisms or even specific molecules that could be leveraged to improve human regenerative therapies*.

Area 1: Regulation of regenerative neurogenesis (funded by NINDS R01)

Specific project objectives include:

- Identification of factors required for dopaminergic neuron regeneration and maintenance in planarians.
- Evaluate the regulation of neurogenesis after injury in planarians.
- Determine whether body polarity cues promote cell type-specific neurogenesis in planarians.

Opportunities, including possibility of collaborations, exist for tool development in new areas of planarian biology (e.g. behavioral analysis, biochemical characterization of transcription factor binding).

Area 2: Glial biology in the context of robust regeneration (currently applying for funding)

Specific project objectives include:

- Characterize factors required for regeneration of glia from pluripotent stem cells.
- Determine how planarian glia respond to injury.
- Evaluate how glia and neurons impact each other's structure and function.

Opportunities, including possibility of collaborations, exist for tool development in new areas of planarian biology (e.g. electron microscopy, single cell sequencing, study of synapses).