Reference Number:190005
Principal Investigator: Stephanie Gupton
Organization: University of North Carolina at Chapel Hill
Period: 04/01/2019-03/30/2020
Grant Title: Netrin-1 Glycosylation Distinguishes Chemotaxis and Haptotaxis
Progress Report:

Abstract: This proposal addresses an outstanding question at the interface of the fields of glycobiology and axon guidance: *How does differential glycosylation of an axon guidance cue distinguish between chemotactic and haptotactic modes of axon guidance?*

Fidelity in axon guidance is critical for appropriate wiring of the nervous system. For the past 7 years, the goal of my independent lab has been to decipher the molecular mechanisms by which guidance cues direct axons to accomplish appropriate nervous system connectivity. We study this in murine embryonic cortical neurons by combining genetic manipulations, state-of-the-art cell biology, protein biochemistry, and microfluidic manipulation of the axonal environment. We employ neuroanatomical and behavioral approaches to reveal the *in vivo* consequences of the mechanisms we define *in vitro*. The guidance cue on which we focus is the **secreted glycoprotein netrin-1**. Netrin-1 is critical in nervous system development from invertebrates to humans, where it promotes both attractive and repulsive axon turning. However, whether netrin-1 functions as a soluble, chemotactic cue and/or as an adhesive, haptotactic cue remains under debate. This is significant, as chemotactic cues can guide axons over long distances, whereas haptotactic cues guide axons locally, and thus they wire the nervous system via fundamentally distinct means. We recently established protocols to separate and purify two **distinctly glycosylated** forms of netrin-1; we found that one of these forms functions as an attractive haptotactic cue (presentation 1); the other acts as a chemotactic guidance cue that elicits concentration-dependent attractive or repulsive responses (presentations 2 or 3). *Here we investigated how differentially glycosylated forms of netrin-1 promote distinct receptor localization, and signal transduction to evoke diverse axonal responses during attractive haptotaxis, attractive chemotaxis, and repulsive chemotaxis* (**Fig.1**).

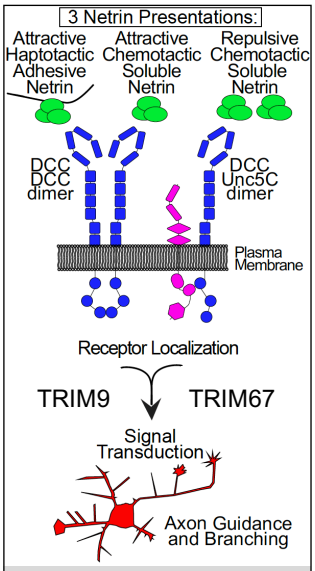

Fig.1: Graphical abstract.