Donnelly Centre
PDF and RA Seminar Series

"Optimizing Protein Stability for Sustained Delivery to the Central Nervous System"

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Severe injuries to the central nervous system (CNS), including stroke and spinal cord injury, have devastating effects on thousands of people each year. Patients suffering from these injuries face significant barriers to recovery due to the formation of a proteoglycan-rich glial scar, which provides a physical and chemical barrier to axonal regrowth and limits the regenerative capacity of the CNS. Chondroitinase ABC (ChABC) is a potent, yet fragile, bacterial enzyme, which can degrade chondroitin sulfate proteoglycans (CSPGs) in the glial scar and promote tissue recovery. However, its use as a therapeutic strategy is limited by its thermal instability and the challenge of achieving sustained delivery to the injury site. We developed an affinity-based delivery platform for ChABC in which the enzyme was expressed as a fusion protein with a Src homology 3 (SH3) domain and encapsulated in an injectable, covalently cross-linked methylcellulose hydrogel containing SH3 binding peptides. This minimally invasive delivery strategy provided tunable release of ChABC from the hydrogel to the site of spinal cord injury in a rat model. More recently, in order to address the intrinsic instability of ChABC, we computationally designed and tested ChABC mutants predicted to possess enhanced stability and covalently modified the enzyme with polyethylene glycol (PEG) chains to improve its *in vivo* presentation. These modifications to ChABC significantly enhanced its stability and prolonged its functional half-life. We are current evaluating the ability of modified ChABC to degrade CSPGs in animal models of stroke and spinal cord injury. Ultimately, we expect that this combinatorial approach will overcome key limitations of using ChABC as a therapeutic strategy to improve tissue and functional recovery after CNS injuries.

DATE: Monday April 30th, 2018
TIME: 12:00 – 1:00 pm
LOCATION: Red Room

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