Supervisor & Project Information Form

Please complete and return via email ONLY to gdip.hres@utoronto.ca by Monday, November 2, 2020

**Supervisor Information**

*MUST have unrestricted University of Toronto School of Graduate Studies (SGS) appointment (to independently supervise graduate students)*

<table>
<thead>
<tr>
<th>Name: Michael G. Fehlings</th>
<th>Email: <a href="mailto:Michael.Fehlings@uhn.ca">Michael.Fehlings@uhn.ca</a></th>
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<tbody>
<tr>
<td>SGS Department: Institute of Medical Science</td>
<td>Field of Research: Spinal Cord Injury, Degenerative Cervical Myelopathy</td>
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<tr>
<td>Research Institution affiliation (if applicable): Krembil Research Institute</td>
<td>Location of Work: Krembil Research Institute, Toronto Western Hospital</td>
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<td>Student contact time (number of hours per week YOU are available to the student for any concerns or to review progress): 1 hour / week</td>
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TITLE:
Repair and Regeneration of the Injured Cervical Spinal Cord

DESCRIPTION (MAX 500 WORDS):
Spinal cord injuries (SCI) have devastating consequences and lack effective regenerative treatments. Cell therapies are attractive for SCI as Neural Precursor Cells (NPCs) can differentiate along all three neuroglial lineages, provide trophic support, and show promise in preclinical models. Mechanistic insight into NPC-mediated repair is critical to overcoming key challenges including 1) poor graft survival due to the cytotoxic post-injury microenvironment; 2) pro-astrocytic biasing of transplanted NPCs, and 3) limited NPC migration and integration due to the glial/chondroitin sulfate proteoglycan (CSPG) scar. To address these barriers, I have 1) genetically engineered human NPCs to conditionally express the pro-survival / proneuronal glial-derived neurotrophic factor (GDNF), and 2) developed bioengineered strategies to locally deliver chondroitinase ABC (ChABC) to degrade the glial/CSPG scar.

My overarching hypothesis is that NPCs will promote neurobehavioral recovery in SCI by integrating with host neural circuits, myelinating denuded axons, and providing trophic support – effects which can be enhanced by bioengineering. This will be explored through 3 aims:

1) Transplanting NPCs after SCI which conditionally express GDNF.
2) Degrading the scar after SCI with highly novel and optimized ChABC delivery.
3) Combining both approaches in a unique combinatorial strategy.

Strong proof-of-concept data have been obtained to support all key aims. GDNF-expression may act by 1) increasing graft survival, 2) biasing NPC differentiation towards a neuronal fate, and/or 3) enhancing synaptic integration of transplanted cells. In our rodent clip-contusion model of chronic cervical SCI, we will explore these mechanisms by comparing transplants of NPCs, GDNF-NPCs, and GDNF-NPCs with CRISPR knockouts of the GDNF differentiation pathways. We will determine the ideal delivery technique for ChABC (cutting edge inducible cell-based vs biomaterial delivery) and the optimal duration for chronic scar degradation. Mechanisms will be examined through analyses of synapse formation, neural networks, myelination, cell signalling and sensorimotor function. Finally, we will combine the two approaches in a combinatorial approach.
All studies will use detailed neurobehavioral and electrophysiological assessments and incorporate treadmill rehabilitation. Viral and non-viral tracing techniques, opto-/chemogenetics and ex vivo patch-clamp electrophysiology will assess network re-organization and integration. Immunogold transmission EM and confocal immunohistochemistry will be complemented by RNA-Sequencing to assess cellular and molecular mechanisms.

If human subjects are involved, have the appropriate Research Ethics Board approvals been obtained?

N/A

Do you expect this work will be published within the 20 months?

☐ Yes

**Student Roles & Responsibilities (please be as specific as possible)**

*Indicate who will serve as the student’s direct report for daily oversight (PI, PhD student, technician, etc...)*

The direct report will be Dr. Mohamad Khazaei, a Scientific Associate in my lab.

*Indicate to what extent the student’s research activities could, if necessary, be completed remotely.*

The bulk of this work will need to be done on site, however, there are opportunities to run analyses and to write remotely.