RESEARCH SCHOLAR PROGRAM – 2018

SUPERVISOR & PROJECT INFORMATION FORM

Please complete and return, via email only (crems.programs@utoronto.ca) by ***November 3rd 2017*** *(forms received after this date will not be posted).*

Supervisor Information

Name: Alain Dabdoub Email:alain.dabdoub@sri.utoronto.ca

Degree: PhD SGS Appointment (IMS, IHPME, LMP etc..): LMP

Academic Rank: Associate professor

Field of Research: Neurobiology, Hearing

Research Institution Affiliation (if applicable): Sunnybrook Research Institute

Allocation of student contact time (number of hours per week YOU are available to the student for any concerns or to review progress): 1 hour per week.

Project Information

Title: Regenerating inner ear vasculature via the Wnt signaling pathway

Description (max 500 words):

Strikingly, no FDA- or Health-Canada-approved therapeutics that can restore hearing are presently available, and the need for such new and innovative therapeutic strategies to improve lives is urgent. Traditionally, research in hearing loss has focused on degeneration of the sensory hair cells or auditory neurons. However, studies in humans have shown that age-dependent degeneration of the inner ear vasculature, the *stria vascularis (SV)*, occurs before clinically detectable hearing loss. The molecular pathways of hearing loss as a result of strial degeneration require further focus. In murine age-related hearing loss (ARHL) there is a significant vessel narrowing and degeneration of strial capillaries and widespread cell death within the SV. This strial degeneration may be closely linked to the lack of angiogenesis, i.e. new vessel formation. We and others have previously shown that vascular maintenance in the adult inner ear and retina is normally controlled by the binding of the growth factor Norrin to its high affinity receptor Frizzled-4, leading to a subsequent induction of the Wnt signaling pathway. Age-dependent degeneration of the SV in humans precedes clinically detectable hearing loss. Precise mechanisms of how the Wnt signaling pathway might become dysregulated and induce strial degeneration in ARHL requires further characterization. This, in turn, will help optimally identify molecular targets and develop therapeutics for hearing restoration. The SV thus plays an important role in endeavors to characterize molecular pathways of hearing loss, for potential hearing preservation and regeneration. This project will explore whether pharmacological manipulation of the Wnt pathway can induce proliferation and angiogenesis of the aged SV. The effect of Wnt pathway activation on proliferation (assessed by BrdU incorporation and immunohistochemistry with an antibody against BrdU) will be assessed in cultured aged strial explants after addition of Wnt small molecule agonists. This provides a quick way to quantify rate of proliferation in Wnt treated explants versus controls. Furthermore, the full transcriptome will be mapped with single cell RNA sequencing in old SV explants that have been treated with a Wnt activator, compared to untreated controls. Analysis of downstream targets and cell cycle genes from the RNA

sequencing results will identify whether Wnt activation promotes regeneration of the SV by activating cell cycle genes, and because analysis is done per cell type screening will also identify whether certain cell populations within the stria are more prone to regeneration. Up- or downregulation of genes of interest will be validated with RT-qPCR. Mapping the inner ear vasculature and its degeneration with age, combined with a regenerative medicine approach to restore vessel maintenance in the aged inner ear, will enable unprecedented advancement for the treatment of hearing loss.

If human subjects are involved, have Ethics been obtained?

☐ YES ☐ NO ☐ Application Submitted ☒ N/A

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

☒ YES ☐ NO ☐ Uncertain

Student's roles and responsibilities (please be specific)

Dissection of mouse inner ear, and culturing of explants; immunohistochemistry, fluorescence & confocal microscopy; RNA extraction, qPCR; some RNA sequencing analysis

Please indicate who will serve as the student's direct report (PI, PhD student, technician etc…)

Postdoctoral fellow, Dr. Sophie Nyberg