Supervisor & Project Information Form

Please complete and return via email ONLY to gdip.hres@utoronto.ca by ***Monday September 30, 2019***

Supervisor Information

MUST have unrestricted SGS appointment (appointment to supervise graduate students)

Name: Alain Dabdoub	**Email:** alain.dabdoub@sri.utoronto.ca
SGS Department: Laboratory Medicine and Pathobiology	**Field of Research:** Inner ear organoids and regenerative medicine
Research Institution affiliation (if applicable): Sunnybrook Research Institute	**Location of Work:** Sunnybrook Health Sciences Centre 2075 Bayview Ave, Toronto, ON M4N 3M5
Student contact time (number of hours per week YOU are available to the student for any concerns or to review progress:	1 - 2 hours/week during academic year 2 hours/week during summers

Project Information (will be posted on GDipHR website for student access)

TITLE:

Human Inner Ear Organoids: a Cutting-Edge Tool in Regenerative Medicine to Develop Novel Therapeutic Strategies

DESCRIPTION (MAX 500 WORDS):

Inner ear disorders affect people of all ages, from newborn to older. Inner ear sensory hair cells (HCs) play an important role in detecting sound (cochlear) and motion (vestibular). Sensory cells are vulnerable to damage, including infections, noise exposure, ototoxic drugs, or ageing. The permanent loss of either cochlear and vestibular HCs leads to hearing and balance disorders respectively and the absence of robust spontaneous regeneration of HCs contributes to the irreversible nature of these disorders, especially with the lack of any treatments. With the expected doubling of the geriatric population in the next 25 years, balance and hearing disorders will reach epidemic proportions and have a profound impact on the quality of life, and economic cost for elder care. The World Health Organization estimates that by 2050 over 900 million individuals will have severe to profound hearing loss. In addition, the economic impact of unaddressed hearing loss has an annual global cost of $750 billion, highlighting the pressing need for a biological solution to progressive, permanent inner ear disorders with a focus on therapeutic developments to restore function.

Currently, there are no effective therapies for inner ear disorders. In this project, we aim to develop human inner ear organoids using 3D culture technology to fill the gap to validate therapeutic strategies *ex vivo* as well as investigate sensory epithelium regeneration. Developing a 3D human cell-based assay, we can mimic physiological tissue architecture, properties, function, and transcriptional profiles. Indeed, organoids recreate tissue microenvironments to elicit *in vivo* structure and function for cells *in vitro*.

In our lab, we are generating organoids from human balance organs (donated from surgical patients) to trigger endogenous regeneration, elucidate regenerative pathways, and develop novel therapeutic strategies for inner ear disorders.

The establishment of the human inner ear organoids as a model system for analysis of regeneration and differentiation pathways represents a significant step toward translation from the basic benchtop research to the clinical population. By conducting our studies on human organoids, we will be able to determine the effectiveness of potential new therapies, accelerate discovery, and reduce the costs of performing clinical trials in patients. We plan to scale-up this 3D system and our approaches will include drug testing and gene therapy studies that will serve as "*clinical trials in a dish*" to screen single and combinatorial transcription factors for regenerative properties and provide further insight into novel therapeutic targets, accelerating discovery. Taken together, this project has transformative potential and translational impact for

treating hearing loss and balance disorders and will establish research protocols that will provide a platform for future gene therapy and drug discovery and development.

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

☒Yes ☐No ☐Application Submitted (Date: _____)

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

☒Yes ☐No ☐Uncertain / Other

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

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

Student role and responsibilities:

The student will investigate sensory cell regeneration in human inner ear balance organs, specifically in inner ear organoids, elucidating key factors involved in the regeneration process. The trainee will dissociate the sensory epithelium of these organs, donated from surgical patients, using a protocol recently established in my lab and will generate organoids to test small molecules to trigger regeneration with the final goal of elucidating regenerative pathways.

To characterize inner ear organoids, the student will have complete training and access to confocal, multiphoton, light-sheet microscopes and scanning electron microscopy as well as to the Huygens deconvolution software to generate high-resolution images.

The student will be partaking directly in the process of scalability of the human inner ear organoid system with particular attention to the standardization of the culture conditions and protocol. The goal is to generate a robust and reproducible expansion of organoids and optimize a cost-efficient protocol to make this tool suitable for drug screening and testing. In fact, we plan to scale up this system to medium- or high-throughput screens to test drug sensitivity, toxicity and/or select compounds, opening a window into novel therapeutic strategies for hearing loss and balance disorders. The student will have a key role in achieving this task.

This project provides unique and unprecedented opportunities to develop personalized therapies to address hearing loss and balance disorders as well as generate a cutting-edge tool to study strategies for inner ear sensory epithelium regeneration.

Student's supervision:

The lead for this project in my lab is Dr. Emilia Luca, a postdoctoral fellow specializing in proteomics and functional genomics. In 2017, she joined my laboratory where she has gained an extensive experience in inner ear biology techniques and in particular for culturing inner ear whole explant organs and human organoids. Dr. Luca has more than 6 years of teaching experience and regularly trains and mentors graduate students as well as new lab members. Emilia will provide daily oversight and support for the student ensuring their success in the project.

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