Graduate Diploma in Health Research
PROGRAM – 2018 SUPERVISOR &
PROJECT INFORMATION FORM

Please complete and return via email only (gdip.hres@utoronto.ca) by September 4, 2018 (forms received after this date will not be posted).

**Supervisor Information**

**Name:** Dr. Julie Lovshin  
**Email:** julie.lovshin@sunnybrook.ca

**Degree(s):** MD/PhD  
**SGS Department:** IMS

**Academic Rank:** Clinician Scientist, Endocrinologist  
**Field of Research:**
Clinical Investigation – Type 2 Diabetes & Complications

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)

- The PI for is available for a minimum of 8 hour a day, 4 days a week to consult with student.
Project Information (for posting on GDipHR website)

Title: The INTRA-RENAL Trial:
INvestigation of Tubular ReAbsorption, REnal hemodynamic function, NAtriuresis, and inflLammation following sustained GLP-1R signaling with semaglutide compared to inhibition of dipeptidyl-peptidase 4 with sitagliptin in participants with type 2 diabetes

Description (max 500 words):
Type 2 diabetes (T2D) is an epidemic in Canada and around the world, and its complications, including diabetic kidney disease (DKD) have enormous implications on health resources. In particular, DKD has a significant impact on the morbidity and mortality of those who develop T2D, as DKD accelerates the risk for premature death due to cardiovascular disease. Presently there are no therapies available that fully protect against the development or slow the progression of DKD in T2DM.

Recently, drugs from two specific classes of antihyperglycemic agents, SGLT-2i (sodium glucose cotransporter-2 inhibitors, empagliflozin and canagliflozin) and GLP-1R agonists (glucagon-like peptide-1 receptor agonists, liraglutide and semaglutide) respectively, have been demonstrated in large, prospective, randomized clinical studies in patients with T2D at heightened cardiovascular risk, to significantly reduce cardiovascular and nephropathy events independent of glucose-lowering. In light of these data, drugs with proven cardio-renal benefit from these two classes, are now prioritized over other antihyperglycemic agents (after metformin) for those with T2D and clinical cardiovascular disease, by several diabetes and cardiology organizations around the world. With the potential to maximize renal and cardiovascular (CV) event reduction with agents from two different drug classes with differing cardio-renal mechanisms, there is now increasing interest in better understanding the physiological effects of these two drug classes in the diabetic heart and kidney.

The non-glycemic renal effects of SGLT-2i are thought to predominantly impact restoration of maladapted tubuloglomerular feedback (which precipitates renal hyperfiltration and glomerular injury in T2D) through stimulating natriuresis (urinary sodium excretion). Similarly, the cardiovascular effects of SGLT-2i are also
attributed to primary renal effects, as increased natriuresis initiates reduction in plasma volume, BP, and vascular stiffening which may partially explain why SGLT-2 inhibition significantly reduces the risk for hospitalization due to heart failure in T2D. In direct contrast to SGLT-2i, the intrarenal mechanisms of GLP-1R agonists are not unknown and are poorly described in the literature. Recently, a long-acting GLP-1R agonist providing sustained GLP-1R signalling allowing for once weekly administration, known as semaglutide, was approved in Canada for treating T2D. While clinical studies have demonstrated reduction in albuminuria with semaglutide in addition to cardiovascular event reduction, the intrarenal mechanisms by which sustained GLP-1R signalling is linked to improved cardio-renal outcomes for T2D patients is unknown. Therefore, defining the CV and renal hemodynamic effects of semaglutide will better inform us about the cardiovascular and renal mechanisms engaged by GLP-1R signalling.

This study will use a randomized, double-blind, double-dummy, active-controlled, parallel-group design in 28 patients with T2D. The aims of the study are to determine the intra-renal effects (renal hemodynamics, renal inflammatory, segemental tubular natriuresis, systemic hemodynamics) of sustained GLP-1R signalling (semaglutide) as compared to inhibition of dipeptidyl peptidase 4 (sitagliptin) in T2D participants with preserved renal function. The primary objective is to determine the acute and chronic effects of sustained pharmacological GLP-1 receptor signalling with semaglutide on natriuresis, and secondly, to determine the effects on inflammation, glomerular filtration, and renal plasma flow compared to sitagliptin, an active-comparator, controlling for endogenous GLP-1 receptor signalling.

If human subjects are involved, have the appropriate Research Ethics Board approvals been obtained?
☐YES ☐NO ☒ REB application is submitted and approval is anticipated shortly
October/November 2018 ☐N/A
Do you expect this work will be published within the 20 months?
☐YES ☐NO ☒ Uncertain
- Publication is dependent on study recruitment but a concerted effort will be made to complete the study for publication as soon as possible

**Student’s roles and responsibilities** (please be as specific as possible):
- The student’s responsibility will be to become familiar with the clinical study protocol and clinical investigation techniques used in this clinical study protocol, they will develop a specialized skill set in measuring renal and systemic hemodynamic function
- The student will be trained in clinical research methods including: screening, direct patient contact by conducting informed consent procedures and informed consent collection, being present at study visits and assisting the study physicians
- The student will participate in direct data collection including clinical laboratory techniques (measuring vascular stiffness, non-invasive cardiac output monitoring), data entry and data analysis.
- The student may participate in literature review, or database development.

*Please indicate who will serve as the student’s direct report for daily oversight (PI, PhD student, technician, etc...):*
- The selected student will be under the oversight of the study PI, Dr Julie Lovshin.
- All of the study related updates and meetings will be with PI, Dr Julie Lovshin.