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: Urban Emmenegger  
Email: urban.emmenegger@sunnybrook.ca

Degree(s): MD  
SGS Department: Institute of Medical Science

Academic Rank: Assistant Professor

Field of Research: Medical Oncology/Prostate Cancer

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)

I am typically available from Mondays to Wednesdays, Tuesday is a fully protected research day (pager signed off, clinical coverage by colleague); Thursdays and Fridays are my clinic days and availability for research issues is limited; I aim to meet at least once per week for ongoing projects, for 30-60 minutes, or more time if needed.
**Project Information** (for posting on GDipHR website)

**Title:** Studying the Role of Denosumab-Induced Severe Hypophosphatemia in Men with Metastatic Castration-Resistant Prostate Cancer (mCRPC)

**Description (max 500 words):**

**Background:**
Prostate cancer is the most frequently diagnosed malignancy in Canadian men, and its lethal form (ie mCRPC) is the third-leading cause of cancer related deaths. Bone is the most common site of CRPC metastases, predominantly accounting for mCRPC-related morbidity (so-called skeletal related events [SREs] such as skeletal pain and pathological fractures) and contributing to mCRPC-associated mortality. Antiresorptive agents such as zoledronic acid (ZA; bisphosphonate) and denosumab (anti-RANKL monoclonal antibody) delay the onset and rate of SREs.

While hypocalcemia is a known side effect of antiresorptive agents, we observed that (i) ZA administration might also result in severe (ie grade 3-4) hypophosphatemia in a sizeable subgroup of patients with mCRPC (around 15%), and that (ii) ZA-induced severe hypophosphatemia predicts poor prognosis (submitted).

Fibroblast-growth factor 23 (FGF23) is the major regulator of circulating phosphate levels. In addition, preclinical evidence suggests that FGF23 contributes to the malignant behavior of prostate cancer cells. Thus, we postulated that FGF23 might be the molecular driver of poor prognosis in patients with ZA-associated severe hypophosphatemia (Lee et al. Med Hypotheses. 2014;83:482-7).

Due to its more potent antiresorptive effects, denosumab is superior to ZA in preventing SREs. Although denosumab-induced severe hypophosphatemia is common (personal observation), it is not known to date whether the aforementioned association of ZA-induced severe hypophosphatemia and poor prognosis also applies to men undergoing treatment with denosumab, and whether pre-treatment FGF23 plasma levels predict the development of severe denosumab-induced hypophosphatemia.

**Hypotheses:**
(1) Denosumab-induced severe hypophosphatemia predicts poor prognosis in men with mCRPC.  
(2) Elevated pre-treatment FGF23 plasma levels are associated with the development of severe denosumab-induced hypophosphatemia.

**Patients and Methods:**
(1) We plan to conduct a retrospective chart analysis of the more than 250 men with mCRPC that have been treated with denosumab at Odette Cancer Centre (OCC) since 2012. Main outcomes
studied will be the rate and degree of hypophosphatemia observed, and a comparison of the outcome of patients with versus without severe denosumab-induced hypophosphatemia. (2) More than 40 mCRPC patients start denosumab therapy at OCC annually. As part of a comprehensive mCRPC biobanking initiative at OCC, we will obtain pre- and on-treatment plasma samples of men starting denosumab therapy for FGF23 analysis using a commercial FGF23 ELISA assay. We plan to analyse correlations between FGF23 levels and (i) the rate as well as severity of hypophosphatemic episodes, and (ii) patient outcome.

Significance:
Malignancy-associated hypophosphatemia, including hypophosphatemia induced by antiresorptive agents in men with mCRPC, typically is refractory to treatment. Our studies (i) have the potential to enable the identification of patients with mCRPC at risk for this complication and its associated poor prognosis, and (ii) may lead the way to studies of fibroblast growth factor inhibitors as a means to both correct severe hypophosphatemia and to help improving the outcome of such patients (Lee et al. Med Hypotheses. 2014;83:482-7).

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

X YES ☐ NO ☐ Application Submitted ☐ N/A

Do you expect this work will be published within the 20 months?
X YES ☐ NO ☐ Uncertain
**Student’s roles and responsibilities** (please be as specific as possible):

The student will work as part of my research team (one medical oncology fellow and typically 1-2 undergraduate students from the coop program at the University of Waterloo), but will be the main person in charge of the outlined research project. The student is expected:

- to extract patient information from electronic charts
- to analyse the extracted information
- to conduct statistical analyses in collaboration with other research team members and/or an external statistician
- to coordinate the collection of plasma samples, and to process the blood samples (in collaboration with coop students year-long attending my clinics)
- to perform the FGF23 ELISA assay
- to prepare according abstracts and manuscripts

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

The PI will be the primary contact for the direction of the project and typically meets at least once per week with each team member. For the proposed project the student will also work closely with the medical oncology fellow. Both the PI and the medical oncology fellow, as indicated, will provide daily oversight.

For the FGF23 ELISA assay the PI will provide the necessary training. The assay will be performed in one of the cancer laboratories at Sunnybrook Research Institute.