Letter of intent

Dear members of the Lung Ambition Awards committee,

We would like to submit to the Lung Ambition Awards program a Canadian prospective cohort study to establish the performance and added value of endobronchial ultrasound (EBUS) in hilar lymph node staging. The recently demonstrated benefits associated with peri-operative immunotherapy in early stage Non Small Cell Lung cancer (NSCLC) with hilar nodal disease have made the preoperative knowledge of hilar nodal status of paramount importance. The presence or absence of hilar nodal disease was previously not an as important clinical information as it only modified post-operative treatment hence it could be detected at surgery without a change in treatment plan. With the recently published data on perioperative immunotherapy in early-stage NSCLC, pre-operative detection of hilar nodal disease by EBUS could change treatment plan and prevent disease recurrences after surgery.

The DETECT study will recruit patients with central or hypermetabolic (SUV >4.0) cT1-2N0M0 NSCLC to undergo pre-operative staging by EBUS. Patients without nodal disease found on EBUS will undergo surgery with lymph node dissection. Surgery will provide the gold standard lymph node staging to establish the performance of hilar EBUS staging. Patients who are not surgical candidates or for who surgical resection is not planned if EBUS is negative will not be recruited to this study. The primary objective of this study is to establish the sensitivity and negative predictive value of EBUS for hilar nodal staging. Secondarily, it will also allow to establish the number needed to screen by EBUS to modify treatment plan.

All participating centers have a vast expertise in EBUS staging of lung cancer and have published landmarks studies in the field. Dr Yasufuku is considered as the “father of EBUS” and Dr Yasufuku and Liberman contributed by their previous publications to establish EBUS as a standard practice for pre-operative mediastinal lymph node staging. I have developed a prediction model to identify higher risk patients who should undergo pre-operative mediastinal staging and published 14 peer-reviewed articles about EBUS in the last 5 years. We have recently completed a randomized controlled trial of over 200 participants in the field of EBUS with the McGill and Calgary teams, demonstrating our capacity to run large prospective multicenter trials. I am a Clinical Research Scholar at the Institut Universitaire de Cardiologie et Pneumologie de Quebec with dedicated research time to run this project.

This study has the potential to improve the investigation pathway of patients with early stage NSCLC and decrease the risk of disease recurrence after surgery. The impact of this study would go beyond pre-operative immunotherapy as hilar nodal status is also important when proceeding to sublobar resection and stereotactic body radiation therapy, which are both treatments on the rise.

Project summary

Detection of Occult Hilar Nodal Disease by Endobronchial Ultrasound in Early Stage Non Small Cell Lung Cancer (DETECT)

Rationale: Early stage non-small cell lung cancer (NSCLC) is generally treated surgically with a curative intent. Conversely, mediastinal nodal involvement (**Figure 1**) indicates more advanced disease and leads to a non-surgical approach in the majority of cases. Therefore, the extent of disease largely dictate treatment in NSCLC. Computed tomography (CT) and positron emission tomography (PET) scans are recommended for preoperative screening of mediastinal nodal disease, but have a suboptimal sensitivity. To overcome this limitation, endobronchial ultrasound (EBUS) (**Figure 2**) can be used to detect and biopsy imaging occult nodal disease[1-2]. EBUS is currently recommended for the detection of imaging occult **mediastinal** nodal disease in patients at higher risk, with the goal of reducing the risk of unanticipated mediastinal nodal disease at surgery[3-5]. There are no recommendations concerning **hilar** disease (**Figure 1**) and EBUS is not recommended in patients without risk factor for mediastinal disease.

Until recently, the detection of **hilar** nodal disease has been of limited interest as surgery followed by adjuvant chemotherapy has traditionally been the treatment of choice for patients with hilar nodal disease documented before or during surgery. However, recent studies have demonstrated a significant reduction in disease recurrence in patients with hilar nodal disease when immunotherapy is administered preoperatively[6-7]. Therefore, the preoperative detection of hilar nodal disease is now of paramount importance, but the feasibility of routine hilar sampling by EBUS remains uncertain as it is technically more challenging than mediastinal sampling. Recent advances in EBUS technology, with a thinner and more flexible scope, are expected to overcome the technical difficulties of hilar staging. More importantly, we have recently identified, and externally validated, risk factors (central tumor location and/or a SUVmax >4.0 on PET imaging) for occult hilar nodal disease, allowing the identification of a subgroup of early stage NSCLC with a 20-30% prevalence of imaging occult nodal disease[8]. With these selection criteria, over 90% of patients with occult hilar nodal disease would have been referred for EBUS but the number of EBUS performed would have been reduced in half.

Objective: The objective of this prospective Canadian national cohort is to evaluate the added value of preoperative EBUS staging in patients with early stage NSCLC presenting risk factors for occult nodal disease. Despite having demonstrated the significant risk of occult nodal disease in this population, it remains to be demonstrated that EBUS can detect nodal disease with sufficient sensitivity to justify its use.

Hypothesis: We hypothesize that occult nodal disease will be detected by preoperative EBUS in approximately 15% of at-risk patients.

Study design: This is a **multicenter prospective cohort study** to evaluate the performance of EBUS for nodal staging in **suspected cT1-2N0M0 NSCLC**. Only patients with risk factors for occult nodal disease (**central tumor location**[9] or **SUVmax >4.0**) and with planned surgical lymph node dissection will be included (**Figure 3**). Patients expected to receive stereotactic body radiation therapy or preoperative immunotherapy will be excluded.

Patients will be invited to participate in this study during their preoperative evaluation at the six participating institutions (Quebec Heart and Lung Institute, University of Montreal Health Center, Foothills Medical Center and South Health Campus of the University of Calgary, Toronto General Hospital and McGill University Health Center). The EBUS procedure will be performed using the novel BF-UC190F EBUS bronchoscope (Olympus™, Japan), which has a thinner outer diameter and is more flexible allowing a thorough staging procedure into the segmental airways. A

systematic examination of all mediastinal and hilar lymph nodes within the drainage territory of the tumor will be performed[10]. All lymph nodes ≥5mm will be sampled. Endoscopic esophageal ultrasound (EUS) for further staging of the mediastinum is allowed at the discretion of the operator. If EBUS shows no nodal disease and the patient is considered a candidate for surgical resection by the treating team, the patient will undergo surgical resection of the lesion with systematic lymph node dissection of lymph nodes within drainage territory of the tumor. If nodal disease is found, the multidisciplinary team will re-evaluate optimal treatment and, potentially, direct the patient to immunotherapy prior to surgery.

Data analysis and sample size: A two-by-two table will be created using EBUS and EUS cytology reports and surgical lymph node dissection pathology report. This will allow calculation of sensitivity, negative predictive value and number needed to screen by EBUS to detect one case of imaging occult lymph node disease. Specificity and positive predictive value will not be calculated as patients with lymph node disease generally do not undergo surgical resection or, if they do, receive prior immunotherapy. The sensitivity of EBUS for radiologically occult mediastinal disease, which has been previously shown to vary with the prevalence of nodal disease, reaches 58% in studies with a prevalence of occult nodal disease of 20-30%[11]. We expect a similar performance in our cohort, leading to the identification of occult hilar nodal disease in approximately 15% of participants. Accordingly, a total of 275 patients will be required to detect a sensitivity of 58% with a confidence interval of ±10% in the context of a prevalence of 25%.

Feasibility and timeline: All participating centers perform >500 EBUS procedures per year, including >100 in patients meeting the proposed inclusion criteria. All have within their equipment park at least one BF-UC190F EBUS scope and the necessary staff to consent patients and collect the data. Most participating centers have previously collaborated on the Stather Canadian Outcome Procedure Database (SCOPE)[12], which recruited over 2000 EBUS procedures for lung cancer, and the Slim Scope Study, a randomized controlled trial of over 200 EBUS procedures which was recently submitted for publication, demonstrating the capacity of our network to conduct this trial. These projects were completed with relatively limited budgets as, similarly to the current project, we were collecting data from procedures performed for clinical indications and cost was limited to research personnel time.
Recruitment will begin in the spring of 2025 and it is expected to take 12 to 18 months to recruit all participants.

Impact and perspectives: This study has the potential to improve the lung cancer investigation pathway and reduce disease recurrence in patients with early stage NSCLC undergoing surgery by identifying potential candidates for preoperative immunotherapy who are currently missed. Extrapolation of the study results to slightly different populations could also have a broader impact on investigation pathway as hilar nodal status is crucial when directing patients for sublobar resection or stereotactic body radiation therapy, two treatments options that are on the rise.

Figure 1 Mediastinal and hilar lymph node anatomy

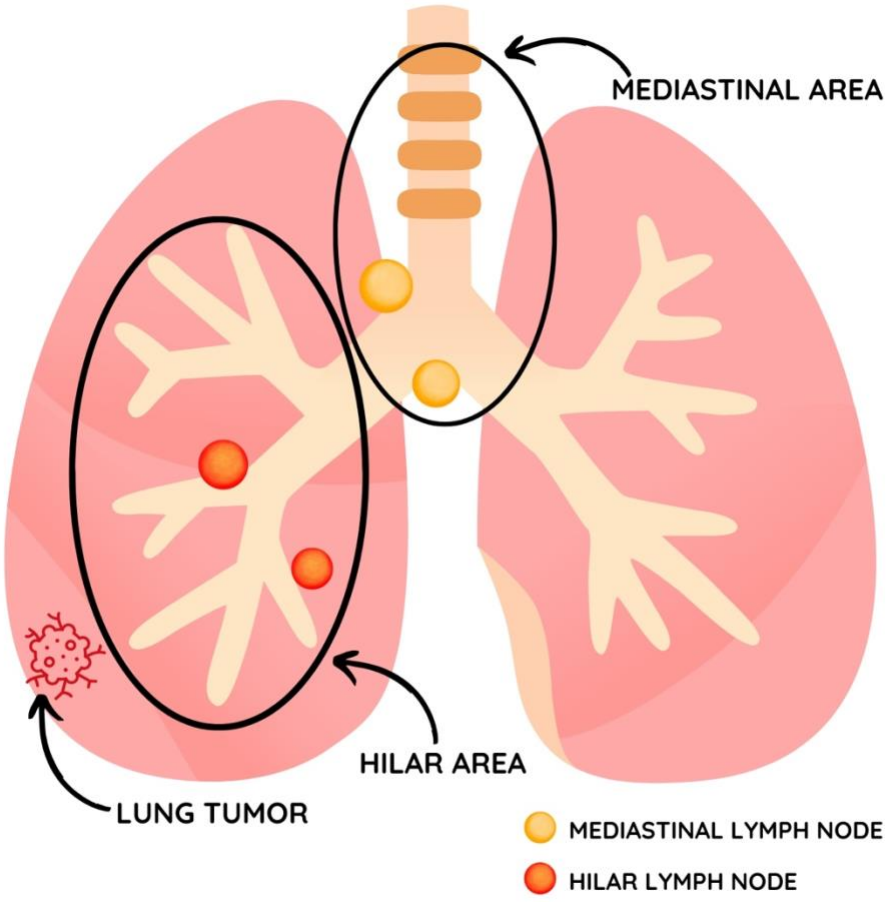
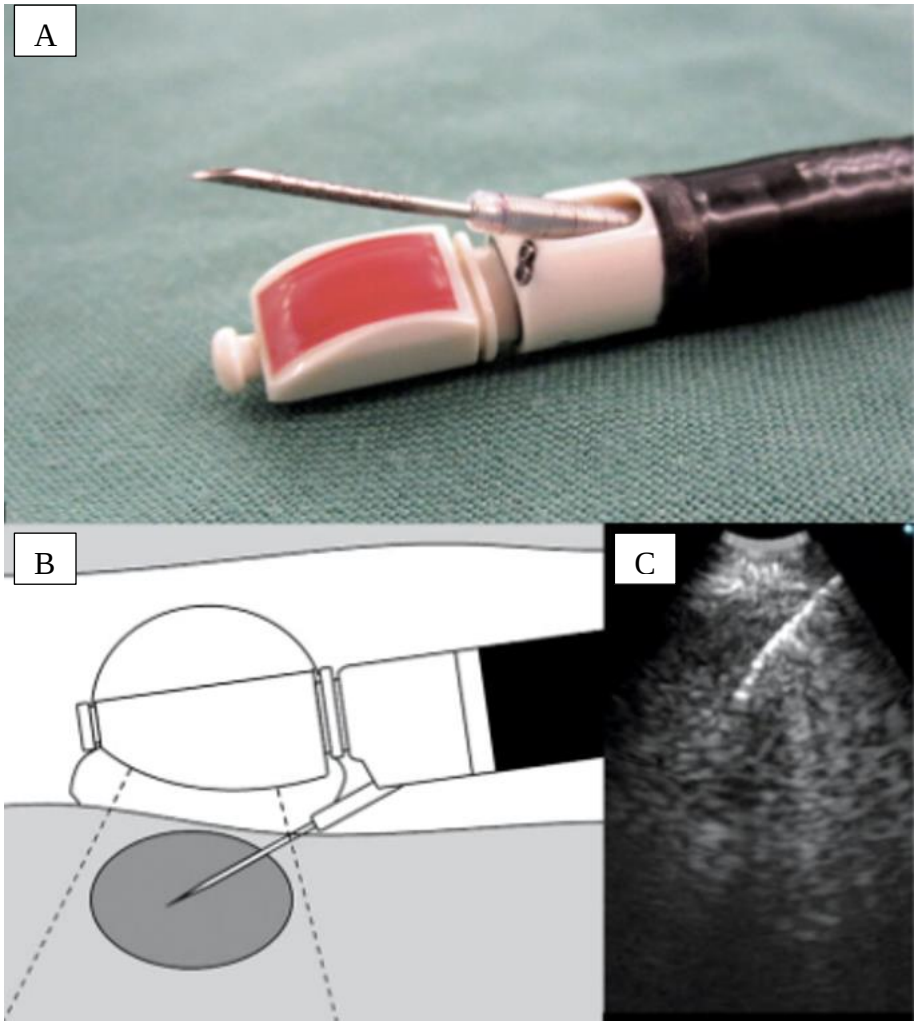
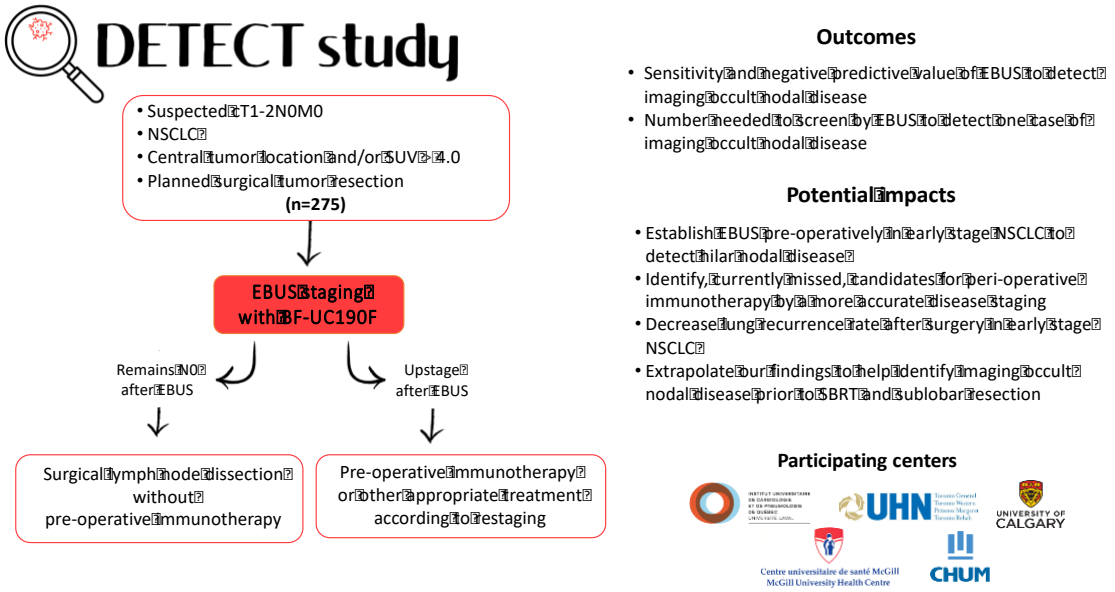


Figure 2 Endobronchial ultrasound (EBUS)



A) Endobronchial ultrasound (EBUS) scope with biopsy needle deployed through the working channel
B) Schematic representation of EBUS guided lymph node biopsy
C) Ultrasound image of EBUS guided lymph node biopsy

Figure 3 DETECT study summary



Outcomes

- Sensitivity and negative predictive value of EBUS to detect imaging occult nodal disease
- Number needed to screen by EBUS to detect one case of imaging occult nodal disease

Potential impacts

- Establish EBUS pre-operatively in early stage NSCLC to detect hilar nodal disease
- Identify, currently missed, candidates for peri-operative immunotherapy by a more accurate disease staging
- Decrease lung recurrence rate after surgery in early stage NSCLC
- Extrapolate our findings to help identify imaging occult nodal disease prior to SBRT and sublobar resection

Participating centers

UHN
UNIVERSITY OF CALGARY
Centre universitaire de santé McGill
McGill University Health Centre
CHUM

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Impact statement

The DETECT study will have a direct impact on clinical practice in the short term. It is a clinical study which explores the added value of a modification, adding EBUS for certain patients at high risk of occult nodal disease, in the early stage NSCLC investigation pathway. This will allow to identify patients who could benefit from perioperative immunotherapy. Two recent landmark studies (CheckMate816 and KEYNOTE-671) have demonstrated a 50% increase in event free survival in patients with hilar nodal disease when treated with immunotherapy before their surgery. The presence of hilar nodal disease makes NSCLC at least stage IIA, according to the 9th edition of the TNM classification, which makes patients eligible for perioperative immunotherapy. Lesions larger than 3cm without nodal disease (stage Ib) were eligible to participate in CheckMate816 (less than 20 were enrolled) but not KEYNOTE-67, hence it is not routine practice to administer perioperative immunotherapy in patients without hilar nodal disease. For these reasons, demonstrating the performance of EBUS in the detection of hilar nodal disease could lead to a modification in practices and guidelines, as EBUS is not routinely performed in early stage NSCLC, and give access to an optimal treatment to more patients.

The detection of occult nodal disease could also be extrapolated to two other frequent clinical situations encountered in the management of early stage NSCLC. First, patients undergoing Stereotactic Body Radiation Therapy (SBRT) do not undergo surgical lymph node dissection, potentially leaving unidentified nodal disease behind during radiation treatments. This can lead to locoregional recurrence as the untreated nodal disease proliferates after SBRT and leads to a recurrence during follow-up. This is demonstrated by the threefold increase in regional recurrence seen after SBRT when compared to surgery. If this disease was detected by EBUS prior to treatment, it could be included in the treatment radiation field and the regional recurrence prevented. Second, sublobar resection was the object of a recent large randomized controlled trial (CALGB140503) demonstrating its non-inferiority to lobar resection. This surgical approach is seeing an increase in popularity. This type of surgery is not indicated in the presence of hilar nodal disease hence the preoperative knowledge of the presence of hilar disease could also change management in this population.

The DETECT study is a clinical and highly pragmatic study which will allow clinicians to better understand the role of EBUS in the detection of hilar nodal disease in early stage NSCLC and, potentially, modify investigation pathways. It will lead to improvements in patient care by improved disease staging, which will lead to treatment plan optimization and, ultimately, improved patient survival.

Public summary

The best treatment for a patient with lung cancer depends on the extent of the disease. If the lung cancer is small and has not spread to other organs (metastasis), it can generally be removed by surgery. When a lung cancer progresses, it spreads first to the hilar lymph nodes (close to the tumor) then to mediastinal lymph nodes (further from the tumor, between the two lungs) and, ultimately, to other organs (figure 1). Traditionally, when cancer had spread to the hilar lymph nodes, but not further, it was removed by surgery (including the affected lymph nodes). To decrease the chances of cancer recurrence, chemotherapy was given, after surgery, to patients with cancer in their hilar lymph nodes. With this treatment sequence, it was not necessary to know if cancer had spread to the hilar lymph nodes prior to surgery. Recently, novel cancer treatments (immunotherapies), started before surgery, have been proven to decrease recurrence rate in patients with cancer in their hilar lymph nodes, hence we now need to know hilar lymph node status before surgery for the patients to benefit from immunotherapy.

Imaging modalities (ex : CT Scan) frequently do not detect the lung cancer in the lymph nodes. Endobronchial ultrasound (EBUS) has been developed to help detect lung cancer cells within the lymph nodes (figure 2). It consists of a camera, which can be guided within the airways by a doctor, and at the end of which is mounted an ultrasound probe. The ultrasound probe provides images of the lymph nodes which can be biopsied with a needle, which can be advanced through a working channel in the camera. EBUS has proven its performance with mediastinal lymph nodes (between the two lungs) but little interest has been given to its capacity to biopsy hilar lymph nodes (closer to the tumor). With the recently demonstrated benefits of immunotherapy, it becomes important to know if hilar lymph nodes are involved before surgery. Hilar lymph nodes are more challenging to biopsy than mediastinal lymph nodes as they are located in smaller airways and at, sometimes, sharper angles. Fortunately, a smaller and more flexible EBUS has recently been developed and could allow us to perform hilar lymph node evaluation.

We will perform a study in six Canadian hospitals to evaluate the performance of this new EBUS camera to detect hilar lymph nodes in patients with early stage lung cancer. After their EBUS procedure, patients will undergo surgery if no disease is found in the lymph nodes. During surgery, the lymph nodes will be removed. We will then be able to evaluate if EBUS performed well in the detection of lung cancer in hilar lymph nodes or not.

If EBUS is good at detecting lung cancer in hilar lymph nodes, we can use EBUS in the future to identify patients who could benefit from immunotherapy before their surgery. This study could rapidly and directly affect the care of lung cancer patients by decreasing recurrences after surgery.

Budget

	Hours (75$/h)[1]	**Cost**
Local start up fees[2]	15h x 6 sites	6 750$
ECRF development	40h	3 000$
Patient recruitment	1h x 140[3] patients	10 650$
Data collection	2h x 140[3] patients	21 300$
Central data monitoring	100h	7 500$
Data dissemination		1250$
Requested funding		**50 000$**

*No supplies or medical equipment fee is necessary as procedures are medically required. Centers already possess the necessary equipment for these routine procedures.

[1]The requested amount will mainly cover research coordinator hours. In all participating centers, research coordinators are nurses with a bachelor in nursing who have been working in clinical research for several years. Two nurses per center will work part time on the project to ensure constant availability of research staff for procedures. A 75$/h salary is planned for all research coordinators.

[2]IRB fees for study initiation will be waived as this is an investigator initiated study

[3]We have secured funding from the Annual IUCPQ Foundation Research Competition to recruit and collect data for 135 patients (30 000$) and request funding for the remaining 140 patients as well as other aspects of the project.

Investigators

-Marc Fortin, Laval University (PI)
-Alain Tremblay, University of Calgary (co-PI)
-Kasuhiro Yasufuku, University of Toronto (co-investigator)
-Moishe Liberman, University of Montreal (co-investigator)
-Anne Valerie Gonzalez, McGill University (co-investigator)

CENTRE DE RECHERCHE
INSTITUT UNIVERSITAIRE
DE CARDIOLOGIE
ET DE PNEUMOLOGIE
DE QUÉBEC
UNIVERSITÉ LAVAL

Quebec, January 28th, 2025

Evaluation Committee
Lung Cancer Canada
133 Richmond St. W., Suite 208
Toronto, ON M5H 2L3

Subject: Institutional Letter of Support for Dr. Marc Fortin's Application to the Lung Ambition Awards

Dear Evaluation Committee,

It is with great privilege that I write this letter in support of Dr. Marc Fortin's application for the Lung Ambition Awards. Dr. Fortin is an assistant professor under a scholarship within the Faculty of Medicine at Université Laval and conducts his research at the Institut universitaire de cardiologie et de pneumologie de Québec -Université Laval (IUCPQ-ULaval), the leading lung cancer investigation center serving the eastern region of the Province of Quebec.

Dr. Fortin has dedicated research time, as well as access to the necessary resources and institutional support to successfully carry out the proposed project. His research program focuses on optimizing lung cancer diagnostics, and the proposed project aligns seamlessly with his area of expertise. Specifically, the project titled "**Detection of Occult Hilar Nodal Disease by Endobronchial Ultrasound in Early-Stage Non-Small Cell Lung Cancer (DETECT)**" will leverage his specialized knowledge in this field.

Dr. Fortin has access to the required equipment, materials, research personnel, and study participants to ensure the project's success. Additionally, he will receive administrative and financial support from the IUCPQ-ULaval Research Center's staff to effectively manage the research award.

I am confident that Dr. Fortin's expertise, dedication, and the robust support system available to him position him exceptionally well to achieve meaningful outcomes in this important area of lung cancer research.

Hoping that the potential of this project and our commitment will be received positively.

Sincerely,

Mathieu Laplante, Ph. D.
Scientific Director of Research

Éric Paradis, Ph. D.
Administrative Research Director