Endoscopic Cryo-Ablative Technologies for the Definitive Treatment of Oligometastatic Lung Cancer

Letter of Intent

Lung cancer (LC) is the most commonly diagnosed and deadliest cancer worldwide. With the implementation of screening programs, there has been a change in the patient landscape in favor of earlier-stage lung lesions. However, regardless of screening, up to 50% of patients with non-small cell LC (NSCLC) will be diagnosed with oligometastatic disease – a stage once considered candidate for palliative treatment. With the poor 5-year survival rates of 10-30%, there is dire need to offer an effective, efficient, minimally invasive and repeatable treatment alternative to surgical resection or definitive chemo-radiation treatment.

In this regard, lung ablation has been suggested as an effective and less traumatic alternative to surgery. While current established ablation modalities have been deemed effective in terms of local recurrence, they present significant risks of complications; a high percentage of which require intervention. Cryotherapy – currently used in interventional bronchoscopy and radiology – may present as an interesting modality for transbronchial ablation. Along with its compelling safety profile, there is strong evidence to suggest that cryoablation in the lung could have a potentiating effect for immunotherapy; thus contributing to the resolve of distant metastases in the context of oligometastatic disease. Hence, leveraging novel robotic navigational bronchoscopy platforms with cryo could result in the development of an efficient, non-traumatic treatment for oligometastatic LC.

To date, no flexible cryoablation or cryoactivation probes have been developed for lung ablation. Based on previous ex-vivo and in-vitro studies, currently available transbronchial cryo devices are ill-suited for ablation and there is little evidence to inform on proper cryoablation or cryoactivation protocols within the lung. The primary objective of this study is to evaluate, in an in-vivo porcine model, the feasibility, efficacy and safety of transbronchial cryoablation and cryoactivation.

We believe that transbronchial cryoablation could become a promising treatment modality for oligometastatic LC by offering both a locally curative treatment as well as contribute to the resolve of distant lesions; significantly reducing the burden of disease of LC for both healthcare systems and patients. Despite promising results from systemic therapies, 5-year survival rates for oligometastatic LC remain low between 10-30% and there is a great unmet need in terms of bringing this statistic closer to 100%. This research program will lay the groundwork for the next steps in clinical a clinical trial for the transbronchial cryoablation of lung lesions in the context of oligometastatic disease.

Summary of Proposed Research

Non-small cell lung cancer comprises around 80% of all lung cancers (LC). Of these cases, up to 50% will be diagnosed with oligometastatic disease – a stage once considered candidate for palliative treatment. With the poor 5-year survival rates of 10-30% for these cases, there is dire need to offer an effective, efficient, minimally invasive and repeatable treatment alternative to surgical resection or definitive chemo-radiation treatment.

In this regard, lung ablation has been suggested as an effective and less traumatic alternative to surgery. While current established ablation modalities – including transthoracic percutaneous thermal, microwave (MWA) and radiofrequency (RFA) ablation as well as stereotactic ablative body radiotherapy (SBRT) – have been deemed effective in terms of local recurrence, they present significant risks of complications; a high percentage of which require intervention.

Cryotherapy – currently used in interventional bronchoscopy and radiology – may present as an interesting modality for transbronchial ablation. Leveraging novel CT-guided robotic navigational bronchoscopy platforms with cryo could result in the development of an efficient, non-traumatic definitive treatment for LC. The sub-zero temperatures achieved at the tip of the probe via the Joules-Thomson Effect cause immediate and delayed cell death by crystallization of the intra and extracellular environments as well as microthrombi formation in the surrounding vasculature; all of which contribute to necrosis of the tumor cells and reduce the risk of bleeding and bronchopleural fistula. When considering the risk of complications during ablation, cryo shows great promise, as it tends to target tissues with higher water content, i.e., tumors, sparing surrounding structures (cartilage, nerve sheath, connective tissue). In addition, similar to the abscopal effect observed with locoregional radiation therapy, there is strong early evidence that the release of the intracellular cellular contents following cryoablation may lead to the systemic emission of specific immunomodulatory signals which may potentiate or “activate” the response to immune checkpoint inhibitors (ICI), thus contributing to the resolve of distance metastases. Although insufficient in itself, the immune activation may lessen the influence of the cellular pathways which lead to primary resistance to ICIs – occurring in 10-27% of patients with non-small cell lung cancer (NSCLC) depending on the chosen regimen.

To date, no flexible cryoablation or cryoactivation probes have been developed for lung ablation. Based on previous ex-vivo and in-vitro studies, currently available transbronchial cryo devices are ill-suited for ablation and there is little evidence to inform on proper cryoablation or cryoactivation protocols within the lung.

The primary objective of this study is to evaluate, in a pre-clinical setting, the feasibility, efficacy and safety of transbronchial cryoablation and cryoactivation.

Using data from previous in-vitro and ex-vivo studies, which respectively aimed to define the efficacy of cryoablation in the context of LC to define appropriate cryoablation protocols and define and compare the efficiency of existing and in-development cryocatheters in the lung, we

have designed a robust in-vivo porcine protocol (ADD ETHICS APPROVAL). This work will be conducted in collaboration with a Montreal-based bioengineering company specialized in the development of transbronchial cryo technologies.

In this context and under general anesthesia, four pigs will be subjected to three cycles of transbronchial cryoablation using biphasic nitrogen. All ablation cycles will be determined pre-procedurally by the algorithm generated from our in-vitro lung cancer model study based on the subject's lung physiology. Adequate positioning of the catheter in the periphery of the lung will be confirmed using bronchoscopy and intra-procedural imaging. Each ablation cycle will be monitored through a live imaging feed. Following ablation, all pigs will be kept alive under anesthesia for a period of two hours before euthanasia, after which post-procedural imaging will be taken. Following necropsy of the chest to ensure no there were no undetected intra-procedural complications or affections to the chest wall or pleural, the ablated region will be resected from the lungs and will undergo complete pathological analysis. Using H&E slides, we will be able to determine the true area of necrosis vs inflammation resulting from cryoablation and correlate these results with the intra-procedural imaging. This data will inform on relevant intra-procedural metric to estimate the true area of cell death from transbronchial cryoablation. Finally, with regards to the abscopal effect, pre, intra and post-procedural blood work will the drawn to measure the acute and longer-term influence of cryoablation on circulating inflammatory markers.

We believe that CT-guided robotic navigational bronchoscopy using cryoablation could become a promising treatment modality for oligometastatic LC by offering both a locally curative treatment as well as contribute to the resolve of distant lesions; significantly reducing the burden of disease of LC for both healthcare systems and patients by completely revolutionizing and streamlining the management of oligometastatic LC. Despite promising results from systemic therapies, 5-year survival rates for oligometastatic LC remain low between 10-30% and there is a great unmet need in terms of bringing this statistic closer to 100%. This research program will lay the groundwork for the next steps in clinical a clinical trial for the transbronchial cryoablation of lung lesions in the context of oligometastatic disease.

Results of this work are expected to have a significant impact on the future management of both early and later-stage LC. These results will be presented at both national and international conferences and be published in a high-impact peer-reviewed journal for maximized exposure and contribution to the field.

Impact Statement

Which addresses the potential of the project to exert a sustained, powerful, influence on the research field(s) involved and how this work will reduce lung cancer incidence, reduce mortality, or improve patient quality of life. The statement should explicitly describe how the project will promote major advancement in lung cancer research, aiming to accelerate and focus the knowledge gained from scientific findings, in the short- to medium-term, into outcomes such as optimized patient care, improved treatment, or reduced burden.

Five-year survival rates for oligometastatic lung cancer (LC) are still as low as 10-30% and there is a great unmet need in terms of bringing this statistic closer to 100%. CT-guided robotic navigational bronchoscopy using cryo-technologies could become a first-line therapy for these patients by offering definitive treatment of nodules within the lung as well as contribute to potentiate systemic therapies for the treatment of distant metastases. Leveraging this technology could significantly reduce the burden of disease of LC for both healthcare systems and patients by completely revolutionizing and streamlining the management of later-stage LC. This research program will lay the groundwork for a future clinical trial for cryoablation of oligometastatic LC.

Public Summary

By 2035, it is estimated that 2.17 million individuals will be diagnosed with lung cancer (LC), a 65% increase since 2010. Although the implementation of LC screening programs has altered the disease landscape by allowing for earlier diagnosis, most LC patients – namely those with non-small cell LC (NSCLC) – are still diagnosed at later stages. Of the 80% of LC patients diagnosed with NSCLC, around 7-50% of them will develop multiple metastases, defined as oligometastatic disease. In past years, these patients were redirected towards palliative care. However, with the desire to improve survival outcomes, there has been a paradigm shift in favor of treatment with curative intent.

In such cases, local ablation therapies with or without systemic therapies may be considered. However, current established modalities are limiting in terms of potential candidates, treatment of recurrence and are associated with significant risks. With the emergence of CT-guided robotic bronchoscopy, it is now possible to accurately target peripheral lesions in a more diverse patient population and encourage the development of novel transbronchial interventions for the definitive treatment of pulmonary lesions. Cryotherapy, currently used in interventional bronchoscopy for biopsy and interventional radiology for transthoracic percutaneous ablation, has the potential to be an interesting opportunity in this rapidly evolving space due to its safety profile, ablation potential and ability to potentiate systemic therapies (abscopal effect).

The primary objective of this research program is to build upon previous in vitro and ex-vivo works to evaluate, in a pre-clinical setting, the safety, feasibility, efficacy and abscopal effect of transbronchial cryoablation of LC. This will be achieved through testing of an in-development cryoprobe in an in-vivo model. To date, no flexible cryoablation probes have been developed for lung ablation.

Transbronchial cryo-technologies could significantly reduce the burden of disease of later-stage LC for both healthcare systems and patients by completely revolutionizing the management of LC. Notwithstanding significant progress in the field, 5-year survival rates for oligometastatic LC are still low at 10-30% and there is a great unmet need to bring this statistic closer to 100%. This research program will lay the groundwork for a clinical trial for cryoablation of oligometastatic LC.

Budget

Item	**Description**	**Total ($)**
Research Supplies		
Cryocatheters	-	25,000
Cryoconsole rental	-	20,000
Cryogen	Biphasic nitrogen: liquid and pressurized gas	2,000
Animal subjects	x4 porcine subjects	8,000
Anesthesia & surgical supplies	Intubation supplies, anesthetics, warming blanket	2,000
Services		
Veterinary	Pre-procedural care, intra-procedural surveillance	4,000
Pathology	Processing and analysis of ablated specimens	4,000
Clinical laboratory	Analysis of blood samples	2,000
Imaging	Intra- and post-procedural computed tomography	4,000
Salaries		
Biostatistician	Data processing and analysis	2,000
Students	PhD and master's student	40,000
Imagery tech	Image tech for the capture and processing of intra- and post-procedural computed tomography	2,000
Other		
Animal laboratory space	Rental of the operating room in the animal lab	2,000
Total	-	**117,000**

As this research program is a larger scale, high-impact initiative, we have applied for various lung cancer specific as well as biomedical engineering research grants. Institutions at which we have or are planning to apply for funding: Canadian Cancer Society, Cancer Research Society, Montreal Cancer Institute, Medtronic Grant Competition and the Cancer Research Institute. In addition, as the cryocatheter tested in this project is still in developmental phases, we will receive support in kind from the Montreal-based company responsible for the engineering of the devices.

This grant will be used to cover the cost of the cryocatheters, as highlighted in the above budget. Any expenses which surpass the amount awarded by the various grants for which we have applied will be covered by the research fund of the principal investigator.

Investigators

PI: Dr Moishe Liberman

Collaborators: Maxime Têtu, Arman Sarshoghi, Dr Gilles Soulez, Dr Étienne Blais, Dr Bertrand Routy

The proposed research team is composed of clinician-scientists in the fields of thoracic surgery, radiology, veterinary medicine and medical oncology as well as research students at both the master's and doctorate levels. We believe that this multi-disciplinary and dynamic team will allow for the successful and timely completion of this research project, as well as contribute to the successful dissemination at large of the results in a meaningful and impactful way.

CRCHUM
CENTRE DE RECHERCHE
Centre hospitalier
de l'Université de Montréal

Université de Montréal

September 10, 2025
Dr. Moishe Liberman
900, St-Denis St
CRCHUM
Montréal, Qc, H2X 0A9

Committee member
Program: Lung Cancer Canada, Give a Breath Research Award

OBJECT: Institutional support for the proposed application "Evaluation of Endoscopic Cryo-Ablative Technologies for the Treatment of Oligometastatic Lung Cancer"

Dear committee,

I hereby wish to express my support for the research proposal of Dr. Moishe Liberman, at the Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM), which will be submitted to Lung Cancer Canada's *Give a Breath Research Award* competition.

Since the start of his career at the CHUM in 2009, Dr Liberman has developed an internationally recognized expertise in minimally invasive thoracic surgery and now heads the CHUM Tracheobronchial and Esophageal Evaluation Center (CETOC). Alongside his clinical expertise, he is also a researcher in the cancer axis of our institution; running one of the busiest thoracic clinical trial programs in the country. His shared proximity to experienced researchers and clinicians with complementary interests and expertise offers many opportunities for collaboration and accelerated acquisition of knowledge.

Over the years, Dr. Liberman has put together a dynamic team of engineers, surgical fellows, research students and others in the objective of fostering a platform for innovation and cutting-edge technological development, altogether forming the Technology, Innovation and Development (TID) Laboratory. Advancements made by this team is namely demonstrated by the recently put forth innovative project on transbronchial cryoablation for the treatment of early-stage lung cancer.

The full researcher status of Dr Liberman in our institution provides support such as a minimum of 50% of protected time for research and remuneration for research time, access to a computer, storage space on the CRCHUM servers, benefit from identified spaces within our institution, usage of shared instruments and services of 19 cores facilities whose services are available at a significant discount; all of which aim at supporting the realization of such ambitious and innovative projects.

We enthusiastically support Dr. Liberman's application to the Give a Breath Research Award competition.

Please accept, dear members of the committee, my warmest regards.

Kathy-Thi Bao Khanh Lê
Director of Research and Innovation by interim – CHUM

Direction de la recherche et de l'innovation
R03.402
Téléphone : 514 890-8000, p.23616
www.crchum.com

Pavillon R
900, rue Saint-Denis
Montréal (Québec)
H2X 0A9

Pavillon S
850, rue Saint-Denis
Montréal (Québec)
H2X 0A9