Associate Professor
École de technologie supérieure
1100 Notre Dame West, Montréal, QC H3C 1K3
alexandre.pellan-cheng@etsmtl.ca

Principal Scientist
Centre de recherche du centre hospitalier de l'université de Montréal
900 Saint-Denis, Montréal, QC H3X 0A9

September 30, 2025

Lung Cancer Canada
133 Richmond St. W., suite 208
Toronto, Ontario
M5H 2L3

Subject: Application to the Geoffrey Ogram Memorial Research Grant (GORMG)

To the members of the GOMRG selection committee,

I am writing to seek your support for a pilot project that directly aligns with Lung Cancer Canada's mission to improve outcomes for patients. This project, titled "**A Multi-omic Blood Test for the Earlier Detection of Lung Cancer**", aims to develop a groundbreaking, non-invasive screening tool for lung cancer.

Lung cancer is the leading cause of cancer mortality, and there is an urgent unmet need to detect this disease much earlier. Unfortunately, existing monitoring tools impede early detection. Computed tomography (CT) scans, the current modality for screening, have an incredibly high false-positive rate (96%). In the US-based National Lung Screening Trial, the positive predictive value (PPV) was less than 10%, obligating screening programs to focus only on high-risk populations where cancer is more likely to exist. As such, lung cancer is often diagnosed at late stages (III-IV), underscoring the need for improved technologies that can sensitively and specifically detect this disease, with the overall goal of reducing the screening age to catch lung cancer early when treatment windows are curative.

Our project will address this critical gap. We propose that complementing CT scans with a highly specific blood-based biomarker will improve the PPV and enable the effective identification of early-stage lung cancer. Here, circulating tumor DNA (ctDNA) is a promising biomarker, but existing ultra-sensitive assays are *tumor-informed*, requiring prior knowledge of tumor mutations and thus cannot be used for early detection, when tumor material is by definition unavailable. Therefore, our work is focused on creating a truly sensitive, *tumor-naïve* ctDNA test for lung cancer.

To achieve this ambitious goal, we will develop and validate a multi-omic classifier that integrates two distinct cancer signals from a single blood draw: genomic mutations and epigenetic methylation patterns. Our central aim for this pilot study is to demonstrate that this integrated approach can accurately distinguish patients with non-metastatic lung cancer from matched, cancer-free controls. As an early career researcher, I have successfully led the development of several liquid biopsy tools that leverage epigenetic and mutational signatures for cancer detection.

A testament to our team's reputation within the genomics community, we are the first research group in Quebec with early access to Illumina's novel 5-base sequencing technology. This cutting-edge assay allows us to measure both mutation and methylation signals simultaneously from the minute quantities of cfDNA available in blood and will be the basis of our platform. We are requesting a grant of $25,000 CAD to support the direct costs of this innovative research. These funds will be allocated exclusively to the reagents and sequencing costs required to analyze our pilot cohort. Personnel and

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computational infrastructure are already supported by our institutional funds, ensuring that the GOMRG's investment will be maximally catalytic in generating the critical proof-of-concept data needed to advance this test toward the clinic.

Thank you for your time and consideration of this exciting project. Please see the attached proposal for a comprehensive review of our methodology, impact statement, and budget. We are confident that this work represents a significant step forward in the fight against lung cancer and are eager to partner with Lung Cancer Canada to achieve our shared goal of reducing the burden of this disease for all Canadians.

Sincerely,

Alexandre Pellan Cheng, PhD

A Multi-omic Blood test for the Earlier Detection of Lung Cancer

Context. Lung cancer is the leading cause of cancer-related death in Canada, primarily because most cases are diagnosed at late stages (III or IV)[1]. While screening with low dose computed tomography (LDCT) can reduce mortality, its application is restricted to individuals with the highest risk for disease. **This narrow scope is a direct consequence of the test's limitations**. LDCT scans suffers from a 96% false positive rate[2], creating downstream harms including patient anxiety, unnecessary biopsies, and increased healthcare costs. Consequently, screening guidelines are constrained to a individuals between the ages of 55-74 with a significant smoking history where the pre-test probability of cancer is high enough to justify these risks[3]. This framework systematically precludes the detection of lung cancer in younger individuals or never-smokers, who represent a growing proportion of new diagnoses[4].

Despite these limitations, studies have shown that lowering the screening age for lung cancer would significantly increase survival[5,6], but the associated false-positive burden is too high for population scale implementation. There is thus a critical need for a test that can complement LDCT to improve specificity, reduce harm, and **justify expanding screening to a larger population.**

There is increasing evidence that liquid biopsy can identify early-stage lung cancer[7,8]. Here, circulating cell-free DNA (cfDNA), which includes fragments of DNA shed from tumor cells (ctDNA), provides a powerful, non-invasive window into nascent malignancy. While ctDNA mutations are specific markers for cancer, their utility in early detection is limited by low concentrations in early disease. **We propose** to augment the detection of ctDNA with genome-wide cytosine methylation (5mC), an orthogonal signal to somatic mutations for cancer. 5mC profiles are tissue-specific and provide a distinct signature that can robustly identify ctDNA[9,10]. However, the standard method for 5mC detection, whole-genome bisulfite sequencing (WGBS), is a chemical process that deaminates unmethylated cytosines into thymines. Thus, WGBS induces widespread cytosine to thymine (C>T) changes throughout the 96% of the genome that is unmethylated, inhibiting the analysis of cancer-intrinsic somatic mutations.

Excitingly, recent innovations in library preparation have enabled the simultaneous measurement of 5mC and mutation on single DNA molecules. For example, the 5-base sequencing assay (Illumina) only modifies methylated cytosines (4% of cytosines) as opposed to unmethylated cytosines (96%). Thus, underlying genomic sequences can be preserved to enable widespread methylation and variant calling.

Objectives and methodology. We hypothesize that multi-omic whole genome sequencing of cfDNA can overcome the limitations of LDCT by integrating orthogonal cancer markers in a single assay (**Fig. 1**). This objective will be addressed across two aims: **1)** Mutational signatures in ctDNA to detect early-stage lung cancer; **2)** Genome-wide DNA methylation to improve liquid biopsy for screening.

Aim 1: Mutational signatures in cfDNA to detect early-stage lung cancer. We hypothesise that tobacco-associated mutational signatures[11] can serve as a biomarker for the detection of early-stage lung cancer. Here, the genotoxic effect of carcinogens results in a pattern of C>A mutations across the genome[11] (**Fig 1A**). In preliminary experiments[7], we showed that tobacco-derived variants were significantly enriched in pre-treatment lung cancer patients compared to cancer-free controls, distinguishing the two groups with an AUC of 0.83 (P=0.01, **Fig. 2A,B**).

We will apply 5-base sequencing to cfDNA from 20 patients with local-regional non-small cell lung cancer (NSCLC, stage II and III) and 20 age, sex and smoking-history matched cancer-free controls from the CRCHUM biobanks. Using our established analytical pipeline (**Fig 2A**), we will quantify the burden of tobacco-derived variants in each sample. The primary statistical analysis will compare variant burden between cases and controls using a Wilcoxon rank-sum test. Our sample size provides over 80% power to detect an effect size similar to that observed in our preliminary data. This analysis will establish the performance of mutational signatures as a biomarker for non-metastatic lung cancer detection.

Aim 2: Genome-wide DNA methylation to improve liquid biopsy for screening. A significant portion of lung cancers, particularly in never-smokers, are driven by genomic alterations (e.g., EGFR or ALK fusions) and lack the tobacco-mutational signature[12] described in Aim 1. To address this critical gap, we will perform 5mC analysis concurrently with mutation profiling. The ability to trace circulating DNA back

to a specific organ via 5mC is a proven principle in liquid biopsy[9,10,13–18]. For example, our work has validated this concept in a recent study on kidney infection, where we demonstrated that cfDNA from these patients was enriched with kidney-derived DNA fragments[17].

We will analyze the 5-base sequencing data from the same cohort of 20 locoregional (stage II and III) NSCLC cases and 20 matched controls. Per-site methylation fractions will be measured as we have previous described[9,17]. Significance will be defined by stringent statistical cutoffs (FDR < 0.05) and a minimum 20% absolute change in methylation. To confirm the biological relevance of our findings, significant DMRs will be cross validated against methylation data from The Cancer Genome Atlas[19] lung adenocarcinoma cohorts. Finally, to establish the standalone predictive power of this modality, we will partition our cohort into training (70%) and testing (30%) sets to build a preliminary DMR-based classifier, with performance evaluated by the area under the ROC curve.

Crucially, 5-base sequencing has the added benefit of more faithfully preserving the native mutations of input DNA. This presents a natural opportunity for extension of our earlier work to enhance our existing tobacco-exposure models (Aim 1). This will allow us to incorporate SNVs in the NSCLC context, where C>A mutations are a hallmark substitution (**see Fig. 1**).

Feasibility and Potential Pitfalls. Our ability to successfully complete this project is grounded in strong preliminary data, access to unique resources and our team's strong track record of developing liquid biopsy technologies for both genomic and epigenetic signals[7,9,17,18,20,21]. Our early data demonstrates a proven ability to deconvolve SNV-based mutational signatures to detect lung cancer (Aim 1). Furthermore, our work in tracing cfDNA back to its precise tissue of origin validates our expertise in analyzing tissue-specific epigenetic signals (Aim 2). This project is further de-risked by our immediate access to a well-annotated patient cohort through the CRCHUM biobank and our access to the 5-base sequencing technology required to execute the work. However, we have identified potential pitfalls:

Pitfall 1: Insufficient ctDNA signal in early-stage disease. The amount of ctDNA in early-stage cancer can be exceptionally low. It is possible the signal may be at or below the limit of detection for a single analyte. **Mitigation: Our proposal is designed to be robust to this challenge.** First, our chosen method, 5-base sequencing, is highly efficient for low-input DNA samples. Second, our multi-omic approach is the key risk mitigation; if the mutational signal is weak (Aim 1), the orthogonal methylation signal may still be strong (Aim 2), and vice-versa. Integrating orthogonal signals provides a more resilient test than relying on either one alone. Moreover, deeper sequencing can be performed beyond standard 30x WGS (>100x) to enhance SNV and 5mC detection given recent sequencing cost reductions[20,22,23].

Pitfall 2: Confounding biological signals. Non-cancerous biological processes, such as clonal hematopoiesis (CHIP) and age-related methylation, can mimic cancer signals. **Mitigation: Our analytical pipeline will be designed to specifically address this.** Our methylation analysis (Aim 2) will include covariates for patient age; CHIP-specific mutational profiles and differentially methylated regions are publicly available and will be accounted for computationally[24–26]. Should the CHIP signal be too strong for analytical denoising, we will concurrently sequence patient peripheral blood mononuclear cells (PBMCs) with the cfDNA to specifically measure a patient's CHIP mutation and methylation landscape and phase it out of the cfDNA signal[20].

Anticipated Outcomes. This pilot project will deliver three key outcomes that provide a direct line of sight toward clinical implementation. **Validated Biomarker Sets:** We will deliver two independently validated sets of blood-based biomarkers for early lung cancer detection: one based on genomic tobacco-mutational signatures and another on epigenetic lung cancer-specific methylation patterns. The performance of each set (as measured by AUROC) will be rigorously benchmarked. **Proof-of-Concept for a Multi-omic Classifier:** By integrating the features from both aims this project will provide the first proof-of-concept for a multi-omic classifier for early lung cancer detection. We will provide a preliminary estimate of the synergistic performance gain from this integrated approach. **Foundation for Future Funding:** This work will generate the critical data and validated methodologies necessary to support larger-scale grant applications (e.g., CIHR, Terry Fox Research Institute) to fund a prospective clinical validation study, which is the next essential step toward clinical implementation.

Impact statement

Lung cancer is an important public health challenge in Canada: approximately 7% of Canadians will be diagnosed with lung or bronchus cancer during their lifetime, and nearly 65% of those diagnosed will die from the disease under current surveillance strategies[1]. Current screening with low-dose computed tomography (LDCT) is limited to a narrow, high-risk population precisely because of its high rate of false positives, which can lead to significant patient anxiety and unnecessary invasive follow-up procedures[2]. This project will promote a major advancement in lung cancer research by developing a highly specific, non-invasive blood test designed to complement LDCT, reduce false positives, and create a safer, more effective screening paradigm. The proposed tumor-naïve ctDNA detection strategy will transform early-stage NSCLC diagnosis by reducing reliance on invasive procedures and enabling broader, timely access to genomic data for personalized treatment. Integration into screening programs will enhance early detection, reduce diagnostic delays, and lower healthcare costs and have the potential to decrease screening age recommendations through enhanced specificity. By improving detection through multi-omic whole-genome sequencing, this approach addresses limitations of current LDCT and liquid biopsy methods.

Reducing the Burden of Lung Cancer and Improving Patient Care

The immediate goal of our project is to reduce the burden of lung cancer by addressing the harms of current screening methods. For the thousands of Canadians who undergo screening and receive an ambiguous result, a highly specific blood test would provide crucial clarity. A negative result could spare them the anxiety and physical risk of follow-up invasive biopsies, directly improving their quality of life.

In the medium-term, by demonstrating a more accurate and reliable screening process, our work aims to provide the foundational evidence needed to safely expand screening guidelines. This could allow for the inclusion of younger individuals or those with less extensive smoking histories who are currently ineligible for screening. By detecting cancers earlier when they are most curable, this work has the potential to directly reduce mortality from lung cancer.

Promoting Health Equity and Scientific Advancement

By relying on a simple blood draw, our approach can help democratize lung cancer screening for urban, rural, and underserved populations across Canada who may have limited access to specialized imaging and follow-up centers. Scientifically, this pilot project will provide the first proof-of-concept for a multi-omic (genomic and epigenetic) ctDNA classifier for early lung cancer detection. The data generated will provide the critical foundation for larger clinical trials aimed at embedding this blood test into routine clinical care.

Ultimately, this work seeks to accelerate the shift in lung cancer management from a late-stage diagnosis to an early, curable one, directly supporting Lung Cancer Canada's mission to optimize patient care and reduce the burden of this devastating disease.

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Public, non-scientific summary

A Smarter Blood Test for Earlier Lung Cancer Detection

Lung cancer is the most common cause of cancer death in Canada, largely because it is often discovered at an advanced stage when it is difficult to treat. While computed-topography (CT) scans are used to screen for lung cancer in high-risk individuals, the technology has a very high false-positive rate. This means that for many healthy people, the scan shows a suspicious spot that turns out to be benign. This can lead to intense anxiety and often requires patients to undergo unnecessary and invasive follow-up procedures, like biopsies, to get a clear answer.

Because of this limitation, screening is currently restricted to a small group of older adults with a long history of smoking. This leaves out many others, including younger people and a growing number of never-smokers who develop the disease. There is an urgent need for a better, more accurate test that can help doctors find lung cancer earlier and more safely.

Our research project is developing an innovative solution: a highly sensitive blood test, often called a "liquid biopsy". When cells in our body die, including cancer cells, they release tiny fragments of their DNA into the bloodstream. By analyzing a simple blood sample, we can search for the specific DNA fragments that come from a tumor.

What makes our approach unique is that we look for different types of cancer clues at the same time from the same DNA fragment. The first clue is the genetic "fingerprint" of the cancer cell itself. For lung cancers linked to smoking, carcinogens leave a distinct pattern of damage on the DNA. Our test is designed to spot this unique signature. The second clue is a set of chemical "tags" on the DNA called methylation. These tags act like an ID card, telling us which organ the DNA came from (e.g., the lungs). Cancer dramatically alters these tags in a way that makes them stand out. This is especially important for finding lung cancer in people who have never smoked.

By combining these two powerful clues, our test aims to be far more accurate than looking for either one alone. To develop this technology, we will analyze blood samples from patients with stage II and III lung cancer and from healthy individuals. Our goal is to create an assay that can reliably identify the combined two-clue signature of lung cancer.

The impact of this work will be transformative. In the short-term, a more accurate blood test could help doctors and patients make better decisions after an unclear CT scan, potentially avoiding many unnecessary biopsies. In the long-term, a safer and more reliable screening process could allow us to offer screening to more people, helping to catch lung cancer earlier when it is most curable and ultimately saving lives.

Budget

The total funds of 25,000$ provided by the GOMRG will be used towards reagent and sequencing costs of 40 plasma samples (see Scientific Proposal and **Table 1** below). The project will be carried out collaboratively by one MSc student (Aliona Bedjegueal) and one PhD student (Elena Fraiji), whose salaries are covered by our startup funds. Collaborators for this project include clinical oncologists Drs. Antoine Desilets, Bertrand Routy (director of the lung cancer biobank at the CRCHUM), Arielle Elkrief, whose salaries are not covered by this grant.

Reagent costs associated with assay development, which include 5-base library preparation kits and next-generation sequencing are estimated at 196.00$/sample, and 434.10$/sample, respectively. **Importantly, Illumina, Inc. fully supports our development of a lung cancer screening device and is significantly offsetting the costs associated with the 5-base sequencing assay (see letter of support).**

Costs associated with international conference attendance are budgeted at 2,250$ per student and will be at premier conferences such as Biomedical Engineering Society or Advances in Genome Biology and Technology. Furthermore, 5,000$ per year will be used to cover open access publication fees related to this project (targeted journals include Nature Biotechnology, Nature Methods and Cell) and will be covered by our startup funds. A detailed budget is presented in **Table 1**. Secured, non-overlapping funding is presented in **Table 2**.

Geoffrey Ogram Memorial Research Grant	**Q1-Q2 spending**	**Q2-Q3 spending**
Aliona Bedjegueal, MSc 1	(startup funds)	(startup funds)
Elena Fraiji, PhD 1	(startup funds)	(startup funds)
5-base assay costs^	**3,136.00**	
Sequencing costs	**17,364.00**	
Conference travel for MSc1		**2,250.00**
Conference travel for PhD1		**2,250.00**
Open-access publication		(startup funds)
Total	**25,000.00$**	

Table 1. Overview of the yearly budget for the duration of the grant.
^ Accounts for the *in-kind* support provided by Illumina, Inc. (see letter of support)

Secured funding (non-overlapping)	**Value**	**Description**
École de technologie supérieure	125,000$	Start-up funds for equipment, reagents and research staff.
Centre de recherche du CHUM	225,000$	
Institut de Cancer de Montreal-Rapatriement des cerveaux	250,000$	
Saputo Family Foundation	1,400,000$	Funding to support a urothelial cancer biobank (unrelated to this project)

Table 2. Overview of secured, non-overlapping funding.

Appendix I: Figures

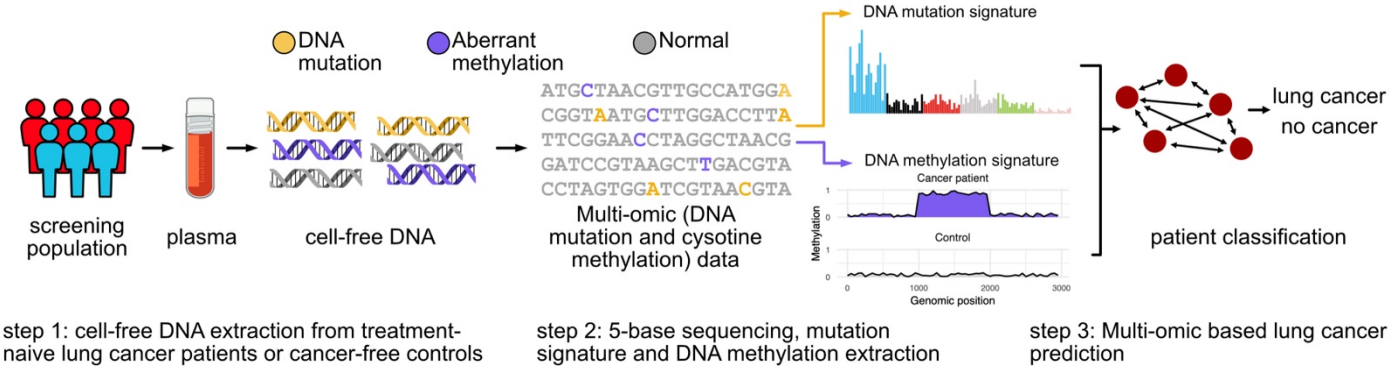

Figure 1. Assay workflow. First, n=20 plasma samples will be sources from the CRCHUM lung cancer biobank (collaborator Dr. Bertrand Routy) and will be compared from n=20 age, sex and smoking-matched controls. **Samples for this study have already been selected**. Then, next generation sequencing libraries will be prepared using the Illumina 5-base sequencing assay. DNA mutational signatures will be measured as described in Cheng et al (Nature Methods 2025, ref. 20). Z-scores will be calculated by comparing a sample to the distribution of cancer-free controls. DNA methylation signatures will be extracted from the cfDNA as described in Cheng et al (PNAS 2022, ref. 9), and Z-scores of methylation percentage will be calculated between a sample to the distribution of cancer-free controls. Cell-free DNA methylation and mutation profiles will be jointly considered to classify the presence or absence of lung cancer by merging Z-scores according to the Stouffer method.

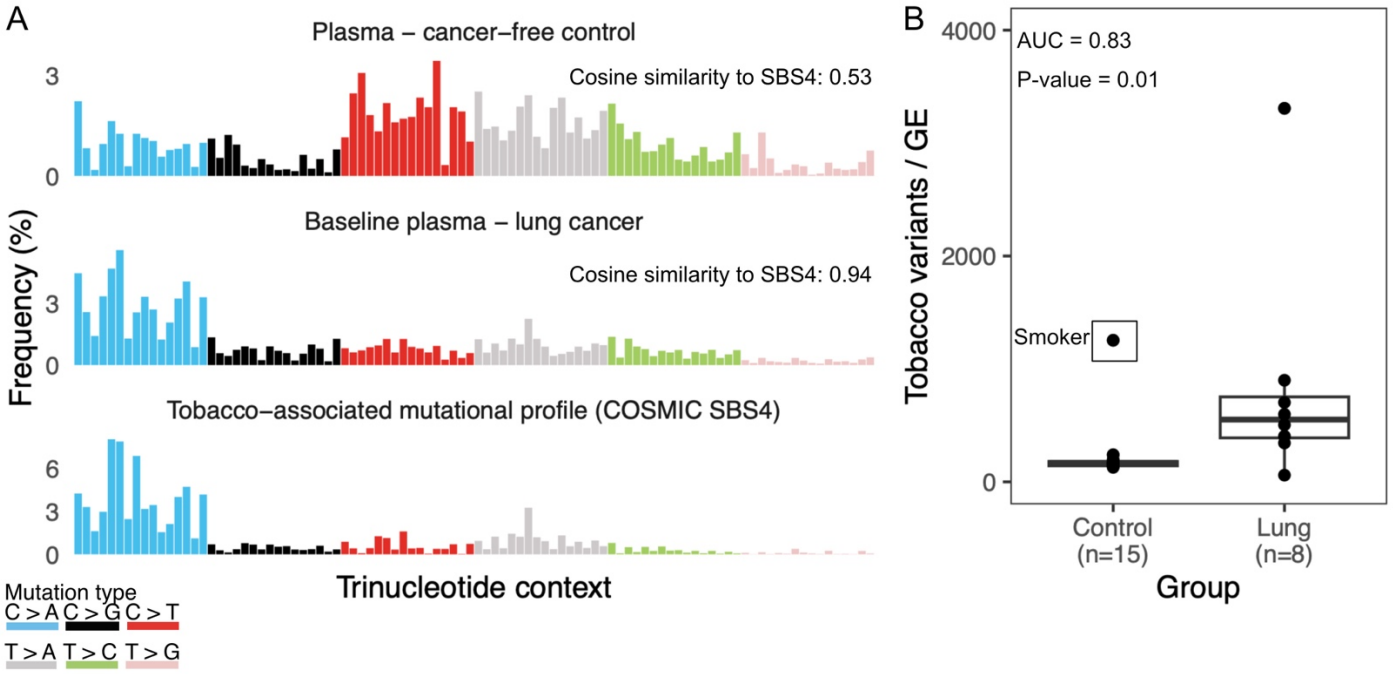

Figure 2. Preliminary data for Aim 1.
A Single-base substitution (SBS) profiles of the plasma from a cancer-free control (row 1), baseline plasma from a lung cancer patient (row 2) and the previously reported tobacco-associated SBS4 (row 3, Alexandrov et al, Nature 2020, ref. 11). Cosine similarities between cfDNA profiles and SBS4 are shown.
B SBS4-derived variants from the cell-free DNA of cancer-free controls (n=15) and lung cancer patients (n=8) (data from Cheng et al., bioRxiv 2025, ***in review at Cell***, ref 7*)*. Of note, the cancer-free control outlier is derived from a smoker.

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

Université de Montréal

Montreal, September 11 2025

Dr. Alexandre Pellan Cheng (Ph.D.)
Centre de recherche du CHUM (CRCHUM)

OBJECT: Letter of institutional support for Dr. Cheng – Lung Cancer Canada – Geoffrey Ogram Memorial Research Grant

To the members of the selection committee,

I hereby wish to express my strong support for Dr. Cheng's application for the Geoffrey Ogram Memorial Research Grant (GOMRG) competition. Dr. Cheng joined the CRCHUM in 2025 within the Cancer Axis and is an Associate Professor of Systems Engineering at the École de Technologie Supérieure (ETS). His regular researcher status at CRCHUM guarantees a minimum of 75% protected time dedicated to his cancer research program, which focuses on innovative approaches to cancer monitoring through liquid biopsies.

Dr. Cheng benefits from a rich and supportive research environment. His mentorship committee includes several accomplished senior investigators: Dr. Francis Rodier, Dr. Réjean Lapointe and Dr. Nicola Hagemeister. Additionally, Dr. Anne-Marie Mes Masson, an internationally recognized expert in the oncology, has committed to mentoring Dr. Cheng specifically for the project submitted to this award. These mentors actively support Dr. Cheng in the development and internal peer review of his grant applications, ensuring scientific rigor and strategic alignment with funding priorities.

The proposed project by Dr. Cheng, aimed at developing a multi-omic liquid biopsy for the early detection of lung cancer, is fully feasible within our institution, as he possesses the requisite infrastructure, resources, and expertise to ensure its successful execution. Specifically, Dr. Cheng's team has access to the state-of-the-art 19 CRCHUM Core Facilities, which house high-throughput sequencers and molecular pathology equipment such as an Agilent TapeStation and Qiagen QiaCube. Dr. Cheng also has access to CRCHUM biobanks, which are essential for his research program. As part of his appointment, Dr. Cheng receives $5,000 in credits for core facility usage, and Core Facilities services are subsidized up to 40% for regular researchers. In addition, Dr. Cheng manages a dedicated wet lab space at the CRCHUM which is comprised of workbenches, refrigerators, freezers and a biosafety hood.

The CRCHUM offers strong administrative support to help researchers secure and manage grants. This includes assistance in identifying funding opportunities, revising grant applications, preparing financial reports, reviewing and signing contracts through specialized units such as the Bureau des Contrats de Recherche, the Bureau d'Aide à la Recherche, and the Finance Department. This ensures compliance with the standards and requirements of financial organizations while also streamlining administrative processes to save researcher's valuable time.

Our institution fully endorses the Lung Cancer Canada guidelines and is committed to supporting Dr. Cheng throughout the duration of the award, including ongoing administrative assistance and financial management.

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 : 514 890-8044, 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

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Monday, September 15, 2025

Alexandre Pellan Cheng, PhD
Associate professor, Dép. de génie des systems, École de Technologie Supérieure
Principal scientist, Centre de Recherche du CHUM

Re: Letter of Support for "Multi-omic liquid biopsy for the early detection of lung cancer"

Dear Dr. Pellan Cheng,

Illumina Canada is pleased to provide this letter in support of your project entitled *"Multi-omic liquid biopsy for the early detection of lung cancer",* submitted for consideration to Lung Cancer Canada's Geoffrey Ogram Memorial Research Grant competition.

As a global leader in genomics, Illumina is committed to enabling the development and application of innovative technologies to the analysis of genetic variation and function, leading to the generation of knowledge and discoveries that will positively impact human health in Canada and around the world. One of Illumina's newest innovations, the Illumina 5-base solution, will deliver simultaneous high-accuracy genomic and epigenomic discovery in a single readout, facilitating methylation studies and the generation of insights to drive advances in life sciences research and healthcare delivery. This new technology presents additional benefits that are of particular relevance to your project, addressing issues such as providing simultaneous variant calling and methylation detection. We believe your proposal strongly aligns with Illumina's vision of *unlocking the power of the genome* to enhance human health and are particularly excited to be supporting you in assessing the diagnostic performance of integrated methylation with circulating free DNA variant detection, potentially leading to novel non-invasive screening tools for early (lung) cancer detection.

As part of the Early Access Program for the Illumina 5-Base Solution, we are pleased to support you with the provision of one Illumina 5-Base DNA prep kit at no cost, representing an in-kind contribution of $4,704.00 CAD.

Illumina supports conducting business in Canada and the return on investment of Canada's research funding. As such, Illumina will work with you and/or the Illumina-enabled core sequencing lab and/or Illumina-enabled sequencing service provider of your choice to enable this contribution and will continue to support this project as long as the genomics work involving Illumina systems is carried out in Canada.

We wish you the best with this application.

Sincerely,

Caitlin Taylor, PhD
Sr. Manager, Commercial Development - Canada
CTaylor1@illumina.com
Illumina Canada