Lung Cancer Canada
Give A Breath Research Award Committee

Subject: Letter of Intent for the Give A Breath Research Award

Dear Members of the Give A Breath Research Award Committee,

I am writing to express my intent to apply for the Give A Breath Research Award in support of my research project, "**Transforming Lung Cancer Care: A Patient-Centered Organ-on-a-Chip Platform for Real-Time Monitoring and Personalized Treatment**." This research aligns with the award's mission to address critical gaps in understanding and treating advanced lung cancer, specifically focusing on patients beyond first-line therapy. By advancing innovative monitoring strategies, my work aims to improve diagnostic precision, predict relapse, and optimize treatment plans for Canadian patients with stage III or IV lung cancer.

My project proposes the development of a vascularized organ-on-a-chip system to embed patient-derived lung tumor spheroids. This platform will enable the real-time collection and analysis of circulating tumor DNA (ctDNA) and cell-free RNA (cfRNA), generating a patient-specific tumor "fingerprint." By comparing this fingerprint to ctDNA and cfRNA collected from patient serum over time, we aim to establish a novel method for monitoring disease progression and treatment response. This approach has the potential to enhance personalized medicine, facilitate timely intervention strategies, and improve clinical decision-making in lung cancer care.

This research is a collaborative effort with **Dr. Rosalyn Juergens,** a leading expert in thoracic oncology and liquid biopsy applications in lung cancer, and **Dr. Boyang Zhang,** a pioneer in organ-on-a-chip technologies. Their expertise in biomarker-driven lung cancer treatment and microfluidic system development, respectively, will be invaluable in ensuring the success and clinical impact of this project.

Designed to address **critical gaps in the understanding and treatment of advanced lung cancer, specifically focusing on post-first-line therapy options**, this project will further drive a transformative shift in how we monitor and treat advanced lung cancer, ultimately improving outcomes for patients.

I appreciate your consideration of my application and look forward to the opportunity to contribute to the advancement of lung cancer research. Please do not hesitate to contact me if you require any additional information.

Sincerely,

Fei Geng

Transforming Lung Cancer Care: A Patient-Centered Organ-on-a-Chip Platform for Real-Time Monitoring and Personalized Treatment

Rationale

Liquid biopsy has emerged as a powerful tool for non-invasive cancer monitoring, yet its clinical application in advanced lung cancer remains hindered by sensitivity and specificity limitations[1]. The biomarkers, including EGFR, ALK, and KRAS mutations detected via circulating tumor DNA (ctDNA)[2] and fusion transcripts or gene expression profiles captured through cell-free RNA (cfRNA)[3,4], provide critical insights into tumor evolution, resistance mechanisms, and therapeutic response.

This project leverages a vascularized organ-on-a-chip platform to enhance the multiplexed detection of ctDNA and cfRNA biomarkers associated with lung cancer progression and therapy resistance. By enabling continuous sampling of tumor-derived nucleic acids in a physiologically relevant microenvironment (Fig. 1), the platform improves diagnostic precision, facilitates real-time treatment adjustments, and enhances relapse prediction, ultimately improving clinical outcomes for Canadian patients with stage III/IV lung cancer.

Hypothesis and Specific Aims

The proposed research hypothesizes that integrating a vascularized organ-on-a-chip system with multiplexing liquid biopsy technologies will enable dynamic tracking of ctDNA and cfRNA profiles, providing a patient-specific tumor "fingerprint"[5]. This approach will facilitate the monitoring of disease progression and treatment response in advanced lung cancer patients, ultimately improving personalized medicine and enhancing monitoring strategies in lung cancer care.

The specific aims of the study are:

1. Develop and validate a vascularized organ-on-a-chip system by designing and optimizing a microfluidic platform embedding patient-derived lung tumor spheroids to recapitulate the tumor microenvironment and allow for ctDNA/cfRNA collection.
2. Characterize tumor dynamics through ctDNA and cfRNA profiling by identifying and validating resistance mutations, gene expression changes from both the organ-on-a-chip platform and patient serum.
3. Correlate molecular profiles with clinical outcomes by integrating ctDNA and cfRNA data with patient clinical parameters to establish predictive biomarkers for therapeutic efficacy, progression, and overall survival.

Methodology

The proposed one-year project will follow a phased approach:

In Phase 1 (Mar 1 – May 31, 2025), we will develop and optimize a vascularized organ-on-a-chip system that accurately replicates the tumor microenvironment of Non-small cell lung cancer (NSCLC). This system will integrate patient-derived lung tumor spheroids (Fig. 1), enabling real-time, dynamic sampling of ctDNA and cfRNA. The platform will simulate tumor-vascular interactions, establishing fluidic conditions that mimic intratumoral blood flow and vascular permeability to ensure physiologically relevant biomarker shedding. A key focus will be modeling clinically relevant NSCLC subtypes, including EGFR-mutant, KRAS-mutant, and ALK-rearranged tumors, validating the system's ability to replicate tumor-driven ctDNA/cfRNA release patterns to enhance precision monitoring.

Phase 2 (Jun 1 – Nov 30, 2025) will focus on longitudinal monitoring of tumor resistance and therapeutic responses. Serial ctDNA/cfRNA samples will be collected from the organ-on-a-chip system (Fig. 1) and compared with matched patient serum samples to track tumor molecular changes over time. By applying next-generation sequencing (NGS) and digital PCR (dPCR), we will detect acquired resistance mutations in key NSCLC oncogenes such as secondary EGFR mutations, MET amplifications, KRASG12C resistance mutations, and ALK inhibitor resistance mutations. Additionally, tumor cells within the platform will be exposed to clinically relevant targeted therapies (e.g., EGFR/ALK inhibitors, KRASG12C inhibitors, and immunotherapies) to assess how molecular changes correlate with therapeutic resistance and adaptation. By comparing ctDNA/cfRNA dynamics from the platform with patient serum, this study will validate whether the organ-on-a-chip system can predict resistance emergence before clinical relapse, offering a potential tool for early intervention.

In Phase 3 (Dec 1, 2025 – Feb 28, 2026), we will integrate molecular insights from the organ-on-a-chip system with clinical outcomes to translate findings into actionable strategies for advanced NSCLC patients. By correlating ctDNA/cfRNA profiles with disease progression, therapy response, and survival metrics, this study aims to develop a predictive biomarker framework for therapy resistance and progression. Machine learning and bioinformatics will be employed to identify key biomarkers associated with treatment response, enabling real-time risk assessment and personalized treatment adaptation. This phase will refine biomarker-driven decision-making to optimize treatment plans, allowing clinicians to switch therapies proactively, reduce reliance on invasive biopsies, and improve patient survival outcomes.

Existing Research Lines

Dr. Fei Geng is a winner of Lung Ambition Award in 2024. Building on significant contributions to mechanobiology, Dr. Geng's research has unveiled critical mechanotransduction pathways relevant to tumor microenvironments[6–8]. Furthermore, studies on biomechanical cues in brain tissues have deepened the understanding of tumor-vascular interactions and their impact on ctDNA/cfRNA dynamics.

Dr. Rosalyn Juergens (Co-PI), is a leading expert in thoracic oncology, specializing in ctDNA liquid biopsy[9] and biomarker-driven treatment approaches for lung cancer[10,11]. As a medical oncologist and researcher, Dr. Juergens has made significant contributions to the development of targeted therapies and immunotherapy for lung cancer patients[5] and the management of Stage III NSCLC[12]. Her expertise in clinical trials, translational research, and biomarker discovery provides essential insights into tumor evolution, treatment resistance, and precision medicine.

Dr. Boyang Zhang (Co-PI) who is a pioneer in the organ-on-a-chip technologies brings essential technical capabilities to this research[13–15]. Dr. Zhang's work on vascularized microfluidic platforms has enabled the development of functional vasculature capable of supporting perfusion, nutrient exchange, and tumor-vascular interactions. These platforms replicate physiological conditions of stage III/IV lung cancer.

By integrating Dr. Geng's research expertise in lung cancer mechanobiology, Dr. Juergens's pioneering work in in biomarker-driven lung cancer treatments, and Dr. Zhang's cutting-edge organ-on-a-chip technology, this project will generate clinically actionable insights, enhancing personalized treatment strategies, improving survival rates, and elevating the quality of life for patients with stage III/IV lung cancer.

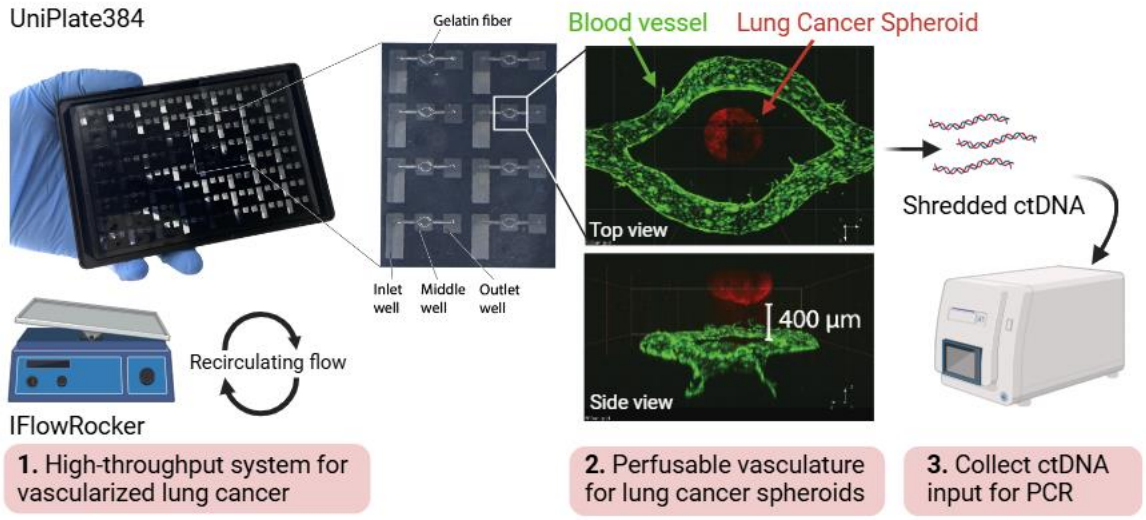

Figure 1. Determination of ctDNA Shedding Kinetics Using a Vascularized Lung Cancer Organ-on-a-Chip System (1) A high-throughput system generates vascularized lung cancer spheroid models with dynamic periodic tilting to simulate physiological flow. (2) Triplicate wells contain perfusable vasculature channels seeded with endothelial cells, integrated with a lung cancer spheroid. The system facilitates ctDNA shedding into the media, which is subsequently collected for analysis. (3) Collected media containing ctDNA is processed for detection and quantification using digital PCR, enabling precise characterization of lung cancer-specific mutations.

Reference

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This research introduces a **first-of-its-kind, patient-specific organ-on-a-chip model** for real-time non-small cell lung cancer (NSCLC) monitoring, with the potential to revolutionize precision medicine approaches in advanced lung cancer. By improving circulating tumor DNA (ctDNA) and cell-free RNA (cfRNA)-based tracking of tumor evolution, this project offers an unprecedented ability to detect treatment resistance early, refine therapeutic strategies, and ultimately extend survival in patients with Stage III/IV NSCLC.

One of the most pressing challenges in managing advanced NSCLC is the limited **sensitivity and specificity** of liquid biopsy in detecting ctDNA and cfRNA. Traditional approaches struggle to differentiate tumor-derived biomarkers from background cell-free DNA, limiting their clinical reliability in tracking disease progression and predicting treatment response. This project directly addresses these limitations by developing a vascularized organ-on-a-chip system that **enables continuous, physiologically relevant sampling of tumor biomarkers**. By faithfully replicating tumor-vascular interactions, this platform allows for a more precise understanding of ctDNA and cfRNA shedding dynamics, a key step toward improving early detection of resistance mutations and disease relapse.

This research also leverages an advanced digital PCR (dPCR) system **capable of simultaneously detecting multiple oncogenic mutations** (**KRAS, ALK, EGFR**, and others), enhancing the specificity, sensitivity, and scalability of liquid biopsy for clinical applications. By providing real-time insights into tumor evolution and therapeutic response, this approach will reduce reliance on invasive imaging modalities such as MRI scans, facilitating earlier intervention, improved treatment personalization, and enhanced survival outcomes for lung cancer patients.

The proposed research project, "Transforming Lung Cancer Care: A Patient-Centered Organ-on-a-Chip Platform for Real-Time Monitoring and Personalized Treatment," is designed to exert a **sustained and transformative impact on lung cancer research and patient care**, with immediate benefits for Canadian patients diagnosed with advanced (Stage III/IV) lung cancer. By introducing a patient-specific, vascularized organ-on-a-chip system, this study will **enable real-time monitoring of tumor evolution and treatment response in patients beyond first-line therapy**, ensuring that clinical decisions are guided by dynamic molecular changes rather than static biopsy-based assessments. This novel approach has the potential to redefine precision medicine by shifting from infrequent, invasive sampling to continuous, non-invasive profiling of ctDNA and cfRNA, thereby optimizing treatment adaptation and response tracking.

By providing a high-fidelity model for evaluating tumor heterogeneity and resistance mechanisms in real time, this study addresses a critical gap in managing advanced lung cancer. **For Canadian patients with Stage III or IV NSCLC, this means earlier detection of therapy resistance, more effective treatment modifications, reduced relapse risk, and improved long-term survival**. Through the integration of multi-omics profiling, this project will facilitate the identification of predictive biomarkers, allowing for timely and personalized intervention strategies tailored to individual patient responses. This capability has the potential to substantially reduce mortality rates by informing

clinicians of the most effective therapeutic regimens based on real-time tumor dynamics, ensuring that patients receive the right treatment at the right time.
Beyond its immediate applications in advanced NSCLC, the organ-on-a-chip platform represents a **scalable, adaptable technology with broad implications for other metastatic and hard-to-treat cancers**. Its ability to replicate the tumor microenvironment in vitro makes it an invaluable tool for drug screening, mechanistic studies, and personalized treatment planning. By accelerating the translation of laboratory discoveries into clinical applications, this research will contribute to optimizing patient care, improving therapeutic efficacy, and ultimately reducing the burden of lung cancer on patients and healthcare systems.

In the short- to medium-term, this project will catalyze advancements in liquid biopsy technologies, promote the adoption of real-time tumor monitoring, and inform clinical decision-making with unprecedented precision. For Canadian patients with Stage III or IV lung cancer, this research will **ensure earlier and more accurate diagnoses, improve relapse prediction, and allow for highly personalized treatment adjustments**. By bridging the gap between experimental models and patient-derived tumor dynamics, this study will fundamentally enhance the standard of care for advanced lung cancer patients and establish a foundation for future innovations in oncology.

Ultimately, this research represents a paradigm shift in lung cancer precision medicine, offering a minimally invasive, high-precision strategy for tracking tumor evolution in real-time, reducing mortality through earlier intervention, and improving patient quality of life by ensuring that treatment decisions are continuously informed by dynamic, patient-specific molecular changes.

Lung cancer remains one of the leading causes of cancer-related deaths worldwide, and many patients with advanced-stage (i.e., stage III or IV) disease face limited treatment options after their initial therapy. Our research project aims to improve how we monitor and treat lung cancer patients by developing a cutting-edge system called a "vascularized organ-on-a-chip." This small, lab-grown model mimics real lung tumors and their surrounding blood vessels, allowing scientists and doctors to study how cancer evolves in response to treatment.

One of the major challenges in treating advanced lung cancer is tracking how tumors change over time. Traditionally, doctors rely on invasive tissue biopsies, which can be painful and do not always capture the full picture of how the disease is progressing. Our approach will use a new technology called circulating tumor DNA (ctDNA) analysis, which can detect tiny fragments of tumor DNA in a patient's blood. By integrating this analysis with our organ-on-a-chip platform, we can create a unique "fingerprint" for each patient's cancer, helping doctors make better treatment decisions without requiring repeated surgeries or biopsies.

This project has the potential to transform lung cancer care for Canadian patients with stage III or IV disease by enabling real-time monitoring of how their cancer responds to therapy. By detecting early signs of drug resistance or disease progression, our system could help personalize treatments and improve patient outcomes. This research is particularly important for those who have already undergone first-line therapy and require more effective strategies to manage their disease.

Beyond lung cancer, the organ-on-a-chip technology could be adapted for other types of cancer and diseases, making it a valuable tool for advancing medical research. By bridging the gap between laboratory studies and real-world patient care, this project aims to bring new hope to Canadian lung cancer patients and their families, offering a more precise and less invasive way to track and treat this devastating disease.

Transforming Lung Cancer Care: A Patient-Centered Organ-on-a-Chip Platform for Real-Time Monitoring and Personalized Treatment

DETAILED BUDGET		**FROM: 3/1/2025**	**TO: 2/28/2026**
PERSONNEL		**SALARY REQUESTED**	
NAME	**ROLE ON PROJECT**	**Year 1**	**TOTALS**
Dr. Fei Geng	PI	$ 0 -	$ 0 -
Dr. Rosalyn Juergens	Co-PI	$ 0 -	$ 0 -
Dr. Boyang Zhang	Co-PI	$ 0 -	$ 0 -
Arjun Raha	Ph.D. Student	$ 12,500	$ 12,500
PERSONNEL TOTAL		$ 12,500	**$ 12,500**
SUPPLIES			
Reagents for circulating tumor DNA (ctDNA) extraction and sequencing including sample preparation kits		$3,500	
Lung cancer cell culture media and extracellular matrix components		$3,000	
Assay materials for multi-omics profiling, including proteomic and metabolomic analyses		$1,500	
Microfluidic chips for maintaining lung tumor spheroids		$2,000	
			$ 10,000
FACILITY USAGE			
Next-Gen Sequencing (NovaSeq)		$2,500	
			$ 2,500
TOTAL DIRECT COSTS			**$ 25,000**
TOTAL COSTS			**$ 25,000**

PERSONNEL

The research team for the proposed study includes PI Dr. Fei Geng (Program Chair in Biotechnology at McMaster), Co-PI Dr. Rosalyn Juergens (Oncologist specializing in lung cancer), Co-PI Dr. Boyang Zhang (Associate Professor specializing in organ-on-a-chip system), and PhD student Mr. Arjun Raha.

Here's the information regarding the personnel required for the study:

Principal Investigator (Lung Cancer Biomarker Analytics): Dr. Fei Geng

Education: Dr. Geng received M.Sc. in Molecular Biology from Fudan University, M.D. from Jining Medical University, and Ph.D. in Biochemistry from McMaster University.

Current Position: Associate Professor and Program Chair in Biotechnology at McMaster University.

Experience: Dr. Geng has been actively engaged in biomarker discovery and lung cancer detection since 2004. As the recipient of the 2024 Lung Ambition Award from Lung Cancer Canada, he has made significant contributions to advancing liquid biopsy technologies. With the support of this award, his research lab successfully established a state-of-the-art 5-color digital PCR system, enhancing the sensitivity and specificity of lung cancer liquid biopsy for real-time monitoring and personalized treatment strategies.

Role: Dr. Geng will oversee the entire study, providing guidance and direction and supervise the graduate student in the area of ctDNA/cfRNA probe design and amplification. Responsibilities include project planning, technical management, securing funding, managing the budget, and ensuring adherence to ethical guidelines.

Co-PI (Leading Oncologist): Dr. Rosalyn Juergens

Education: Dr. Juergens received her medical degree from Georgetown University and Ph.D. in Clinical Investigation from The Johns Hopkins Bloomberg School of Public Health.

Experience: Dr. Juergens is an oncologist specializing in lung cancer at Hamilton Health Sciences. She has clinical expertise in lung cancer and has held various leadership positions in cancer research and patient advocacy.

Role: Dr. Juergens will contribute to the study as a Co-PI, leveraging her expertise in oncology and contribute to the patient recruitment process and clinical analysis. Dr. Juergens brings extensive clinical expertise in lung and esophageal cancer, making her a valuable asset in understanding the practical aspects of lung cancer early detection under the proposed study.

Co-PI (Leading Expert in Organ-on-a-Chip): Dr. Boyang Zhang

Education: Dr. Zhang received his Bachelor of Science in Chemical and Biomolecular Engineering from Georgia Institute of Technology and PhD in Biomedical Engineering from the University of Toronto. Dr. Zhang is the established expert in microfluidic and organ-on-a-chip platforms.

Current Position: Associate Professor at McMaster University

Experience: Dr. Zhang is a leading expert in microfluidic engineering and organ-on-a-chip systems. He has contributed significantly to the development of bioengineered tissue models for disease modeling and drug testing. His research is highly regarded in the fields of tissue engineering, biomaterials, and lab-on-a-chip technology.

Role: Dr. Zhang will bring his expertise in microfluidic-based organ-on-a-chip system development. He will provide technical guidance in optimizing the vascularized organ-on-a-chip platform, oversee the integration of patient-derived tumor spheroids, and supervise graduate students working on system fabrication and validation.

PhD student: Mr. Arjun Raha

Education: Mr. Arjun Raha received his Bachelor's in biotechnology and Master's degree in Mechanical Engineering at McMaster University and he is in his first year of PhD studies in School of Biomedical Engineering at McMaster University.

Current Position: Researcher at the Biointerfaces Institute, McMaster University.

Role: The PhD student will be responsible for conducting experiments and analyzing data. They will work closely with the PI and Co-PIs to ensure the study is conducted rigorously and scientifically.

McMaster University | Research Office for Administration, Development & Support

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January 30, 2025

Dear Lung Cancer Canada:

McMaster enthusiastically supports the proposed research project by Dr. Fei Geng, associate professor at McMaster University. The project, titled “Transforming Lung Cancer Care: A Patient-Centered Organ-on-a-Chip Platform for Real-Time Monitoring and Personalized Treatment” and submitted for consideration within the Give a Breath Research Award competition, is a compelling and innovative endeavor that aligns seamlessly with our institution's research objectives and goals.

Having thoroughly reviewed the details of the proposed research, we are confident in its feasibility within our institution. Our institution possesses the necessary infrastructure, resources, and expertise to facilitate the successful execution of this project. Furthermore, we acknowledge Dr. Fei Geng's expertise and dedication to their work. Their proven track record and commitment to excellence make us confident in their ability to carry out this research successfully. We anticipate that the outcomes of this research will not only enhance the academic reputation of our institution but also contribute meaningfully to the broader scientific community.

McMaster University intends to provide support for this project in the areas of grant fund administration, data management consultations, and institutional administrative support. We look forward to the positive impact Dr. Fei Geng’s research will have on our institution and the broader academic community.

Sincerely,
Sherrise Webb

Director, Research Office for Administration, Development and Support