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Provincial Health Services Authority

September 30, 2025

Lung Cancer Canada
133 Richmond St West #208
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RE: Give A Breath Research Award Application – Dr. William W. Lockwood

Dear Review Committee,

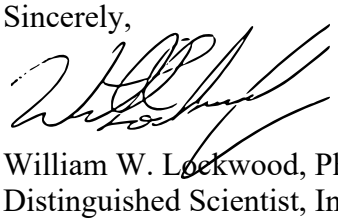
Please find attached my application for the 2025 Give A Breath Research Award, including all required documents and CVs as instructed.

My research program is dedicated to uncovering novel therapeutic strategies for patients with advanced lung adenocarcinoma who relapse on targeted therapies. With this award, we will test an innovative concept: exploiting ERK hyperactivation as a vulnerability in drug-resistant lung cancers. Specifically, we will conduct pilot studies to determine whether drug withdrawal in "drug-addicted" resistant models or inhibition of the ERK regulators DUSP4 and DUSP6 can selectively induce cancer cell death. These studies will be carried out in resistant cell lines and short-term xenograft models already established in my laboratory, ensuring feasibility within the one-year funding period.

This award will provide critical support to generate the preliminary data necessary for advancing this new therapeutic paradigm. By demonstrating proof-of-concept that resistant lung cancers can be eliminated by deliberately pushing ERK signaling beyond tolerable thresholds, we will lay the foundation for future preclinical studies in patient-derived xenografts and genetically engineered mouse models. Ultimately, our goal is to translate these discoveries into novel strategies that extend survival and improve quality of life for patients with advanced, drug-resistant lung cancer—a population with particularly poor outcomes and limited treatment options.

Thank you very much for your consideration.

Sincerely,



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Title: Combating targeted therapy resistance in lung cancer through hyperactivation of oncogenic signaling

Background and Rationale

Lung cancer remains the leading cause of cancer-related death in Canada and worldwide, with non-small cell lung cancer (NSCLC) accounting for the vast majority of cases [1,2]. Lung adenocarcinoma (LUAD), the most common histological subtype, is often driven by oncogenic alterations in EGFR or KRAS [3]. The development of targeted therapies such as third-generation EGFR inhibitors (e.g., osimertinib) and $KRAS^{G12C}$ inhibitors has dramatically improved patient outcomes in these subsets, yet these therapies are not curative. Virtually all patients relapse due to resistance mechanisms, including secondary EGFR mutations, amplification of bypass pathways such as MET, or reactivation of KRAS signaling [4,5]. Once resistance occurs, treatment options are limited to chemotherapy or supportive care, which rarely offer durable benefit. There is an urgent need for innovative approaches that directly address resistance and expand treatment options for patients with advanced disease.

Our work has uncovered an exploitable vulnerability in resistant LUAD cells. These tumors are constrained by a narrow "fitness window" of ERK activity: too little signaling, as achieved by targeted inhibition, suppresses growth, but excessive signaling is toxic [6,7]. Resistant tumors adapt by buffering ERK activity to maintain viability. However, this balance can be disrupted in two ways. First, resistant models often become "drug addicted," dependent on continuous pathway inhibition; drug withdrawal leads to a rebound in ERK activity beyond tolerable levels and triggers apoptosis [8]. Second, resistant cells depend on the phosphatases DUSP4 and DUSP6, which act as brakes on ERK activity. Disabling these negative regulators unleashes ERK hyperactivation and induces cell death [7,9,10]. Together, these observations suggest that deliberately pushing ERK activity above a critical threshold, either through drug withdrawal or through DUSP4/6 inhibition, could provide a powerful and generalizable strategy to eliminate resistant LUAD.

Hypothesis

We ***hypothesize*** that drug-resistant LUAD can be eradicated by inducing ERK hyperactivation. This can be achieved by exploiting drug addiction through targeted therapy withdrawal or by pharmacologically inhibiting the ERK phosphatases DUSP4 and DUSP6. We further propose that combining these approaches will act synergistically to push ERK activity beyond the survival threshold of resistant tumours.

Aim 1: Define the therapeutic potential of drug withdrawal in resistant LUAD.

Our laboratory has already established a panel of osimertinib-resistant EGFR-mutant and $KRAS^{G12C}$-inhibitor-resistant cell lines through dose escalation (**Figure 1**). Many of these models exhibit drug addiction, where continuous exposure to the inhibitor is required for survival and removal of the drug leads to rapid ERK rebound, endoplasmic reticulum stress, and apoptosis (**Figure 2**). To investigate this phenomenon, resistant cultures will be shifted to drug-free conditions and monitored at serial time points. We will quantify ERK phosphorylation by immunoblotting and mass spectrometry, track apoptotic events using annexin V staining and PARP cleavage assays, and follow cell viability in real-time using nuclear fluorescent markers and confluence analysis. To directly visualize ERK dynamics during withdrawal, we will deploy a live-cell kinase translocation reporter system, which measures the nuclear-to-cytoplasmic redistribution of ERK substrates and correlates activity kinetics with subsequent cell death (**Figure 3**).

To understand the mechanisms underlying lethality, transcriptomic and phosphoproteomic profiling will be performed after drug withdrawal to capture early signaling changes, and genome-wide CRISPR dropout screens will be applied – as we previously have described[7] - to identify genes required for survival under these conditions. Integrating these datasets will allow us to define pathways that mediate sensitivity. As a proof-of-concept *in vivo* pilot, resistant LUAD cell lines will be used to establish short-

term xenograft models in immunodeficient mice, where tumors will be allowed to establish and then subjected to controlled withdrawal to assess tumor growth, ERK dynamics, and apoptosis. These short-term xenograft studies will provide early translational support for withdrawal as a potential strategy. More comprehensive evaluation in patient-derived xenografts and genetically engineered mouse models (GEMMs) of EGFR and KRAS-driven LUAD (which we routinely use[6]) will be pursued in future studies beyond the scope of this one-year award.

Aim 2: Evaluate DUSP4/6 inhibition as a strategy to drive ERK hyperactivation and overcome resistance.

LUAD cells upregulate DUSP6 as a feedback mechanism to buffer ERK activity[7], and genetic suppression of DUSP6 alone or in combination with DUSP4 inhibition induces apoptosis through uncontrolled ERK hyperactivation (**Figure 4**). To translate this observation into a therapeutic approach, we will leverage candidate small molecules identified through prior chemical screens targeting the DUSP4/6 allosteric site. These compounds will be tested for enzymatic activity in phosphatase assays using recombinant DUSP4 and DUSP6 proteins, and their binding will be validated through thermal proteome profiling. The most active inhibitors will then be evaluated in resistant EGFR- and KRAS-mutant LUAD cell lines. ERK activity will be measured in real time using the kinase translocation reporter system, and cell viability will be assessed in dose-response assays.

The most promising inhibitors will then be evaluated in resistant EGFR- and KRAS-mutant LUAD cell lines. ERK activity will be tracked in real time using the kinase translocation reporter system, and cell viability will be quantified by dose-response assays. We will next test whether DUSP4/6 inhibition amplifies the lethal effects of drug withdrawal, by treating resistant lines with inhibitors during or after withdrawal and quantifying synergy using cell viability and apoptosis assays. Mechanistic biomarkers such as ER stress and DNA-damage signaling will be assessed to clarify how inhibition enhances ERK-induced lethality. As in Aim 1, initial *in vivo* work will focus on resistant cell line xenograft models to rapidly evaluate whether DUSP4/6 inhibition produces measurable tumor regression and whether it enhances the effects of withdrawal. Full-scale preclinical evaluation in patient-derived xenografts and GEMMs will be pursued in future studies as the next step toward clinical translation.

Significance

This project addresses one of the most urgent unmet needs in lung cancer: treatment strategies for patients with advanced LUAD who relapse on targeted therapy. By exploring two complementary approaches that converge on ERK hyperactivation, we will rigorously test the feasibility of exploiting this vulnerability to kill resistant tumors. The first aim will determine whether targeted therapy withdrawal can be rationally deployed in specific resistance genotypes, providing a potential clinical strategy for patients with otherwise limited options. The second aim will provide proof-of-concept that pharmacological inhibition of DUSP4 and DUSP6 induces lethal ERK hyperactivation, and will establish whether this approach enhances the effects of drug withdrawal. Because resistant cell lines, patient-derived xenografts, and preclinical mouse models are already established in our laboratory, the proposed work is highly feasible within the one-year award period. Ultimately, these studies will lay the groundwork for translating mechanistic insights in ERK signaling into novel therapies for patients with advanced, refractory lung cancer.

Appendix

References (those from our lab in bold)

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3. Skoulidis, F. & Heymach, J. V. Co-occurring genomic alterations in non-small-cell lung cancer biology and therapy. *Nat. Rev. Cancer* 19, 495–509 (2019).

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5. Chour, A., Toffart, A.-C., Berton, E. & Duruisseaux, M. Mechanisms of resistance to KRASG12C inhibitors in KRASG12C-mutated non-small cell lung cancer. *Front. Oncol.* 14, 1328728 (2024).

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10. Shojaee, S. *et al.* Erk negative feedback control enables pre-B cell transformation and represents a therapeutic target in acute lymphoblastic leukemia. *Cancer Cell* 28, 114–128 (2015).

Title: Combating targeted therapy resistance in lung cancer through hyperactivation of oncogenic signaling

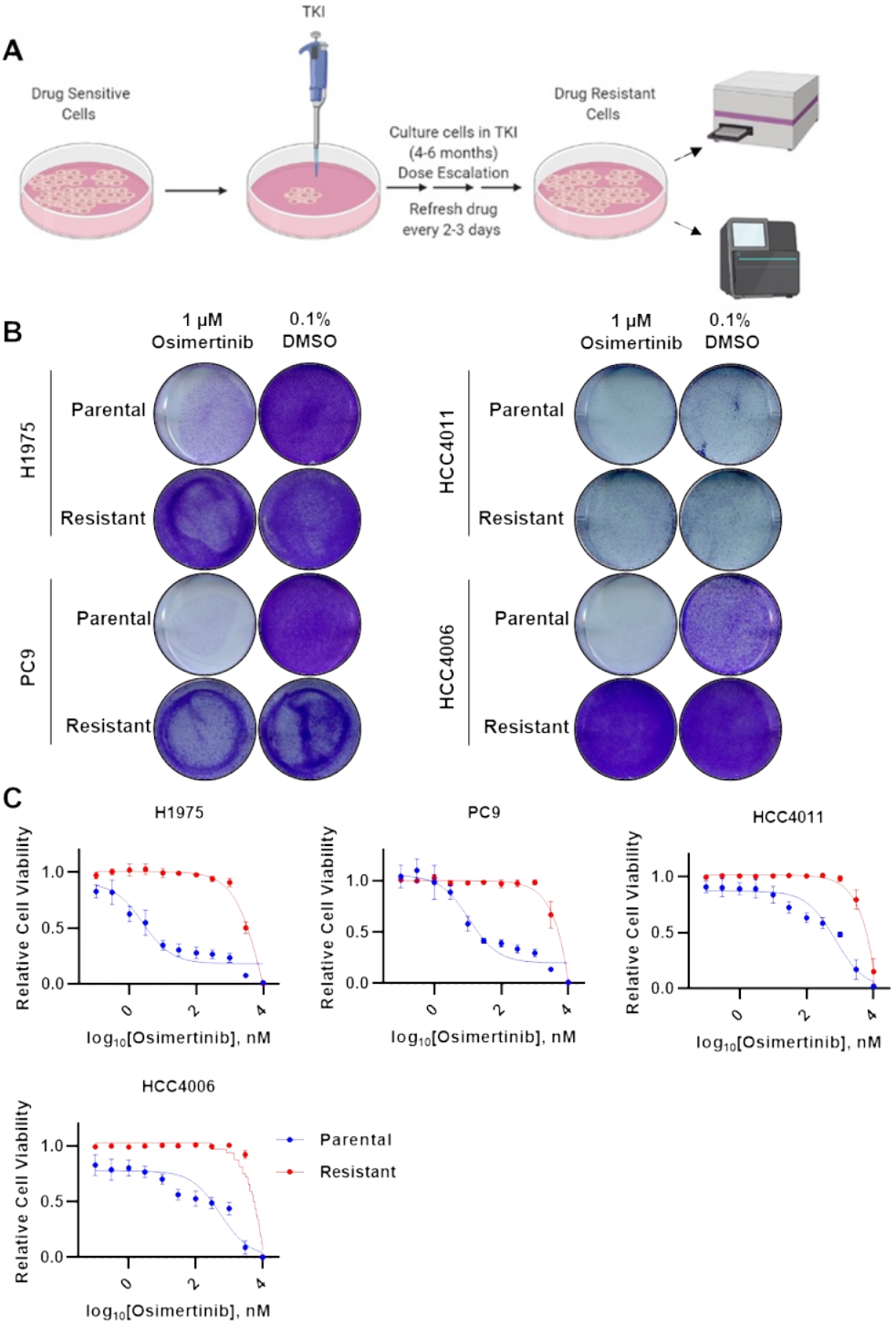

Figure 1: Generation of osimertinib resistant cell lines.
A Dose escalation study workflow. Figure made with BioRender. B Crystal violet proliferation assay on parental and osimertinib resistant cells. C IC_{50} assay on parental and resistant cell lines. Cell viability was measured at endpoint by Resazurin. Viability relative to 0.1% DMSO treatment shown for each cell line. Error bars represent SD from N=4 experimental replicates.

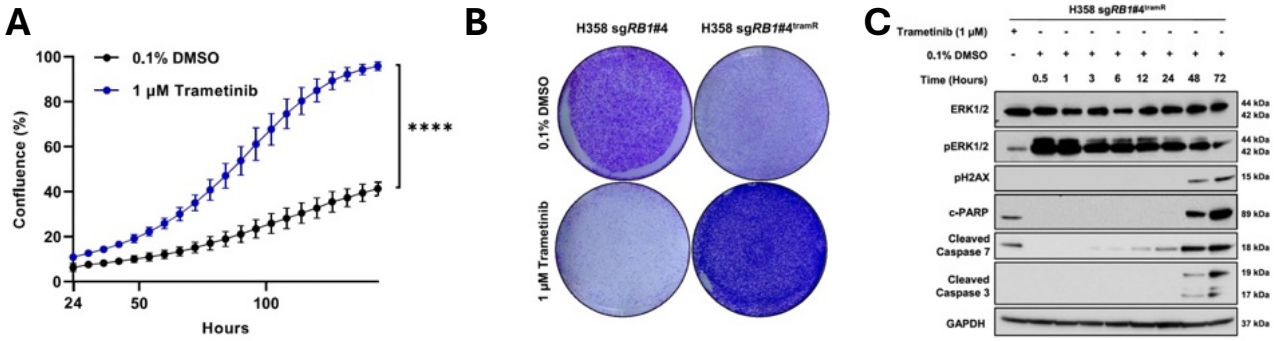

Figure 2: Resistant LUAD cells addicted to continued drug treatment.
A H358 KRAS mutant LUAD cells were made resistant to the inhibitor trametinib through continued dose escalation. The resistant cells (H358 sgRB1#4tramR) demonstrated decreased fitness when drug was removed (DMSO condition) vs when in 1uM of drug. Cell growth measured by IncuCyte S3 live-cell imaging system. Error bars represent SD from 4 independent experiments. P value from extra sum-of-squares F test on calculated logistic growth rate are indicated. ****p < 0.0001. **B** H358 sgRB1#4tramR cells were grown in either 0.1% DMSO or 1 μM trametinib for 7 days, then stained with crystal violet. C ERK2 hyperactivation mediates trametinib addiction. H358 sgRB1#4tramR were treated with 0.1% DMSO or 1 μM trametinib, harvested after the indicated time periods, and immunoblotted for the proteins shown. Starting at 30 minutes after drug removal, and persisting past 72 hours, there is a strong pERK rebound, as well as induction of markers of apoptosis and DNA damage.

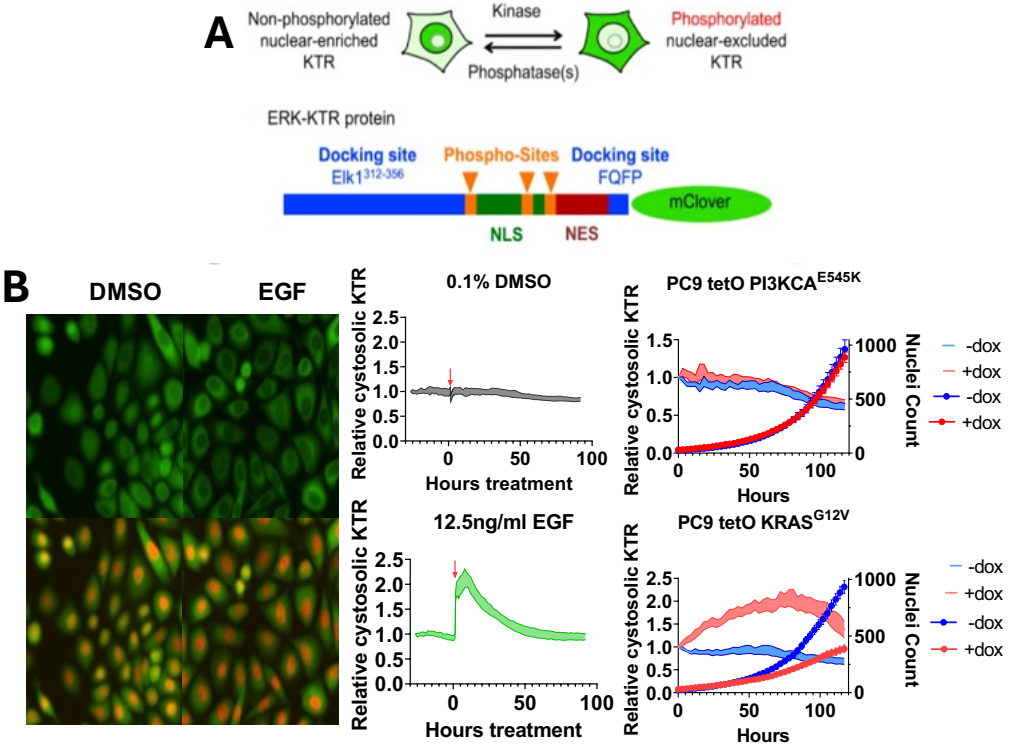

Figure 3: Live cell imaging of ERK status using a translocation assay.
A Schematic of the live cell ERK translocation assay (ERK-KTR). **B** PC9 EGFR mutant LUAD cells expressing the ERK-KTR show increased cytoplasmic localization (ERK activity) +EGF vs DMSO. PC9-TetO-PI3KCAE545K and PC9-TetO-KRASG12V with the KTR were treated with Dox at time zero, leading to increased ERK activity and decreased cell growth as measured by nuclei count in the TetO-KRASG12V but not in the TetO-PI3KCAE545K line.

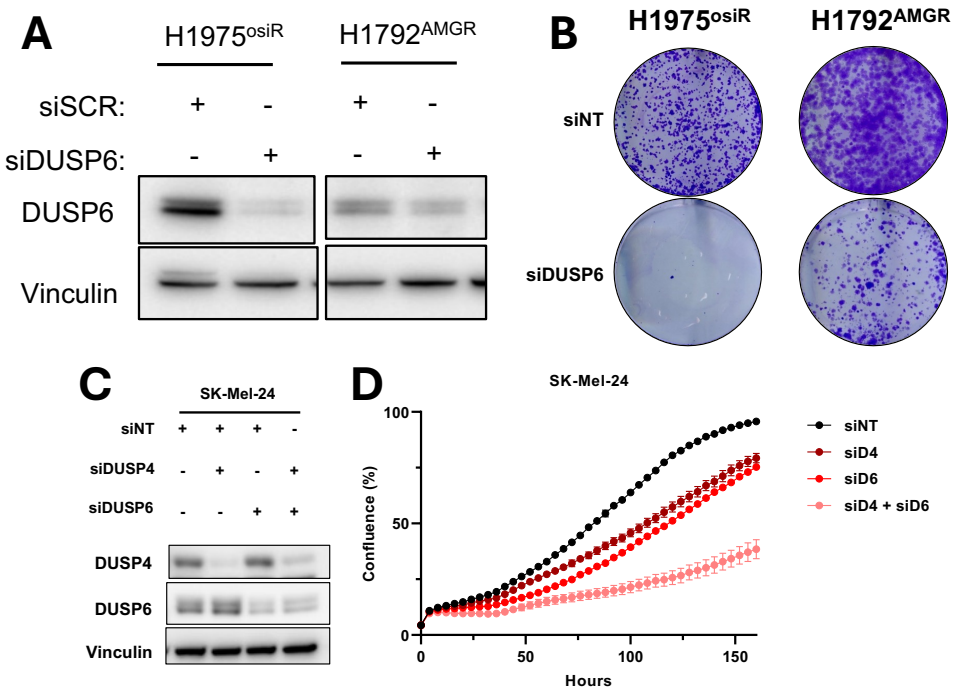

Figure 4: DUSP4/6 genetic inhibition is lethal in drug resistant LUAD cells.
A Knockdown of DUSP6 using siRNA in EGFR mutant H1975 cells resistant to the EGFR TKI osimertinb (H1975^{osiR}) and KRAS mutant H1792 cells resistant to the KRAS inhibitor AMG-510 (H1792^{AMGR}). **B** siDUSP6 leads to decreased viability as indicated by crystal violet staining compared to siNT control. **C** Dual knockdown of DUSP4 and DUSP6 in SK-Mel-24 cells. **D** Knockdown of DUSP4 or DUSP6 alone decreases viability of, whereas dual DUSP4/6 knockdown is synergistic in inducing cell death in SK-Mel-24 cells.

Impact Statement

Lung cancer is the leading cause of cancer-related death in Canada, accounting for more lives lost each year than breast, prostate, and colorectal cancer combined. For patients with advanced lung adenocarcinoma (LUAD), treatment advances over the past decade have centered on precision medicines that target mutations in genes such as EGFR or KRAS. While these therapies initially improve survival and quality of life, virtually all patients relapse as their cancers evolve resistance, leaving chemotherapy or palliative measures as the only remaining options. At this stage, outcomes are poor, and patients and families face devastating prognoses.

This project addresses one of the most urgent unmet needs in lung cancer: new treatments for patients whose tumors have become resistant to targeted therapies. Our laboratory has uncovered a vulnerability shared by resistant LUAD cells. To survive, these tumors must maintain ERK signaling—a critical growth pathway—within a narrow "fitness window." Too little ERK activity, achieved by targeted inhibition, blocks tumor growth. Too much ERK activity, however, is toxic and causes cell death. Resistant tumors adapt by buffering ERK activity, but this balance can be disrupted. We have shown that resistant cancers often become "addicted" to continued drug exposure, such that drug withdrawal causes ERK rebound and apoptosis. We have also identified phosphatases DUSP4 and DUSP6 as crucial ERK regulators; inhibiting them drives hyperactivation and cancer cell death. These insights open the door to therapies that deliberately push ERK activity above the tolerable threshold to kill resistant tumors.

The sustained influence of this project lies in advancing a completely new therapeutic concept: hyperactivating, rather than inhibiting, oncogenic signaling as a means of killing cancer cells. By piloting strategies based on drug withdrawal and DUSP4/6 inhibition, this work has the potential to rapidly inform translational research and clinical practice. In the short term, our studies will provide proof-of-concept that resistant LUAD can be selectively targeted through ERK hyperactivation. These findings will guide patient stratification, identifying genetic resistance profiles most likely to benefit from drug withdrawal regimens, and will deliver early evidence for pharmacological strategies targeting DUSP4/6.

In the medium term, this knowledge will translate into novel clinical trial concepts. Patients whose resistant tumors exhibit drug addiction could be candidates for carefully monitored drug holidays, a low-cost, immediately deployable strategy that could prolong survival and improve quality of life. Meanwhile, pharmacological inhibitors of DUSP4/6—identified and refined through our pilot studies—could be advanced into preclinical testing and, ultimately, human trials. By opening entirely new therapeutic avenues, this work could provide options for patients who currently have none.

In the long term, this project will reduce mortality by improving survival for patients with advanced, drug-resistant LUAD, a population with particularly poor outcomes. It will also improve quality of life by delaying the need for toxic chemotherapy and by enabling more rational, personalized treatment strategies. More broadly, the principle of hyperactivating oncogenic signaling could be extended beyond lung cancer to other malignancies driven by MAPK pathway alterations. By challenging conventional paradigms and offering new strategies, this project has the potential to transform how drug resistance is managed in lung cancer and beyond.

Public Lay Summary

Lung cancer is the deadliest form of cancer in Canada and worldwide. Every year, more people die of lung cancer than of breast, prostate, and colorectal cancers combined. Although new "targeted therapies" have improved treatment for many patients, these drugs are not cures. They work by shutting down genetic mutations that make lung cancer grow, but eventually the cancer finds ways to get around them. When this happens, patients are left with very few options, and survival is often measured in months.

Our research focuses on finding new ways to treat lung cancers that have become resistant to these targeted therapies. We have discovered something surprising about how these cancers work. Lung cancer cells depend on a pathway called ERK to grow. If ERK activity is too low, the cancer cannot grow. But if ERK activity becomes too high, the cells actually die. This means that the cancer must keep ERK activity "just right" to survive, like balancing on a tightrope.

We found two ways to knock cancer cells off this tightrope. The first is through what we call "drug addiction." When cancers are treated with targeted drugs for a long time, they can become dependent on those drugs. If the drug is suddenly removed, ERK activity shoots up and the cells die. The second is through blocking proteins called DUSP4 and DUSP6. These proteins normally keep ERK levels under control. If we block them, ERK activity goes out of balance and the cancer cells self-destruct.

Our project will test both of these strategies—drug withdrawal and blocking DUSP4/6—in lung cancer cells that are already resistant to standard therapies. By studying how these approaches work in the lab, we hope to show that they can kill resistant cancers and point the way toward new treatments. This is especially important because patients who relapse on targeted therapies have very few options and urgently need better ones.

The potential impact of this research is significant. In the future, patients whose cancers are found to be "drug addicted" could benefit from carefully planned "drug holidays," giving them more time before needing chemotherapy. At the same time, new drugs that block DUSP4/6 could be developed and tested in clinical trials, offering an entirely new treatment option. Both strategies could extend survival and improve quality of life for people with advanced lung cancer.

In simple terms, our goal is to turn the cancer's strength into its weakness. By pushing its growth signals beyond the safe zone, we can force resistant lung cancers to collapse. This new way of thinking about cancer treatment could change how we care for patients with advanced disease and give hope to many families facing lung cancer in the years to come.

Budget and Justification

Graduate Student (1.0 FTE at $10,000/yr): Katie Sew, MSc. Student. Katie is a second year MSc student with a thesis focused on studying the effects of ERK hyperactivation on lung cancer development and response to therapy. Katie has partial coverage of her stipend ($35,000 total) through other sources. This will cover the remaining portion of her yearly pay, and she will dedicate 100% of her time to this project

Cell culture and molecular biology reagents ($15,000/yr): Costs associated with cell culture work, establishment of modified cell lines, and routine molecular biology will be required. These include plastic wear and disposables (such as tissue culture plates for cell maintenance, multi-well plates for viability and cell assays, filters for media preparation, etc.), tissue culture supplies (cell culture medium, matigel, FBS, antibiotics etc.) and molecular biology supplies (PCR reagents, primers, siRNAs, vectors, enzymes, DNA/RNA extraction kits, cloning reagents, Western blot supplies, antibodies, mini/maxiprep kits, gel electrophoresis, buffer etc). Dox food and Osi in quantities and purity sufficient for the in vivo work are required as are general lab supplies such as pipette tips, gloves, disposable plasticware etc. Based on past experience with similar projects, we estimate that these cell culture and molecular biology lab supplies are estimated to average $15,000/year per FTE.

Total = $25,000

Other Personel

PI – Dr. William Lockwood (CV attached).

BC CANCER RESEARCH INSTITUTE
Provincial Health Services Authority

September 25st, 2025

RE: Letter of Institutional Support for Will Lockwood, Lung Cancer Canada Grant

On behalf of the Department of Basic and Translational Research (BTR) at the BC Cancer Research Institute (BCCRI), it is a pleasure for me to write in support of Dr. William Lockwood's application for this Lung Cancer Canada Grant. Dr. Lockwood is an exceptionally talented researcher, having received outstanding training at (BCCRI, Memorial Sloan-Kettering Cancer Centre (MSKCC) and the National Institutes of Health (NIH). He was recruited from Nobel laureate Harold Varmus's laboratory into an independent position by BC Cancer in 2014 with a corresponding appointment in the Department of Pathology and Laboratory Medicine (PaLM) at UBC. Since this time, Dr. Lockwood has established himself as a rising star in the field of lung cancer research, applying his unique expertise in cancer genomics and mouse models to develop novel diagnostic and treatment strategies for this deadly disease with major implications for the health care system in Canada.

Dr. Lockwood was recruited specifically to join the emerging lung cancer program at BCCRI and is pursuing several interrelated research themes that synergize with ongoing research at the BCCRI and at UBC. He has built his research program by identifying and pursing critical gaps in our understanding of lung tumour biology, using a multifaceted approach that combines clinical, functional and chemical genomics. His areas of expertise fill an important niche within the BCCRI and the UBC Department of PaLM and align perfectly with the Faculty of Medicine's strategic goals to improve the health of Canadians, of which sustaining and growing pre-eminence in research and translation in the fields of cancer as well as heart and lung disease constitute two of the three major goals. Dr. Lockwood's research themes are well integrated into a cohesive health research program designed to increase the long-term survival of lung cancer patients. Dr. Lockwood's expertise has enabled him to address extremely complicated research questions with a unique set of research skills and knowledge base, an insatiable curiosity, and an exemplary drive to produce data of the highest quality.

Dr. Lockwood has an extremely impressive publication record for a mid-career investigator with 96 total publications, consisting of influential papers in high-impact journals that address key unanswered questions about the genetic mechanisms driving cancer development and targeted therapy resistance. Many of these have been highly cited, covered in the press and highlighted by commentaries as major developments in lung cancer research. Importantly, he is senior author on 22 of these publications that span the last six years, highlighting his group's ability to initiate and lead studies and drive their completion. Through these efforts, Dr. Lockwood's group has identified new mutations and disrupted signalling pathways in lung cancer as well as novel lung cancer cell dependencies and small molecules for therapeutic intervention. Furthermore, they have defined biomarkers for early cancer detection and targets to tailor subtype specific therapeutic strategies. More recently, his group has applied chemical genomics to screen for novel compounds with anticancer activity while exploring mechanisms of resistance to current targeted agents to define new targets for drug development. For example, through a screen of over 200,000 small molecules, a compound termed LCS3 was uncovered that demonstrated potent activity against lung cancer, but not normal lung, cells. Using thermal proteomic profiling (TPP), his group found that this compound dually inhibits the enzymes TXNRD1 and GSR, which are essential for mediating redox hemostasis in the transformed state. They showed that combined inhibition of TXNRD1 and GSR is synthetically lethal in lung cancer cells, suggesting a new avenue for therapeutic exploitation. In parallel, they unexpectedly found that hyperactive oncogenic signalling

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is toxic to lung cancer cells and have explored how we can use this information to treat cancer patients. They identified ERK activity as essential in this process and uncovered that lung cancer cells depend on the negative feedback phosphatase DUSP6 to restrain ERK activity below a lethal threshold. Inhibiting DUSP6 or hyperactivating ERK in the resistant state through drug withdrawal leads to cancer cell death and differentiation, suggestive of a new vulnerability to target with anti-cancer agents. Together, his work offer progress towards developing new classes of drugs and strategies for the treatment of targeted therapy resistant lung cancer - ultimately leading to improved survival rates for patients - that forms the basis of this current research proposal.

Dr. Lockwood's track record of innovation is also reflected in his ability to obtain peer reviewed funding. Since becoming an independent investigator, he has secured five Canadian Institutes of Health Research (CIHR) Project Grants as PI along with numerous foundation grants (>5 million dollars total), indicative of the judged novelty and scientific thoroughness of his initiatives. These include investigations into tumour-immune cell interactions, novel therapeutic strategies based on newly discovered genetic interactions and translational research into early detection. Together, this provides an excellent foundation for this proposed research project and we expect Dr. Lockwood to continue to demonstrate a high degree of productivity and quality in these regards during the coming years. In light of this, he has already been internationally recognized since establishing his independent program, receiving a Young Investigator Award from the International Association for the Study of Lung Cancer, invited to present his results in symposia at major conferences in the field such as the World Conference on Lung Cancer, and taking part in international collaborative efforts to combat drug resistance in lung cancer. He serves on both national (ie CIHR) and international (ie. Medical Research Council UK, see CV) grant panels as a reviewer/scientific officer, is on the Scientific Advisory Board for the Lung Cancer Research Foundation, and act as Associate Editor for multiple journals in the field including Translational Lung Cancer Research. Together, these accomplishments clearly demonstrate his track record of consistently producing high quality research outputs that are both valued by and influence the lung cancer community, signifying his place as an internationally recognized leader which we expect will continue to develop in the coming years.

Dr. Lockwood has abundant experience in communicating information to the lung cancer community by presenting material at international conferences, invited lectures and scientific journals and this - particularly knowledge-translation to end-users - will continue to be a major focus of his moving forward. Dr. Lockwood has been active at engaging the public more in this discourse, conveying the importance of scientific findings, listening to patient concerns and engaging young people in health research. His efforts include organizing and attending conferences, meetings and science outreach programs as well as giving public lectures, engaging with government and policy makers and importantly, directly involving patient stakeholders. He has formed a group for scientific outreach, writes blogs and conducts interviews to inform the public on lung cancer research efforts and advances and helps shape research directions based on patient engagement as part of his role at the Lung Cancer Research Foundation. He recognizes the importance of Equity, Diversity, and Inclusion (EDI) in advancing scientific research and promoting better health outcomes for all populations affected by lung cancer, ensuring that his projects are inclusive of all individuals. He actively promotes EDI principles throughout all stages of the research process, from study design to dissemination of results. Specifically, he takes measures to recruit a diverse team of researchers and participants, considers the impact of socio-economic and cultural factors on lung cancer, and prioritizes open communication and collaboration with stakeholders from underrepresented groups. By adopting this EDI-focused approach, he aims to foster a more equitable and impactful research environment that ultimately benefits all individuals affected by lung cancer and specifically the problem of drug resistance.

Dr. Lockwood involved in all aspects of trainee education, structuring and teaching classes at UBC, serving on student committees and mentoring graduate students as well as postdoctoral fellows. Currently, his group has six graduate students in different stages of study (three MSc, three PhD) and will take on two more this year in addition to three undergraduate students, a postdoc and a senior technician. He plans to continue his long-standing track record of mentoring students and technical staff, providing them with a stimulating, collaborative, multidisciplinary environment with exposure to different areas of study from the angle of various health care professionals, which will allow them to make informed decisions about their career paths. He is committed to promoting EDI throughout the learning process. His research team is diverse (60% female, 80% visible minority) and he promotes an inclusive learning environment that respects and values the experiences, perspectives, and contributions of all individuals. His program provides mentorship and support to ensure that trainees from underrepresented groups thrive and reach their full potential. He is dedicated to fostering a healthy research environment in his department and UBC in general, organizing trainee functions to inform on career options; initiating work in progress meetings with members from diverse labs to gain insight into complementary methods of investigation; and inviting prominent lung cancer researchers and patient advocates to give seminars to inform the local community on the latest advances in research and clinical care. Through these efforts he aims to prepare the next generation of researchers to address the complex challenges of lung cancer in a way that is inclusive and equitable for all.

Dr. Lockwood is currently appointed as a Professor in PaLM and a Distinguished Scientist at the BCCRI. His research home is in the BCCRI Department of Basic and Translational Research located in the BC Cancer Research Centre (BCCRC). The BCCRC houses pre-clinical laboratories of the BCCRI, and most of these laboratories are under the direction of other highly successful cross-appointed members of the UBC Faculty of Medicine. The BCCRI therefore serves as his immediate host organization, underwriting his personal salary, benefits, laboratory space (currently 1200 ft^2), and office space, while also providing administrative support, IT support, and an exceptional research environment for his staff and trainees. Within his Department, he also has free, unlimited access to fluorescence microscopes, cryostats, a small-animal procedures room, radioisotope rooms and cold rooms. His lab also has access to all of the fee-for-service operated core facilities available at the BCCRI, including an Animal Resource Centre that provides mouse transgenic, breeding, imaging, and irradiation facilities, a flow cytometry core facility, a Tumour Tissue Repository and biobanking facility, a Level III biohazard containment facility, a high-content high-throughput sgRNA and chemical library screening facility, and a high-throughput sequencing and bioinformatics facility. He recruits graduate and undergraduate students through his affiliations with UBC PaLM and the Interdisciplinary Oncology Program. Outstanding grant development and administration services are also provided by BCCA and UBC. The BCCRI and the Department of PaLM are committed to guaranteeing a total of 85% of protected time for his research enterprise with the remaining 15% comprised of scheduled undergraduate, graduate, postgraduate, and resident teaching, service on graduate student supervisory and examination committees, and service on select academic and professional committees at the BCCRI and at UBC.

Dr. Lockwood's Departmental colleagues at the BCCRI include geneticists, biochemists and cell biologists, all of whom share a common interest in the development and evaluation of new diagnostic and therapeutic strategies that can be applied to improving the detection and treatment of cancer in the clinic. This Department provides an ideal day-to-day environment for his academic development and that of all trainees. Dr. Lockwood has a wealth of experience working in collaborative, multidisciplinary teams that are necessary to achieve the aims of the cutting-edge research proposed. He has built several strategic collaborations with Canadian and international partners with the most prominent with members of the BC Lung Tumor Group (BCLTG) and the newly establish **P**revention

and **R**esearch to improve **O**utcomes (PRO-Lung) group. These diverse group consists of respirologists, oncologists, pathologists, surgeons and other scientists providing synergy between all aspects of lung cancer research and patient care, which will greatly benefit areas of research he proposes. Dr. Lockwood's research fills a key need within these strong programs in early detection, screening, clinical trials and genomic analyses that aims to provide top-quality, innovative care to patients. Dr. Lockwood serves as a steering committee member and director of Platform II: Biology and Therapeutics of the PRO-Lung program, which recently received a record 17 million dollar donation from the Blackmore Foundation to grow early detection/treatment research, including adding faculty, that will complement and interconnect with his efforts to address key needs in patient care on an internationally recognized scale. Thus, his proposed research is integrated into a cohesive health research program designed to increase the long-term survival of lung cancer patients.

In summary, Dr. Lockwood has demonstrated his independence and initiative in building an internationally recognized research laboratory that produces important data to improve our understanding of lung cancer. I strongly support his nomination for this Lung Cancer Canada award to allow his continued work on the problem of targeted therapy resistance and his innovative strategy proposed to combat this issue and improve patient survival rates.

Sincerely,

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