2024 Geoffrey Ogram Memorial Research Grant Competition

Deadline Date: September 30, 2024 @ 11:59pm PST
Anticipated Notice of Decision: November 1, 2024
Funding Start Date: December 1, 2024

Application Form

Applicant:

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Project Title

Endothelial PD-L1 expression as a potential predictive biomarker in lung cancer treatment.

Project Description

The PD-L1 ligand and the PD-1 receptor are immune checkpoint proteins that inhibit anti-tumor cytotoxic T cells, effectively reining in their ability to kill cancer cells. Targeting this pathway with immune checkpoint inhibitors (ICIs) has shown efficacy in a subset of non-small cell lung cancer patients. The biomarker currently used in clinic – the PD-L1 tumor proportion score (TPS) – is only semi-predictive, potentially because it focuses on PD-L1 expression on tumor cells, while ignoring stromal PD-L1 expression. Preclinical studies suggests that PD-L1 expression on endothelial cells within the tumor microenvironment may play an underappreciated role in cancer immune evasion. Endothelial PDL1 (ePDL1) is dynamically influenced by inflammatory cytokines, tumor-infiltrating lymphocytes, as well as antiangiogenic drug exposure. Due to ePDL1, an anti-tumor T cell may be inhibited at the extravasation step prior to even entering the tumor microenvironment. Potentially, the blockade of ePDL1 function may be key to the mechanism of action of anti-PD-1/PD-L1 ICIs in some lung cancers. Our goal is to develop a new and clinically translatable immunohistochemistry assay to specifically quantify ePDL1 within the tumor microenvironment. A new combined ePDL1+TPS is anticipated to refine PD-L1 scoring and increase its predictive value. An improved predictive biomarker will enhance patient stratification within approved indications for ICIs (one hypothesis is that patients with TPS-high but ePDL1-low NSCLCs without a driver mutation may benefit from adding chemotherapy to ICI therapy). ePDL1 scoring may also bolster the development of promising new ICI combination strategies in expanded indications (another hypothesis is that a baseline TPS-positive but ePDL1-low subgroup may be driving recent phase III clinical trial successes of combined ICI + antiangiogenic combination strategies in EGFR+ NSCLCs after progression on targeted therapies).

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1. Letter of Intent

Dear Lung Cancer Canada & the 2024 GOMRG adjudication panel,

We are pleased to submit an application for the Geoffrey Ogram Memorial Research Grant that seeks to deepen our understanding of the etiology of lung cancers in different subpopulations and improve our ability to predict risk of recurrence after surgical resection of early-stage lung cancers. The knowledge we hope to gain through this proposed work will accelerate therapeutic innovations to impactfully reduce lung cancer burden and optimize patient care.

We hypothesize that the PD-L1 expressed on tumor-associated endothelial cells plays an underappreciated role in lung cancer immune evasion. Preclinical studies have found ePDL1 to be inducible by inflammatory cytokines, tumor-infiltrating lymphocytes, as well as antiangiogenic drug exposure. Endothelial PDL1 (ePDL1) may halt an anti-tumor T cell at the extravasation step prior to T cell infiltration into the tumor microenvironment. ePDL1 may thus be crucial to the therapeutic mechanism of action of anti-PD-1/PD-L1 immune checkpoint inhibitors (ICIs).

We postulate that the biomarker currently used in clinic to guide ICI therapy use – the PD-L1 tumor proportion score (TPS) – is only semi-predictive because it focuses on PD-L1 expression on tumor cells, while ignoring ePDL1 as background. The goal of our project is to develop a clinically translatable immunohistochemistry assay that specifically quantifies ePDL1 within the tumor microenvironment. A new combined ePDL1+TPS is anticipated to refine PD-L1 scoring in a way that will improve patient stratification within approved indications of ICIs in the advanced and early-stage settings of NSCLCs. ePDL1 scoring may also be of relevance for promising ICI + antiangiogenic treatment strategies in subpopulations where upfront ICI monotherapy is not indicated (e.g., ivonescimab, a bispecific antibody to PD-1 and VEGF, is currently under clinical trial investigation for EGFR+ lung cancers after progression on EGFR tyrosine kinase inhibitor therapy).

We thank the adjudication panel for considering our application and we sincerely hope to have the opportunity to pursue the work outlined.

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PGY6, UBC Clinician Investigator Program, Vancouver
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Dr. Cheryl Ho
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2a. Research Proposal

Background

Since 2014, Health Canada (HC) has approved five different immune checkpoint inhibitor (ICI) antibody drugs directed against PD-1 or PD-L1 as treatment for non-small cell lung cancer (NSCLC)[1,2]: pembrolizumab, nivolumab, atezolizumab, and cemiplimab in the metastatic disease setting; consolidative durvalumab in the unresectable locally advanced setting; as well as neoadjuvant nivolumab and adjuvant atezolizumab in the operable early-stage settings[1,2]. Despite these advances, **tumor expression of PD-L1 as defined by the tumor proportion score (TPS) remains an imperfect biomarker**[3,4]. A correlation between higher TPS scores and greater clinical efficacy was observed in some trials (KN042 [5]; IMpower010[6]), but not consistently seen in others (e.g., KN189[7]; PEARLS[6]). Some TPS^{high} tumors do not respond to ICIs – e.g., in KN024, overall response rate (ORR) was only 44.8% in the TPS≥50% population[8]. Conversely, $TPS^{-/low}$ tumors can respond to ICI-based treatment – e.g., in KN189, an overall survival (OS) benefit was seen in both TPS<1% and TPS>1% subgroups[7]. In the peri-operative setting, no statistically significant interaction was found between TPS status and the risk ratio of achieving pathologic complete response (pCR) after neoadjuvant ICI+chemotherapy[9].

Although TPS measures PDL1 on tumor cells, **PD-L1 is also expressed by immune cells (ICs) fibroblasts and endothelial cells (ECs)[10–12] (Fig. 1A).** It has long been postulated that the TPS is inadequate in part because it overvalues the constitutive or intrinsically driven component of PD-L1 expression by tumor cells (e.g. secondary to underlying genomic or epigenetic alterations), while undervaluing the dynamic or reactive PD-L1 expression that occurs at the tumor-stroma interface (e.g. in response to IFNγ secreted by tumor-infiltrating lymphocytes (TILs))[3]. ECs can express PD-L1 when induced by inflammatory cytokines (including IFN-γ/α/β, TNF-α, IL-2) *in vitro* [13–15] (Fig. 2A) or *in vivo* (Fig. 2B). Our *in vitro* pilot experiments demonstrate a striking difference in the amount of inducible PDL1 expression between tumor cells and endothelial cells (Fig. 2A). Intriguingly, in the organ transplant literature, loss of host ePDL1 has been shown to accelerate rejection of cardiac allografts in mice[16]. Thus, ePDL1 may play an unappreciated but key role in anti-tumor immunity. Mechanistically, cytotoxic T cells confront endothelial PD-L1 (ePDL1) during the extravasation process before they even infiltrate the tumor microenvironment (TME) to encounter and kill tumor cells (Fig. 1A; 2B). The *IASLC Atlas of PD-L1 Immunohistochemistry (IHC) Testing for Lung Cancer* currently advises pathologists to disregard ePDL1 staining as background noise[18]. **We hypothesize that a new scoring system which incorporates endothelial PDL1 scoring would yield greater predictive value than the TPS currently used in clinic (Fig. 1B-C).**

Preclinical evidence supports ePDL1 as a therapeutic target of ICIs. $PD\text{-}L1^{+}$ $CD31^{+}$ ECs were shown to contribute to immune evasion through inhibition of cytotoxic T cells in murine melanoma models [19]. Furthermore, upregulation of ePDL1 was observed in murine pancreatic and breast cancer models after antiangiogenic therapies against VEGFR2 (expressed on ECs) or VEGF (the ligand of VEGFR2), and this was implicated in the enhanced anti-tumor efficacy seen when further combined with ICIs[20,21]. These **preclinical studies suggest that ePDL1 warrants investigation as a predictive biomarker for combined antiangiogenic + ICI strategies**[22,23].

While adding atezolizumab to bevacizumab (anti-VEGF) with chemotherapy showed promising benefit in EGFR/ALK-altered metastatic NSCLC in the IMpower150 phase III trial[24], there was too much uncertainty regarding the benefit in this subgroup and therefore it is not a publicly funded treatment option in Canada. Antiangiogenic therapies + ICI combinations may still have a role in future treatments for the EGFR/ALK-altered subgroup, given the promising results coming in from phase III trials, ATTLAS (second-line atezolizumab+bevacizumab+chemotherapy[25]) and HARMONI-A (second-line ivonescimab, a VEGF/PD-1-bispecific antibody[26]). **Thus, investigating**

the predictive potential of ePDL1 in both wildtype and oncogenic-driven NSCLCs at this critical juncture may be fundamental in determining the ideal patients for ICI combination therapy.

Hypotheses: IHC-based scoring of ePDL1 will augment the current clinical standard, TPS, for predicting clinical response and survival benefits from ICI therapy in NSCLC. More specifically:

- A ePDL1$^{+/high}$ subset of TPS$^{-/low}$ NSCLCs may respond exceptionally to ICIs.
- A ePDL1$^{-/low}$ subset of TPS$^{+/high}$ NSCLCs may not respond to single-agent ICIs, and may warrant combination with chemotherapy and/or VEGF pathway inhibition.
- A subset of NSCLCs with EGFR mutations or ALK alterations may be constitutively TPS$^{+/high}$, baseline ePDL1$^{-/low}$, with inducible ePDL1 when exposed to antiangiogenic therapies .

Objectives

Aim #1. Develop a clinically translatable assay to score ePDL1. Work will be performed at the UBC-affiliated Molecular and Advanced Pathology core (MAPcore) facility with REB approval (H22-01017). A 2-color IHC assay will be developed using a rabbit anti-human PD-L1 antibody (clone 73-10)[27] and DAB to stain PD-L1 brown on any cell type, as well as a chimeric mouse anti-human ERG antibody (clone EPR3864) and AP Red to stain the nucleus of endothelial cells red. Work will be performed on a Leica staining platform and visualized under light microscopy. Optimization will be based on manufacturer recommendations and a published protocol showing PD-L1 staining by 73-10 to be comparable to other assays (including the current clinical standard, 22C3 pharmDx) [27,28]. We will use 4µm whole-slide sections (n=20 cases) from archived surgically resected NSCLC covering a range of TPS scores (<1%, 1-49%, ≥50%) for optimization. TPS and ePDL1 (Fig. 1B-C) will be scored on dual stain and compared with historical TPS from clinical-grade 22C3-stained slides.

Aim #2. Contextualize ePDL1 expression within the tumor microenvironment (TME). Through separately funded work (TFRI grant & MSHRBC HPI award), a tissue microarray (TMA #1, n=89) was constructed from resected early-stage NSCLCs, and another (TMA #2, n=90) was constructed using lung resections from patients who subsequently had metastatic relapse treated with ICI therapy (Fig. 3). Multiplex immunofluorescent (mIF) using the Lunaphore platform was used to explore cell-cell spatial relationships on TMA #1 using 14 markers including PD-L1. With additional GOMRG funding, there will be an opportunity to add EC markers (e.g., CD31) to an expanded 30-marker mIF panels. mIF analysis of TMAs #1+2 (Fig. 3) offers the opportunity to assess the distribution of PD-L1 staining across endothelial-cell vs. immune-cell vs. tumor-cell compartments in the presence vs. absence of EGFR/ALK alterations, as well as explore conditional spatial requirements for inducible ePDL1 expression (e.g., when adjacent to GzmB$^+$ PD1$^+$CD8$^+$ activated cytotoxic T cells). 2-color IHC scoring of the TPS≥50% TMA #2 (Fig. 3B) offers the opportunity to identify ePDL1 subgroups that correlate with outcomes post-ICI therapy at metastatic relapse.

Aim #3. Explore predictive potential of ePDL1. Aim#3 will proceed concurrently with Aim #2. Whole slides will be cut from diagnostic core biopsies from deceased patients who had *de novo* metastatic NSCLC: n=40 with no driver mutations (Fig. 4A); and n=40 with EGFR mutations or ALK rearrangements (Fig. 4B). A greater discordance between ePDL1 scores and TPS status at baseline is expected in EGFR/ALK-altered NSCLC (Fig. 4B) compared to wildtype NSCLC (Fig. 4A). The predictive value of ePDL1 will be compared against that of TPS, in terms of predicting time to next treatment (TTNT) and OS after ICI (Fig. 4A). An n=10 peri-operative pilot (Fig. 4C) involving early-stage NSCLC treated with neoadjuvant ICI therapy is included in this proposal. Both the initial diagnostic core biopsy and post-treatment resected surgical specimens will be scored by our 2-color IHC assay, to assess temporal changes in ePDL1 and TPS, and test for correlation between baseline ePDL1/TPS versus outcomes (pCR; major pathologic response; relapse-free survival).

2b. References

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2c. Appendix

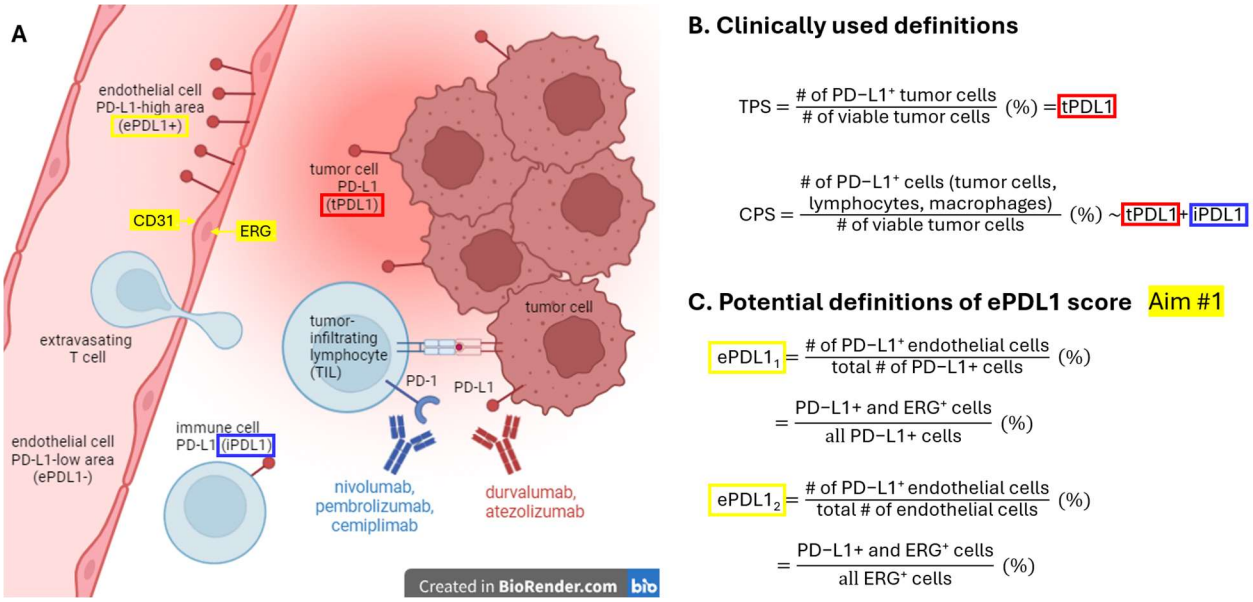

Figure 1. Cell-type specific PD-L1 expression & proposed scoring systems for Aim #1.

A. PD-L1 is expressed on the surface membranes of tumor cells (tPDL1), immune cells (iPDL1), and a variety of stromal cells including endothelial cells (ePDL1).

B. Current companion IHC assays for immune checkpoint inhibitors only quantify tPDL1 staining (by the tumor proportion score (TPS) as used in lung cancers) or tPDL1+iPDL1 staining (by the combined positive score (CPS) as used in head & neck, cervical, gastroesophageal, and breast cancers).

C. The goal of our project is to develop a scoring system to quantify ePDL1 staining in NSCLC. Two potential definitions are illustrated here, using ERG as a nuclear endothelial cell marker commonly used by clinical pathologists in IHC-based applications (www.pathologyoutlines.com/topic/stainsERG.html).

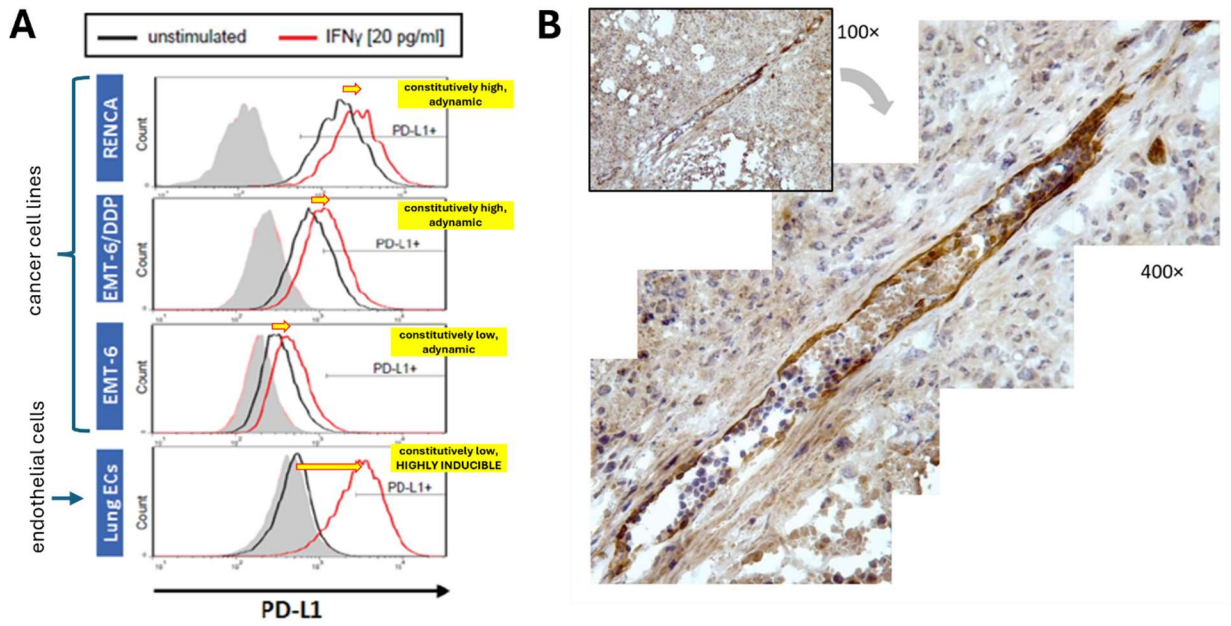

Figure 2. Inducible PD-L1 expression on mouse endothelial cells compared to adynamic constitutive PD-L1 expression on tumor cells (unpublished data, FTH Wu & RS Kerbel).

A. Flow cytometry detection of *in vitro* PD-L1 expression on VeraVec™ murine lung microvascular endothelial cells (Lung ECs), murine kidney cancer cells (RENCA), and murine breast cancer cells (parental EMT-6 and cisplatin-resistant EMT-6/CDDP) at baseline versus after stimulation with IFNγ (20pg/mL). Solid lines represent mouse PD-L1 staining (PE rat IgG2b,κ, clone 10F.9G2, Biolegend #124308). Shaded histograms represent isotype controls (eBioscience #12-4032-82).

B. Endothelial PD-L1 staining within orthotopically grown primary EMT6/CDDP murine breast tumors. Frozen histological sections were subjected to IHC staining for mouse PD-L1 using a staining antibody GEN130-47-4 from Genentech.

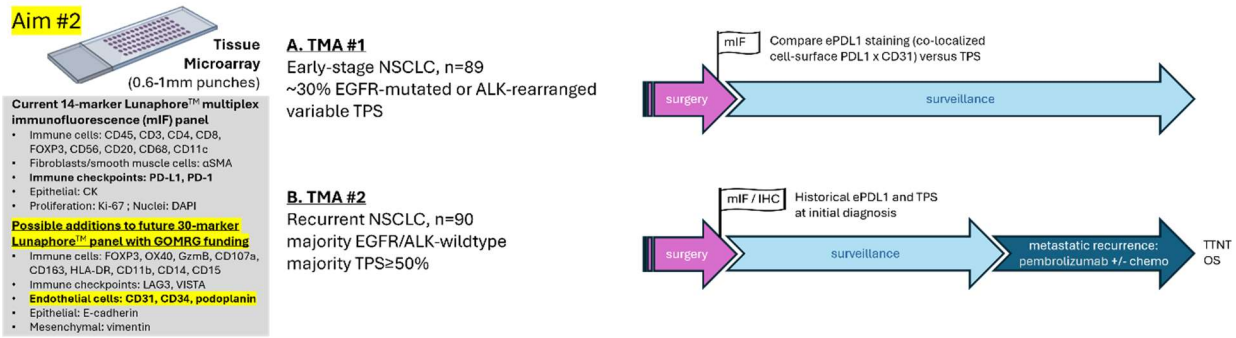

Figure 3. Schema for Aim #2: Contextualizing ePDL1 within tumor microenvironment using multiplex immunofluorescence (mIF) analysis and NSCLC tissue microarrays (TMAs).

OS = overall survival. TTNT = time to next-line systemic therapy or best supportive care. See Fig. 1 for definitions of endothelial PD-L1 (ePDL1) and tumor proportion score (TPS).

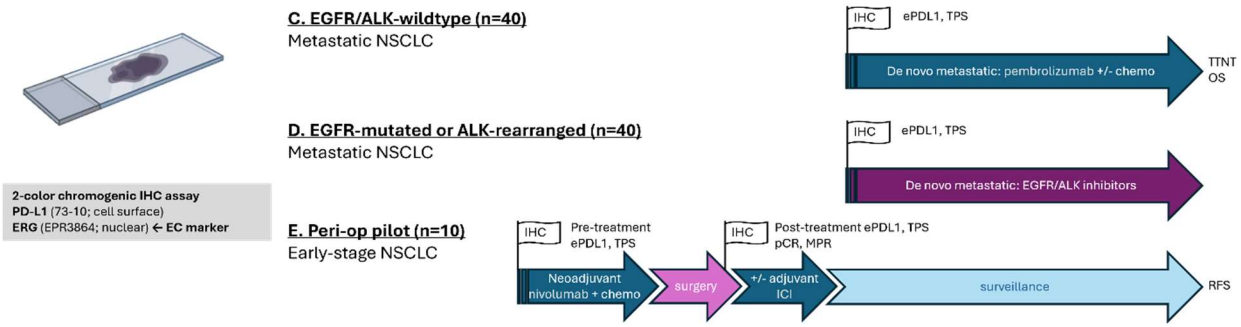

Figure 4. Schema for Aim #3: Exploring predictive potential of ePDL1.

OS = overall survival. TTNT = time to next-line systemic therapy or best supportive care. RFS = recurrence-free survival. pCR = pathologic complete response. MPR = major pathologic response. See Fig. 1 for definitions of endothelial PD-L1 (ePDL1) and tumor proportion score (TPS).

3. Impact Statement

Our goal with this project is to develop a new and improved immunohistochemistry (IHC)-based companion diagnostic assay for immune checkpoint inhibitor therapies (ICIs) that target the PD-1/PD-L1 pathway. We propose to do so by distinguishing between PD-L1 expressed on endothelial cells (ePDL1) versus PD-L1 expressed on tumor cells (measured by the tumor proportion score, or TPS) within the tumor microenvironment of non-small cell lung cancers (NSCLC).

Our assay has the potential to immediately improve predictions of clinical responders versus suboptimal/non-responders to ICIs within established indications for NSCLC. For example, in a patient with metastatic NSCLC that is EGFR/ALK-wildtype and PD-L1 TPS≥50%, additional scoring of ePDL1 might help oncologists/patients decide between single-agent ICI (if ePDL1^{high}) versus escalated ICI + chemotherapy combinations (if ePDL1^{low}).

In the future, our assay may improve predictions for response to promising new ICI + antiangiogenic therapies in the second-line setting (e.g., ivonescimab, a PD-1/VEGF-bispecific antibody) and help bolster their success in NSCLC subpopulations where upfront ICI monotherapy has previously not been successful (e.g. EGFR+ or ALK+ NSCLCs)

In the operable early-stage disease setting, if combined baseline ePDL1 scoring proves to be better than TPS alone in predicting pathologic responses and/or risks of relapse after neoadjuvant ICI combination therapy, this can help adaptive escalation of neoadjuvant therapy and de-escalation of adjuvant therapy, with the goal of limiting treatment duration and toxicity to patients, as well as reducing financial costs to publicly funded healthcare systems.

Finally, while this project focuses on quantifying ePDL1 in NSCLC, it is also a proof-of-concept that can have broader implications for other thoracic malignancies (including small cell lung cancers and pleural mesotheliomas) and beyond, wherever ICIs are already relevant (e.g. kidney, bladder, colorectal, gastroesophageal, liver, cervical, endometrial, breast, and skin cancers). In cancer types where ICI are not yet relevant (e.g., gliomas), ePDL1 may be the gateway to successful combinations of ICI + antiangiogenic therapies.

4. Public, non-scientific summary

85% of lung cancers are non-small cell lung cancers (NSCLCs). These can be broadly divided into two categories – those driven by oncogenic driver alterations (such as in EGFR/ALK) versus those that are not. Targeted therapies (e.g. EGFR/ALK inhibitors) are currently first-line treatment for EGFR/ALK-altered NSCLCs, and the specific driver alteration itself is highly accurate in predicting treatment efficacy. In contrast, immunotherapies (e.g., PD-1/PD-L1 pathway inhibitors, which activate the immune system to eliminate cancer cells) are the mainstay of treatment of NSCLCs without targetable driver mutations, but in this case, we do not have a good biomarker assay to predict which patients will benefit or not.

The biomarker assay routinely used in clinic in relation to immunotherapies is the TPS (tumor proportion score), which measures the PD-L1 expression on *tumor cells* only, while ignoring the PD-L1 expression on their neighboring supportive cells. Currently in clinic, the TPS score is used to decide whether it is best to recommend upfront immunotherapy like pembrolizumab if the score is high or a combination with chemotherapy if the score is low. However, up to 55% of TPS-high NSCLCs do not respond to single-agent immunotherapies. It is currently very difficult for oncologists and patients to decide whether to escalate treatment by adding chemotherapy to first-line immunotherapy for patients with TPS-high NSCLCs.

We hypothesize that the TPS is not optimally predictive because it ignores the PD-L1 expression on supportive cells in the vicinity of tumor cells – in particular, blood vessel *endothelial cells* which are gatekeepers through which immune cells must pass through before they can infiltrate tumors to kill off individual tumor cells. With this proposal, we seek to develop a novel but practical assay that measures endothelial PD-L1 expression within the neighborhood of tumor cells, to help us refine our predictive biomarker for immunotherapy use in wildtype NSCLC. The goal of this work is to improve patient selection for immunotherapies by developing a superior biomarker that provides more information for decision making. Improved selection of patients will allow us to provide immunotherapy only to patients likely to respond, while omitting immunotherapy in patients unlikely to respond and thus avoid side effects like autoimmunity.

In addition, recent studies suggest that immunotherapies may be useful when given alongside drugs that block blood vessel growth in patients with EGFR/ALK-altered NSCLCs if EGFR/ALK-targeted therapies fail. A refined biomarker that incorporates scoring of PD-L1 on blood vessel endothelial cells may help identify patients most likely to benefit from this type of combination strategy. Adding this combination to our drug repertoire may help patients avoid chemotherapy combinations in patients with EGFR/ALK-altered NSCLCs when targeted therapies fail.

5. Budget

Aim #1 ($5,622)

- Anti-PD-L1 [73-10] Rabbit IgG, Abcam (ab228415) = CAD $715 (50µL) x 2 vials = **$1,430**
- Anti-ERG [EPR3864] Mouse IgG2b (Chimeric), Abcam (ab214341) = CAD **$642** for 100uL
- Shipping antibodies from Abcam to MAPcore = **$50**
- $25 per retrieval from archives x 20 FFPE blocks = **$500**
- $75 staining per slide (MAPcore) x 40 slides including optimization = **$3,000**

Aim #2 ($10,150)

This aim piggybacks on a currently funded project where our co-investigators have already constructed two tissue microarrays and set up a 16-color multiplex immunofluorescence platform to study spatial relationships between tumor and immune cell subpopulations in the MacAulay Lab (funded by a Terry Fox Research Institute grant). Work is underway to correlate cell sociology data with clinical outcomes (funded by a Michael Smith Health Research BC Health Professional-Investigator Award). The budgeted expansion of this project to explore ePDL1 is as follows:

- Lunaphore™ reagents (IF antibodies to CD31 and CD34 as endothelial cell markers) **$5,000**
- Lunaphore™ consumables + technician **$5,000**
- Clinical translation: Anti-PD-L1 [73-10] x Anti-ERG [EPR3864] IHC staining of 2 TMA slides **$150**

Aim #3 ($9,000)

- $25 per retrieval from archives x 90 FFPE blocks = **$2,250**
- $75 staining per slide (MAPcore) x 90 slides including optimization = **$6,750**

TOTAL ($24,772)

6. PIs & co-PIs

(PI; Main Supervisor) Cheryl Ho**,** MD, MSc CCV attached separately
Medical Oncologist, BC Cancer Vancouver
Clinical Assistant Professor of Medicine, University of British Columbia

(Co-PI; Fellow) Florence T.H. Wu, MD/PhD CCV attached separately
PGY6, University of British Columbia Clinician Investigator Program, Vancouver, BC
Post-Doctoral & Clinical Fellow, Princess Margaret Cancer Centre, Toronto, ON

(Co-Investigator) Julia Naso, MD/PhD
Anatomic Pathologist, Vancouver General Hospital
Clinical Assistant Professor, Department of Pathology and Laboratory Medicine, UBC

(Co-Investigator) Spencer D. Martin, MD, PhD
PGY5, Anatomic Pathology, University of British Columbia

(Co-Investigator) John English, MD
Anatomic Pathologist, Vancouver General Hospital & VGH Research Institute
Clinical Professor, Department of Pathology and Laboratory Medicine, UBC

(Co-Investigator) Anna McGuire, MD, MSc
Thoracic Surgeon, Clinician Scientist, Vancouver General Hospital & VGH Research Institute
Clinical Associate Professor of Surgery, University of British Columbia

(Co-Investigator) Calum MacAulay, PhD
Head of Integrative Oncology, Distinguished Scientist, BC Cancer Research Centre
Clinical Associate Professor, Department of Pathology and Laboratory Medicine, UBC

(Co-Investigator) Martial Guillaud, PhD
Senior Scientist, Integrative Oncology, BC Cancer Research Centre
Assistant Professor, Department of Pathology and Laboratory Medicine, UBC
Adjunct Professor, Department of Statistics, UBC

(Co-Investigator) Robert S. Kerbel, PhD
Senior Scientist, Biological Sciences, Odette Cancer Research, Sunnybrook Research Institute
Professor, Medical Biophysics, University of Toronto
Tier 1 Canada Research Chair (2001-2015), Tumor Biology, Angiogenesis & Antiangiogenic Therapy

7. Statement of support from applicant's institution

LETTER #1

Dr. Christian Kollmannsberger, MD, FRCPC
Clinical Professor of Medicine
Head, Department of Medical Oncology
BC Cancer - Vancouver Cancer Centre
Division of Medical Oncology
University of British Columbia

Dr. Stephen K. Chia, MD, FRCPC
Medical Oncologist, BC Cancer Vancouver
Professor of Medicine, University of British Columbia (UBC)
Head, Division of Medical Oncology, UBC
Co-chair, Breast Disease Site, Canadian Cancer Trials Group

LETTER #2

Dr. Sian D. Spacey, MBBS, FRCPC
Clinical Associate Professor, Division of Neurology
Program Director, UBC Clinician Investigator Program
University of British Columbia

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www.med.ubc.ca

September 23, 2024

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

Dear Lung Cancer Canada,

As Division Head, I am providing this letter of support to confirm the feasibility of this outstanding research proposal put forward by Dr. Cheryl Ho as supervising Principal Investigator.

The proposed project is very innovative and highly translational – with the potential to reshape the use of immune checkpoint inhibitors within thoracic oncology and beyond.

The team assembled here includes world-class senior scientists and oncologists crossing multiple disciplines with all the necessary expertise. There is no better team than the one proposed here to carry this project through.

In terms of laboratory infrastructure and personnel support, they collectively have full institutional support from the BC Cancer Vancouver Centre (BCC-VC), the BC Cancer Research Institute (BCCRI), the Vancouver Coastal Health Research Institute (VCHRI), as well as the UBC Department of Pathology & Laboratory Medicine.

All of tissue samples needed for the proposed histological analysis either have already been collected (Aims #1-4) or are being collected (Aim #5), which makes the proposed work realistically completable within the 1-year funding period. The required UBC BC Cancer REB approvals are also already in place (# H22-01017, H18-03744, H18-03295) for the work proposed, and our processes for minor amendments are typically efficiently processed.

The only ingredient missing is the research funding for direct costs as outlined in a very sound budget of $25,000. I hereby strongly recommend Dr. Ho and her team to be considered for the Geoffrey Ogram Memorial Research Grant, as we eagerly await the outcome of their planned studies.

THE UNIVERSITY OF BRITISH COLUMBIA

Faculty of Medicine
The University of British Columbia
317-2194 Health Sciences Mall
Vancouver, BC V6T 1Z3

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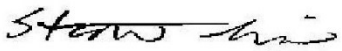
Sincerely,



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Dr. Stephen K. Chia, MD, FRCPC
Medical Oncologist, BC Cancer Vancouver
Professor of Medicine, University of British Columbia (UBC)
Head, Division of Medical Oncology, UBC
Co-chair, Breast Disease Site, Canadian Cancer Trials Group

THE UNIVERSITY OF BRITISH COLUMBIA

Dr. Siân Spacey Inc., MBBS, FRCPC
GENERAL NEUROLOGY AND NEUROGENETICS

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Lung Cancer Canada
133 Richmond St. W., Suite 208
Toronto, ON M5H 2L3
416-785-3439/1-888-445-4403

September 18, 2024

Dear Lung Cancer Canada,

Re: Geoffrey Ogram Memorial Research Grant (GOMRG) 2024 competition

I am writing this letter of support to confirm that Dr. Florence Wu will concurrently be a PGY6 resident enrolled in the UBC Clinician Investigator Program (CIP) as well as a Fellow training at the Princess Margaret Cancer Centre in Toronto throughout the entire Dec 1, 2024 – Nov 30, 2025 funding period of the GOMRG. Over the next 2 years, Dr. Wu has full stipend support from UBC CIP to maintain 80% dedicated research time.

The work proposed here is an extension of a highly innovative and promising project that she has been working on as a PGY4/5 Medical Oncology resident, under the close mentorship of Dr. Cheryl Ho, with strong support from a multidisciplinary team of experts. As such, the UBC CIP is fully supportive of this grant application by Dr. Wu & Dr. Ho to continue this work.

Dr. Wu aspires to become a clinician-scientist and lung cancer specialist. As Program Director, I can vouch for her research potential and exceptional track record in getting projects completed and published. Dr. Wu is highly deserving of consideration for a GOMRG, which would undoubtedly be instrumental in kick-starting her career as lung cancer researcher.

Sincerely,

Dr. Sian D. Spacey, MBBS, FRCPC
Clinical Associate Professor, Division of Neurology
Program Director, UBC Clinician Investigator Program
University of British Columbia