Lung Cancer Preclinical Landscape - DRAFT

Organization Name	Project Leader	Project Title	OniX Summary

DIVISION OF BASIC SCIENCES - NCI	HASSAN, RAFFIT	Immunotherapy for Malignant Mesothelioma and Lung Cancer	**Research Question:**
			• Develop more effective therapies for thoracic cancers (mainly mesothelioma and lung adenocarcinoma).
			Stage:
			• This research involves both in vitro (lab experiments with cells) and in vivo (experiments with animal models) studies.
			Methods:
			• The study focuses on two main therapeutic approaches:
			  ○ Targeting mesothelin, a protein highly expressed on mesothelioma and some lung adenocarcinoma cells. This involves using immunotoxins (toxins linked to antibodies), antibody-drug conjugates (antibodies linked to chemotherapy drugs), and CAR T-cell therapy (genetically engineered immune cells).
			  ○ Immunotherapy with checkpoint inhibitors (drugs that boost the immune system's ability to fight cancer).
			Drug Development:
			The article discusses the development of several drugs targeting mesothelin and the evaluation of their safety and efficacy in clinical trials (studies in patients). It also mentions ongoing research on immunotherapy for lung cancer.
			Key Findings:
			• The article highlights the promise of mesothelin-targeted therapies for mesothelioma and lung adenocarcinoma.
			• It explores the potential of combining immunotoxins with checkpoint inhibitors to improve treatment efficacy.
			• The research also identifies genetic factors that may influence mesothelioma development and treatment response.

MAYO CLINIC JACKSONVILLE	FIELDS, ALAN P.	Therapeutic targeting of Kras-driven Lung Adenocarcinoma	**Research Question:** • Can targeting protein kinase Cι (PKCι) be a therapeutic approach for KRAS-driven lung adenocarcinoma (KRAS LADC)? **Stage:** • This research is primarily in vitro (lab experiments with cells) with some preliminary data from animal models planned.

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			Methods: • The study investigates the role of PKCι in maintaining a cancer stem cell population in KRAS LADC. • Researchers will examine how PKCι activates a protein called ELF3, which then regulates another protein, NOTCH3, potentially important for cancer stem cells. • They will test a newly developed PKCι inhibitor to see if it can reduce cancer stem cell activity in KRAS LADC cells. **Drug Development:** • The research focuses on developing a PKCι inhibitor as a potential treatment for KRAS LADC. **Key Findings (preliminary):** • PKCι seems to play a role in maintaining cancer stem cells in KRAS LADC. • PKCι might activate NOTCH3 through a protein called ELF3. • A new PKCι inhibitor shows promise in reducing cancer stem cell activity in KRAS LADC cells. **Future Work:** • Validate the role of PKCι-ELF3-NOTCH3 signaling in KRAS LADC using animal models. • Evaluate the effectiveness of the PKCι inhibitor in KRAS LADC animal models. • Identify additional targets regulated by PKCι and ELF3.
DANA-FARBER CANCER INST	PAWELETZ, CLOUD PETER	Early change in plasma tumor DNA as a patient and trial-level diagnostic in advanced lung cancer	**Research Question:** • Can changes in circulating tumor DNA (ctDNA) be used as a marker to monitor treatment response in advanced non-small cell lung cancer (NSCLC)? **Stage:** • This research is primarily focused on analyzing existing data from clinical trials (involving patients) but does not mention using animals. **Methods:** • The study will analyze ctDNA levels in blood samples from patients with NSCLC who are starting new treatments.

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			• Researchers will compare ctDNA changes with standard methods for measuring treatment response, such as imaging scans, to identify a reliable ctDNA cut-off point that indicates treatment benefit. • They will also analyze data from multiple clinical trials to see if ctDNA response can predict overall trial outcomes. • Finally, they plan a clinical trial where ctDNA response will be used to guide treatment decisions for patients with NSCLC receiving immunotherapy. **Drug Development:** • This research does not focus on developing new drugs, but on using ctDNA as a tool to improve treatment decisions for existing therapies. **Key Findings (preliminary):** • Early ctDNA changes may be a more sensitive way to monitor treatment response than traditional methods like scans. **Future Work:** • Validate a ctDNA cut-off point for predicting treatment benefit in NSCLC. • Evaluate ctDNA as a tool for clinical trial analysis. • Test the feasibility of using ctDNA to guide treatment decisions in a clinical trial. **Potential Impact:** • This research could lead to a new, non-invasive way to monitor treatment response in lung cancer, potentially allowing for earlier adjustments to treatment plans and improved patient outcomes.
VIRGINIA COMMONWEALTH UNIVERSITY	LITOVCHICK, LARISA	Role of the DREAM complex in the lung tumor suppression	**Research Question:** • Does the DREAM complex, a group of proteins that suppresses cell cycle progression, play a role in preventing lung cancer development? **Stage:** • This research involves both in vitro (experiments with cells) and in vivo studies with a newly developed mouse model. **Methods:** • Researchers will use a mouse model with a mutated Lin52 gene, which disrupts the DREAM complex, to see if these mice are more susceptible to lung cancer development.

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			• They will expose the mice to genotoxic stress (factors that damage DNA) and a specific KRAS mutation, both known risk factors for lung cancer, and see if tumors develop more readily in the mice lacking DREAM function. **Drug Development:** • This research does not focus on developing new drugs, but on understanding the role of the DREAM complex in lung cancer development. **Key Findings (background):** • The DREAM complex suppresses cell cycle progression and DNA repair. • Disrupting DREAM function allows cells to bypass senescence, a protective state that prevents uncontrolled cell growth. • KRAS mutations are common in lung cancer and can drive tumor development. **Future Work:** • Investigate if mice lacking DREAM are more prone to developing lung cancer. • Analyze the mechanisms by which DREAM disruption promotes lung cancer. **Potential Impact:** • This research could provide new insights into the early stages of lung cancer development and identify potential targets for lung cancer prevention strategies.
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	BANDYOPADHYAY, SOURAV	Organoid Acquired Resistance	**Research Question:** • How does non-small cell lung cancer (NSCLC) develop resistance to targeted therapies? **Stage:** • This research is in vitro (experiments with cells) and in vivo (with animals) using patient-derived samples. **Methods:** • The study will use two main approaches: ○ **Organoid cultures:** These are 3D structures grown from patient tumor biopsies or tumor pieces implanted in human immune system-engrafted mice. The researchers will use two types of organoids: epithelial-only and air-liquid interface (ALI) cultures, which also include tumor-associated fibroblasts and immune cells.

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			○ **Proteomics:** This technique analyzes the proteins present in cells or tissues. Researchers will compare protein profiles of treatment-naive, resistant, and residual tumors to identify changes associated with resistance. **Drug Development:** • The goal is not to develop new drugs directly, but to understand how resistance develops to existing targeted therapies for NSCLC. This knowledge may inform the development of new treatment strategies in the future. **Key Findings (background):** • Many targeted therapies for NSCLC eventually lose effectiveness due to acquired resistance. • The reasons for resistance can be due to changes within the tumor itself (tumor-intrinsic) or due to the surrounding tumor microenvironment (TME). • Current research models often lack the complexity of the TME, making it difficult to study its role in resistance. **Future Work:** • Identify genetic mutations that may overcome resistance to targeted therapies (Aim 1). • Analyze protein changes associated with resistance using mass spectrometry (Aim 2). • Investigate the role of specific TME pathways in resistance using ALI organoids (Aim 3). **Potential Impact:** • This research can improve our understanding of how lung cancer develops resistance to treatment and may lead to the development of new therapeutic strategies to overcome resistance.
ROSWELL PARK CANCER INSTITUTE CORP	FANG, JIA	Dissecting the Mechanism of SETDB1 and its K867 Monoubiquitination in Lung Cancer Progression	**Research Question:** • Does a protein called SETDB1 and its specific modification (monoubiquitination) play a role in the progression of KRAS-mutant non-small cell lung cancer (NSCLC)? **Stage:**

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			• This research proposes a combination of in vitro (cell experiments) and in vivo (animal models) studies. **Methods:** • Researchers will investigate the effect of SETDB1 loss on lung cancer cell migration, invasion, and metastasis. • They will use genetically engineered mouse models and xenografts to examine the role of SETDB1 in KRAS-mutant lung cancer progression in vivo. • Additionally, they will explore the mechanism by which monoubiquitination at a specific site (lysine-867) affects SETDB1 activity. **Drug Development:** • The main goal is not to develop new drugs directly, but to identify SETDB1 as a potential target for lung cancer therapy. **Key Findings (background):** • KRAS mutations are common in NSCLC and promote tumor growth and metastasis. • SETDB1 is a protein involved in gene expression regulation and is upregulated in some cancers, including lung cancer. • Preliminary data suggests that SETDB1 loss reduces metastasis in KRAS-mutant lung cancer models. • SETDB1 can be modified by monoubiquitination, which might influence its activity. **Future Work:** • Validate the role of SETDB1 in KRAS-mutant lung cancer progression using animal models. • Understand how monoubiquitination regulates SETDB1 function in lung cancer. **Potential Impact:** • This research could identify SETDB1 as a new therapeutic target for KRAS-mutant lung cancer, a currently difficult-to-treat form of the disease. By understanding how SETDB1 contributes to metastasis, researchers may develop new strategies to prevent lung cancer spread.

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CINCINNATI CHILDRENS HOSP MED CTR	MAEDA, YUTAKA	Patho-Genetic Analysis of Invasive Mucinous Adenocarcinoma of the Lung	**Research Question:** • Can researchers identify new therapeutic targets and biomarkers for invasive mucinous adenocarcinoma of the lung (IMA), a currently untreatable form of lung cancer? **Stage:** • This research will involve a combination of in vitro (cell experiments) and in vivo (animal models) studies, along with analysis of human tissue samples. **Methods:** • The study will focus on the HNF4A pathway, which appears to be important for IMA growth. Researchers will investigate whether targeting this pathway or its downstream genes can be an effective treatment strategy. • They will use single-cell RNA sequencing, a technique that allows analysis of gene expression in individual cells, to explore the molecular heterogeneity of IMA tumors. • Additionally, they will develop 3D tumoroid (organoid) cultures from a large number of IMA samples to study the disease and identify potential targets. • Animal models, including genetically engineered mice and patient-derived xenografts (PDX), will be used to test the effectiveness of potential therapeutic drugs. **Drug Development:** • The main goal is to identify new therapeutic targets for IMA, which could then be used to develop drugs in the future. **Key Findings (background):** • IMA is a difficult-to-treat lung cancer with no effective therapies currently available. • The HNF4A pathway seems to play a role in IMA development. • IMA can be difficult to distinguish from some other cancers due to its similar appearance under a microscope (histology). **Future Work:** • Evaluate HNF4A and related genes as potential drug targets for IMA (Aim 1). • Analyze the molecular makeup of IMA tumors at the single-cell level (Aim 2). • Identify biomarkers that can help diagnose IMA (Aim 3).

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			• Test potential therapeutic drugs in animal models (not mentioned in the specific aims but implied based on the overall approach). **Potential Impact:** • This research could lead to the development of new therapies for IMA, a currently untreatable lung cancer. By identifying unique molecular features of IMA, researchers may also develop more accurate diagnostic tools for the disease.
GIGAMUNE, INC.	SPINDLER, MATTHEW JAMES	Engineered TCR-T Cell Therapy Targeting Driver Mutations in NSCLC	**Research Question:** • Can T cells engineered with receptors specific to lung cancer driver mutations (like KRAS, EGFR) be used as a therapy for non-small cell lung cancer (NSCLC)? **Stage:** • This is an early-stage project (Phase I SBIR) that focuses on developing tools and not directly testing a therapy in patients (in silico or in vitro). **Methods:** • Researchers will use a microfluidic technology to create a large library of natural human T cell receptors (TCRs) that specifically target mutated proteins from common driver genes in NSCLC. **Drug Development:** • This research proposes a foundation for developing TCR-T cell therapy, a type of immunotherapy where T cells are engineered to recognize and attack cancer cells. • This project focuses on creating the tools to identify TCRs, and future studies would involve testing these TCRs in animal models and eventually clinical trials. **Key Findings (background):** • Existing CAR-T cell therapy has been successful for some blood cancers but not yet for most solid tumors. • Driver mutations in genes like KRAS and EGFR are common in NSCLC and could be good targets for immunotherapy. • These mutations can create unique proteins (neoantigens) that the immune system can potentially recognize and attack.

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			Future Work: • Build a library of TCRs that target NSCLC driver mutations. • Validate and select the most promising TCR candidates for further development. • (In later stages not covered by this proposal) Test TCR-T cells in animal models and potentially clinical trials. **Potential Impact:** • This research could lay the groundwork for a new type of immunotherapy for NSCLC by targeting cancer driver mutations. TCR-T cell therapy holds promise for overcoming some of the limitations of current lung cancer treatments.
Tottori University	Takashi Ohno	Relationship between Maspin expression status and clinicopathological factors in lung adenocarcinoma	**Research Question:** • Is there a correlation between maspin expression levels and clinicopathological factors, including invasion diameter, in lung adenocarcinoma? • Can maspin expression be used as a prognostic marker for lung adenocarcinoma patients? **Stage:** • This research will likely involve analyzing data from existing patient samples (in silico or retrospective analysis), but the abstract doesn't explicitly mention using cell lines or animal models (in vitro or in vivo). **Methods:** • Researchers will likely examine maspin expression levels in lung adenocarcinoma tissues and compare them with various clinicopathological factors, including the diameter of the tumor invasion. • Statistical analysis will be used to determine if a relationship exists between maspin expression and prognosis (patient outcome). **Drug Development:** • This research is not focused on developing new drugs. **Key Findings (background): • Maspin is a tumor suppressor gene, and its loss is associated with poor prognosis in lung cancer.

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			• Cytoplasmic maspin localization is linked to worse outcomes in lung cancer patients. • The size of tumor invasion is a recently recognized prognostic factor in lung cancer. • There is a lack of research on the combined impact of maspin expression and invasion size on lung cancer prognosis. **Future Work:** • Analyze maspin expression in lung adenocarcinoma tissue samples. • Evaluate the correlation between maspin levels, invasion diameter, and patient outcomes. • Determine if maspin can be a useful prognostic marker for lung adenocarcinoma. **Potential Impact:** • This study could improve our understanding of how maspin and tumor invasion size influence lung cancer prognosis. If maspin proves to be a reliable prognostic marker, it could inform treatment decisions and patient care.
Kyushu University	Katsuya Nakamura	Development of a new lung cancer therapy targeting a MAML3-Hh/NOTCH signaling pathway	**Research Question:** • Can targeting the MAML3 protein, which enhances both Hh and NOTCH signaling pathways, be a novel therapeutic strategy for non-small cell lung cancer (NSCLC)? **Stage:** • This is likely an in vitro (cell experiments) or in silico (computer modeling) study based on the proposal to examine the possibility of a new treatment. **Methods:** • Researchers will likely build on their previous findings on the role of MAML3 in small cell lung cancer (SCLC) and investigate its function in NSCLC. • They may use cell lines or computer models to test how inhibiting MAML3 affects lung cancer cell behavior. **Drug Development:** • The main goal is to identify MAML3 as a potential therapeutic target for lung cancer. This knowledge could be used to develop new drugs in the future.

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			Key Findings (background): • The Hh and NOTCH signaling pathways are important for development and can be abnormally activated in cancer. • Researchers previously identified MAML3 as a protein involved in enhancing SMO (Hh pathway) activity in SCLC. • Low-oxygen environments (hypoxia) common in tumors can further increase SMO activity. **Future Work:** • Investigate the role of MAML3 in the Hh/NOTCH pathways of NSCLC. • Evaluate the potential of MAML3 as a therapeutic target for NSCLC. **Potential Impact:** • This research could lead to the development of new drugs targeting MAML3 for the treatment of both SCLC and NSCLC. By inhibiting both Hh and NOTCH signaling pathways simultaneously, this approach could be more effective than targeting each pathway alone.