Colorectal Cancer Preclinical Landscape - DRAFT

Organization Name	Project Leader	Project Title	OniX Summary
DIVISION OF BASIC SCIENCES - NCI	GONZALEZ, FRANK J	Xenobiotic metabolism, cancer chemoprevention and cancer biomarkers	**1. Withaferin A for Nonalcoholic Steatohepatitis (NASH)** • **Research Question:** To investigate the effects of Withaferin A (WA) on NASH. • **Stage:** In vivo (animal models) using methionine-choline-deficient diet and high-fat diet. • **Methods:** Administered WA or control vehicle to assess effects on liver injury. • **Drug Development:** Investigates WA as a potential therapeutic option for NASH. **2. Rutaecarpine for Inflammatory Bowel Disease (IBD)** • **Research Question:** To explore the mechanism by which Rutaecarpine (RUT) improves IBD. • **Stage:** In vivo (animal models) using DSS-induced colitis and cell-based studies. • **Methods:** Investigated the effect of RUT on colonic inflammation, NRF2 signaling, and antioxidant response. • **Drug Development:** Suggests RUT as a potential therapeutic option for IBD patients. **3. Sex Steroid Hormones and CYP2D Regulation** • **Research Question:** To determine the role of sex steroid hormones in regulating CYP2D, a drug-metabolizing enzyme. • **Stage:** In vivo (animal models) using female mice across estrous cycle stages and ovariectomy models. • **Methods:** Evaluated Cyp2d22 expression based on estrous cycle, sex, and hormone supplementation. • **Drug Development:** Not directly related to drug development, but provides insights into CYP2D regulation which is important for drug metabolism.

RLR VA MEDICAL CENTER	FRANCIS, HEATHER L	BLR&D Research Career Scientist Award	• **Research Question:**
			  ○ Identify biomarkers for Primary Sclerosing Cholangitis (PSC) and Cholangiocarcinoma (CCA).
			  ○ Develop novel therapies to alleviate PSC symptoms and offer curative options without transplantation.

Organization Name	Project Leader	Project Title	OniX Summary
			○ Understand the transition of PSC to CCA and signaling mechanisms involved. • **Stage:** Not directly mentioned (likely in vitro and/or in vivo studies planned). • **Methods:** Not explicitly stated (proposal focuses on outlining research goals). • **Drug Development:** Proposes development of novel therapies for PSC.
STATE UNIVERSITY OF NEW YORK AT BUFFALO	EGILMEZ, NEJAT K	Oral Immune Modulatory Adjuvants for Treatment of Colorectal Carcinoma	• **Research Question:** ○ Evaluate the effectiveness of oral immune-modulatory therapies for colorectal cancer (CRC) treatment. ○ Compare two strategies: a) promoting Treg cell generation and b) suppressing pro-inflammatory T cells and mast cells. • **Stage:** In vivo (animal models using APCMin/+ mice). • **Methods:** ○ Administering oral sustained-release formulations containing: ▪ TGF-β and all-trans retinoic acid (ATRA) to promote Treg cells (Aim 1). ▪ Anti-IL-9 antibody and Masitinib to suppress pro-inflammatory cells (Aim 2). ○ Evaluate effectiveness in reducing or eliminating established polyps and adenocarcinomas. • **Drug Development:** Develops and tests novel oral therapies for CRC.
ST. JUDE CHILDREN'S RESEARCH HOSPITAL	KANNEGANTI, THIRUMALA-DEVI	NLR signaling in intestinal inflammation	• **Research Question:** ○ Investigate the role of Nod-like receptors (NLRs) and their adaptor proteins in the development of intestinal inflammation and colon cancer. ○ Identify specific NLR family members that mediate pro-inflammatory responses and protect against colitis. • **Stage:** Not directly mentioned (likely in vitro and/or in vivo studies planned based on preliminary data). • **Methods:** Not explicitly stated (proposal focuses on outlining research goals).

Organization Name	Project Leader	Project Title	OniX Summary
			• **Drug Development:** Not directly proposing drug development, but research may provide insights for future therapeutic targets.

WILKES UNIVERSITY	GUTIERREZ, LINDA S	Thrombospondin in ulceractive colitis and carcinogenesis	• **Research Question:**
			  ○ Investigate the role of thrombospondin-1 (TSP1) in intestinal inflammation and colitis-related colon cancer.
			  ○ Identify specific molecular targets of TSP1 and its effects on cell signaling pathways.
			  ○ Evaluate the therapeutic potential of TSP1 peptides for treating IBD.
			• **Stage:** In vivo (animal models using DSS-induced colitis).
			• **Methods:**
			  ○ Analyze gene expression associated with TSP1 in colitis.
			  ○ Identify molecular targets of TSP1 in intestinal inflammation.
			  ○ Evaluate the effects of TSP1 on pathways related to colitis-associated carcinogenesis.
			  ○ Test the therapeutic effects of specific TSP1 peptides on inflammation, proliferation, apoptosis, and angiogenesis.
			• **Drug Development:** Proposes development of TSP1 peptides as a novel therapy for IBD.

DIVISION OF BASIC SCIENCES - NCI	SCHLOM, JEFFREY	Human Immune Responses to Tumor Antigens for Cancer Immunotherapy	• **Research Question:** Evaluate the immune response and clinical benefit of NHS-IL12, an immunocytokine, in patients with metastatic solid tumors.
			• **Stage:** Clinical Trial (Phase I)
			• **Methods:**
			  ○ Administered NHS-IL12 subcutaneously to patients at varying doses and schedules.
			  ○ Analyzed immune cell subsets, serum analytes, and complete blood counts before and after treatment.
			  ○ Evaluated response based on changes in immune markers and clinical outcome.
			• **Drug Development:** Investigates NHS-IL12 as a potential immunotherapy for metastatic solid tumors.
			Summary of Research Proposal 2: Bintrafusp Alfa for HPV-Associated Malignancies

Organization Name	Project Leader	Project Title	OniX Summary

			• **Research Question:**
			  ○ Identify immune profile characteristics associated with response to bintrafusp alfa, a novel immunotherapy for HPV-associated malignancies.
			  ○ Investigate the mechanism of action of bintrafusp alfa.
			• **Stage:** Clinical Trial (not specified - Phase I/II)
			• **Methods:** Analyzed peripheral immune cells, soluble factors, and HPV-specific T cell responses before and during bintrafusp alfa treatment.
			• **Drug Development:** Not directly proposing drug development, but research may provide insights for optimizing bintrafusp alfa therapy.

OHIO STATE UNIVERSITY	CLINTON, STEVEN K	Project 04: Molecular Carcinogenesis and Chemoprevention (MCC)	• **Research Question:** Broadly focused on understanding the causes and prevention of cancer.
			• **Stage:** Includes in vitro, in vivo (animal models), and human clinical trials.
			• **Methods:**
			  ○ Studies the genetic, molecular, and cellular changes that lead to cancer development (Carcinogenesis).
			  ○ Develops and tests new agents for preventing cancer (Chemoprevention).
			  ○ Investigates the role of diet, nutrition, and lifestyle in cancer risk.
			• **Drug Development:** Develops and characterizes novel cancer chemopreventive agents.
			• **Public Health Relevance:** Aims to reduce cancer incidence, mortality, and morbidity through public policy and dietary interventions.
			Additional Notes:
			• The program is highly collaborative and multi-disciplinary.
			• They have a strong track record of publications and clinical trial participation.
			• Their future research focus includes metabolic signatures, the microbiome-immunity interface, and collaborations with cancer engineering efforts.

UNIV OF NORTH	SERODY, JONATHAN S.	Immunology Research Program	• **Research Question:** Focuses on the immune system's role in cancer and improving cancer immunotherapy.

Organization Name	Project Leader	Project Title	OniX Summary

CAROLINA CHAPEL HILL			• **Stage:** Includes in vitro and in vivo (animal models) studies, with a focus on translation to clinical trials.
			• **Methods:**
			  ○ Investigates the role of innate immune receptors and the microbiome in cancer (Aim 1).
			  ○ Studies immune cells and pathways within the tumor microenvironment (Aim 2).
			  ○ Develops novel immunotherapies for cancer treatment (Aim 3).
			  ○ Identifies targets to improve outcomes for patients undergoing stem cell transplantation (Aim 4).
			• **Drug Development:** Develops CAR T-cell therapies targeting novel antigens on cancer cells.
			• **Public Health Relevance:** Aims to improve cancer immunotherapy through a better understanding of the immune system and the tumor microenvironment.
			Additional Notes:
			• The program is highly collaborative and includes researchers from various departments.
			• They have a strong track record of publications and are actively translating research into clinical trials (e.g., CAR T-cell therapy).
			• Their future research focus includes the microbiome's impact on immunity and further development of CAR T-cell therapies.

SINAI HEALTH SYSTEM	SILVERBERG, MARK S.	Genomic and Immunologic Characterization of Inflammatory Bowel Disease and its Phenotypes	• **Research Question:**
			  ○ Investigate the functional impact of genetic variations associated with inflammatory bowel disease (IBD).
			  ○ Understand the pathophysiology of:
			  ▪ Acute severe ulcerative colitis.
			  ▪ Perianal Crohn's disease.
			  ▪ Persistent inflammation and relapse in ulcerative colitis.
			  ▪ Treatment-resistant Crohn's disease.
			  ○ Identify cellular and microbial factors contributing to IBD and its complications.

Organization Name	Project Leader	Project Title	OniX Summary

			• **Stage:** In vitro and potentially in vivo studies using biospecimens from a large, well-characterized IBD patient registry.
			• **Methods:**
			  ○ Analyze genetic variations in non-European ancestry IBD populations.
			  ○ Integrate advanced techniques like imaging mass cytometry, spatial transcriptomics, scRNA-seq, and microbiome analysis on tissue samples.
			• **Drug Development:** Not directly proposing drug development, but research may provide insights for future therapeutic targets.
			• **Public Health Relevance:** Aims to improve understanding of IBD pathophysiology and develop tools for better clinical outcomes.

Gunma University	Yuta Shibasaki	Establishment of Innovative Therapeutic Strategies for Refractory Colorectal Cancer Focusing on Amino Acid Transporters	• **Research Question:**
			  ○ Investigate the role of L-type amino acid transporter 1 (LAT1) in:
			  ▪ The effectiveness of anticancer drugs.
			  ▪ Immunotherapy response.
			  ▪ The tumor microenvironment of colorectal cancer.
			• **Stage:** Not explicitly stated (likely in vitro and/or in vivo studies planned).
			• **Methods:**
			  ○ Analyze the effects of LAT1 expression on cancer cells.
			• **Drug Development:** Not directly proposing drug development, but research may provide insights for improving existing therapies and developing new therapeutic targets.
			• **Public Health Relevance:** Aims to improve treatment outcomes for colorectal cancer by understanding the role of LAT1 in drug resistance and tumor microenvironment.

Hiroshima University	Shintaro Akabane	The role of KIFC1 in 5-FU resistance of colorectal cancer	• **Research Question:** Investigate the role of Kinesin Family Member C1 (KIFC1) in 5-FU resistance of colorectal cancer. • **Stage:** Not explicitly stated (likely in vitro studies with potential for in vivo studies). • **Methods:** Analyze the mechanism by which KIFC1 contributes to 5-FU resistance.

Organization Name	Project Leader	Project Title	OniX Summary
			• **Drug Development:** Proposes KIFC1 inhibitors as a strategy to overcome 5-FU resistance in colorectal cancer. • **Public Health Relevance:** Aims to improve the effectiveness of 5-FU treatment for colorectal cancer by overcoming drug resistance.