Crohn's Disease Preclinical Landscape - DRAFT

Organization Name	Project Leader	Project Title	OniX Summary
KEYBIOME LLC	POHL ROBINSON, CATHERINE	Aim protein-based anti-inflammatory therapeutic for the treatment of IBD	**Research Question:** Can AimA, a protein from zebrafish gut bacteria, be a therapeutic for Inflammatory Bowel Disease (IBD)? **Stage:** In vivo (using animals) - This project will use a mouse model of IBD. **Methods:** • Evaluate AimA's effectiveness in reducing inflammation and neutrophil levels in the colon. • Assess AimA's ability to modulate the gut microbiome, potentially reducing harmful bacteria. **Drug Development:** This project aims to establish AimA as a potential future treatment for IBD. It targets both inflammation and microbiome dysbiosis, offering a potential advantage over current therapies.
RISE THERAPEUTICS, LLC	FANGER, GARY	A Novel Immunological-Directed Live Biotherapy Product for Treating Ulcerative Colitis	**Research Question:** Can a genetically modified Lactococcus lactis strain expressing SlpA protein be a safe and effective oral treatment for IBD? **Stage:** Moving towards human studies (in vitro and animal studies likely already conducted). This project proposes a Phase 1 clinical trial. **Methods:** • Develop a manufacturing process for capsules containing the engineered L. lactis strain. • Conduct a Phase 1 clinical trial to assess safety and potential effectiveness in humans with IBD. • Analyze patient samples to evaluate the drug's impact on inflammation and gut health. **Drug Development:** This project focuses on a specific strain of L. lactis engineered to produce SlpA, a protein with anti-inflammatory properties. The engineered bacteria target the gut immune system and potentially restore a healthy microbiome composition. This approach offers a potential new therapy with a good safety profile due to L. lactis' history of use in humans.
UNIVERSITY OF UTAH	ROUND, JUNE LOUISE	Bacteriophage pathobiology of	**Research Question:** Do bacteriophages (viruses infecting bacteria) produced by adherent invasive E. coli (AIEC) contribute to Inflammatory Bowel Disease (IBD) pathogenesis?

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		inflammatory bowel disease	**Stage:** In vitro and potentially early animal studies (based on existence of a wound infection model). **Methods:** • Investigate how inflammation triggers phage replication in the gut. • Analyze how broadly phages are recognized by the immune system. • Develop and test an anti-phage vaccine strategy for IBD treatment. **Drug Development:** This project explores a new approach to IBD treatment by targeting phages instead of bacteria directly. By understanding how AIEC-produced phages influence the immune response, researchers aim to develop a vaccine against these phages. This could potentially offer a novel therapeutic strategy for IBD.
RISE THERAPEUTICS, LLC	FANGER, GARY	A Novel Immunological Probiotic for Treating Inflammatory Bowel Disease	**Research Question:** Can a genetically modified Lactobacillus acidophilus strain expressing SlpA protein be a safe and effective oral probiotic treatment for IBD? **Stage:** In vivo with animals (likely building on successful Phase I study). **Methods:** • Optimize the manufacturing process for the engineered L. acidophilus strain. • Conduct animal studies to determine the optimal dose and evaluate potential biomarkers for efficacy. • Perform toxicology studies following Good Laboratory Practice (GLP) guidelines. **Drug Development:** This project focuses on developing a new probiotic strain of L. acidophilus engineered to produce SlpA, similar to the research on L. lactis. This SlpA-expressing bacteria targets the gut immune system and potentially restores a healthy microbiome composition. This Phase II study aims to optimize the product and prepare for future clinical trials in humans.
YALE UNIVERSITY	ROULIS, MANOLIS	Generation and characterization of a	**Research Question:** Can researchers develop a humanized mouse model that accurately reflects Crohn's Disease (CD) pathology? **Stage:** In vivo with animals (using innovative engineering techniques).

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		humanized mouse model of Crohn's disease	**Methods:** • Combine a genetic mouse model mimicking CD with a humanized mouse model (MISTRG6) to create a human immune system within the CD-like mouse. • Optimize the immune system transfer and functionality in the humanized mice. • Analyze the development of CD-like symptoms and immune responses in the humanized mice. **Drug Development:** This project focuses on creating a new research tool: a humanized mouse model specifically designed for Crohn's Disease. This model will allow researchers to study the human immune system's role in CD and potentially test new therapeutic targets more effectively than with traditional mouse models. It represents a significant advancement in pre-clinical CD research.
RISE THERAPEUTICS, LLC	FANGER, GARY	A Novel Immunological Probiotic for Treating Inflammatory Bowel Disease	**Research Question:** Can a genetically modified Lactococcus lactis strain expressing SlpA protein be a safe and effective probiotic for long-term maintenance therapy in IBD? **Stage:** In vivo with animals (likely building on successful in vitro work). **Methods:** • Develop L. lactis strains that stably express SlpA protein. • Select the best candidate strain based on SlpA production, growth characteristics, and functionality. • Test the selected strain's effectiveness in a mouse model of T-cell induced colitis. **Drug Development:** This project explores a similar concept to the previous L. lactis research, but focuses on developing this approach for long-term maintenance therapy in IBD. The SlpA-expressing L. lactis aims to regulate gut immune responses and promote a healthy microbiome for sustained control of inflammation. This study emphasizes safety and functionality for long-term use.

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CASE WESTERN RESERVE UNIVERSITY	HO, WON JIN	Exploring 15-hydroxyprostaglandin dehydrogenase as a molecular target for treating inflammatory bowel diseases	**Research Question:** Can inhibiting 15-hydroxyprostaglandin dehydrogenase (15-PGDH) be a new and effective treatment for Inflammatory Bowel Disease (IBD)? **Stage:** In vivo with animals **Methods:** • Use a newly developed inhibitor (SW033291) to block 15-PGDH in a mouse model of ulcerative colitis. • Analyze the effects of this inhibition on disease severity and colonic cell health. • Investigate the potential impact on IBD-associated colon cancer risk. **Drug Development:** This project proposes a novel drug target: 15-PGDH, an enzyme that breaks down PGE2, a molecule important for gut health. By inhibiting 15-PGDH, researchers aim to increase PGE2 levels and promote healing in the colon. The project will assess the effectiveness and safety of this approach in a mouse model, laying the groundwork for future studies in humans.
UNIVERSITY OF MICHIGAN AT ANN ARBOR	BISHU, SHRINIVAS	CD4+ Tissue resident memory T-cells in Crohnâ??s Disease	**Research Question:** Do tissue-resident memory T-cells (TRM) play a role in Crohn's Disease (CD) and can they be targeted for new therapies? **Stage:** In vivo with animals (and potentially some human tissue analysis) **Methods:** • Investigate how a molecule called PRDM1 regulates TRM in CD and its potential as a therapeutic target. • Analyze the role of IL-15 in promoting inflammation caused by TRM. • Use humanized mice with gut bacteria from CD patients and healthy controls to see if CD bacteria specifically induce pathogenic TRM. **Drug Development:** This research focuses on understanding a specific type of immune cell, TRM, and its potential role in CD. The project investigates how these cells are regulated and how they might be influenced by gut bacteria. By understanding TRM function, researchers may be able to develop new therapies targeting these cells or the factors that control them.

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NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	STROBER, WARREN	Clinical Studies of Inflammatory Bowel Diseases	**Research Question:** • Can LRRK2 inhibitors be a new treatment for IBD regardless of a patient's LRRK2 risk polymorphism? • Is Vorinostat, an HDAC inhibitor, safe and effective for treating Crohn's disease? **Stage:** • In vivo with animals (for LRRK2) • Clinical trial (Phase I) for Vorinostat **Methods:** • LRRK2: Study how LRRK2 inhibitors reduce inflammation in a colitis model. • Vorinostat: Evaluate the safety and immunological effects of Vorinostat in patients with Crohn's disease who haven't responded to other therapies. Monitor changes in regulatory T cells and disease activity. **Drug Development:** • LRRK2: This research suggests LRRK2 inhibitors may be a potential future treatment for IBD, but more studies are needed. • Vorinostat: Early results from one patient showed some improvement in symptoms, but further studies with a larger group are necessary to determine effectiveness.
PANORAMA RESEARCH, INC.	WRIGHT, SUSAN C	Novel Anti-inflammmatory Antibody Therapy for Inflammatory Bowel Disease	**Research Question:** Can a human monoclonal antibody that neutralizes melanin-concentrating hormone (MCH) be a new and effective treatment for Inflammatory Bowel Disease (IBD)? **Stage:** In vitro and in vivo with animals (Phase I project) **Methods:** • Develop and characterize a human monoclonal antibody that neutralizes MCH. • Evaluate the antibody's effectiveness in reducing inflammation and fibrosis using cell cultures and animal models of colitis. **Drug Development:**

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			This project focuses on a new biologic therapy targeting MCH, a molecule potentially involved in IBD inflammation. Researchers will develop a human antibody that neutralizes MCH and assess its ability to reduce inflammation and fibrosis in cell and animal models. If successful, this approach could lead to a new treatment for IBD with fewer side effects compared to existing medications.
CEDARS-SINAI MEDICAL CENTER	RABIZADEH, SHERVIN	Role of Innate Immunity and Stat3 Activation in Colitis Mouse Model	**Research Question:** How do innate immune system pathways (NOD/Rip2 and TLR/MyD88) contribute to ETBF-induced colitis and Stat3 activation? **Stage:** In vivo with animals **Methods:** • Use genetically modified mice lacking MyD88 or Rip2 to assess their susceptibility to ETBF-induced colitis and Stat3 activation. • Analyze the role of Stat3 in the development of colitis in these mice. • Employ bone marrow transplantation to differentiate between the roles of immune cells vs. other cell types in Stat3 activation during ETBF colitis. **Drug Development:** This research focuses on understanding the role of the innate immune system in IBD. By investigating how specific pathways are involved in ETBF-induced colitis, researchers may gain insights into potential therapeutic targets for IBD treatment. The project utilizes animal models and immunological assays to explore these mechanisms.
Kansai Medical University	Yusuke Motozawa	Development of treatment for intestinal stricture in Crohn's disease intestinal using the collagen-specific molecular chaperone HSP47	**Research Question:** 1. Can Heat Shock Protein 47 (HSP47) be a therapeutic target to control intestinal fibrosis in Crohn's Disease (CD)? 2. How do inflammatory cytokines and the immune system influence HSP47 and fibrosis development? **Stage:** In vitro and in vivo with animals **Methods:** • Analyze how inflammatory cytokines (IL-1β, IL-18, IL-10, and IL-13) affect HSP47 and collagen production in human cells.

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			• Investigate the role of inflammasomes in IL-1β production in CD patients with a Mediterranean fever (MEFV) gene mutation. • Compare cytokine profiles and fibrosis in intestinal tissues from CD and ulcerative colitis (UC) patients. • Analyze the effects of IL-10 knockout in mice on intestinal inflammation and fibrosis. **Drug Development:** This research explores the mechanisms of intestinal fibrosis, a complication in CD that can lead to surgery. The project focuses on HSP47, a protein involved in collagen production, and how it's influenced by inflammatory signals. By understanding these mechanisms, researchers hope to develop new treatments to control fibrosis and potentially avoid surgery for CD patients.
The Tazuke Kofukai Medical Research Institute	Kento Yamamoto	Clinical Impact of the FGFR Gene on the Sensitivity to Novel Molecularly Targeted Therapeutics in Colorectal Cancer	**Research Question:** Can the expression level ratio (F/E) of Fibroblast Growth Factor Receptor (FGFR) gene to Epidermal Growth Factor Receptor (EGFR) gene be used as a biomarker to predict the effectiveness of FGFR inhibitor drugs in treating colorectal cancer? **Stage:** In vitro with potential future clinical application **Methods:** • Analyze the correlation between F/E and FGFR inhibitor sensitivity in colorectal cancer cell lines. • Measure F/E in resected colorectal cancer tissue samples and circulating tumor DNA (ctDNA) in blood. **Drug Development:** This project investigates a potential biomarker for colorectal cancer. By establishing a link between the F/E ratio and response to FGFR inhibitors, researchers hope to enable more personalized treatment decisions for patients. The current stage focuses on cell line studies, but future studies may involve human tissue and blood samples.