Obesity Preclinical Landscape - DRAFT

Organization Name	Project Leader	Project Title	OniX Summary
NATIONAL INSTITUTE ON AGING	GREIG, NIGEL H.	Neuroprotective role of GLP-1 receptor agonists	**Research question:** • Can drugs targeting the GLP-1 receptor be used to treat neurodegenerative diseases like Alzheimer's disease (AD) and Parkinson's disease (PD)? **Stage:** • In vitro and in vivo (animal models) **Methods:** • Studying how GLP-1 receptor agonists affect neurons in cell cultures. • Testing the effects of GLP-1 receptor agonists in animal models of neurodegenerative diseases. • Examining existing drugs that target the GLP-1 receptor (like Exendin-4) for potential use in treating neurodegenerative diseases. • Designing new drugs that target the GLP-1 receptor or related pathways. **Drug development:** • This research directly aims to develop new drugs for treating neurodegenerative diseases by targeting the GLP-1 receptor or related pathways.
UNIVERSITY OF PITTSBURGH AT PITTSBURGH	KHOO, NICHOLAS	Targeting Uric Acid as a Therapeutic for NASH	**Research question:** • Does uric acid (UA), a byproduct of purine breakdown, play a key role in the development of non-alcoholic steatohepatitis (NASH), a serious form of non-alcoholic fatty liver disease (NAFLD)? **Stage:** • In vivo (animal models) **Methods:** • Feeding mice a high-fat, high-fructose, and high-cholesterol diet (to mimic a fast-food diet) and see if it causes hyperuricemia (high blood levels of uric acid) and promotes NASH development. • Testing if lowering uric acid levels protects against NASH development in mice on a high-fat diet. • Comparing two drugs: febuxostat (targets the enzyme that produces uric acid) and nitro-oleic acid (has multiple targets). **Drug development:**

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			• This research aims to identify new therapeutic targets for treating NASH. It investigates whether lowering uric acid levels with febuxostat or using a multi-target drug like nitro-oleic acid could be effective treatments for NASH.
AUGUSTA UNIVERSITY	BELIN DE CHANTE MELE, ERIC J	Leptin in HIV associated vascular diseases	**Research question:** • How does HIV infection and antiretroviral therapy (cART) affect the risk of cardiovascular disease (CVD) in HIV patients, considering the observed paradox of increased adiposity (fat gain) not leading to higher CVD risk? **Stage:** • In vitro and in vivo (animal models) with some human tissue data **Methods:** • Using animal models of HIV infection and lipoatrophy (fat loss), researchers will investigate the role of leptin signaling and oxidative stress in endothelial dysfunction (a risk factor for CVD). • They will examine the effects of leptin treatment and drugs that target oxidative stress on blood vessel function. • They will compare the effects of HIV infection and cART on body weight, adiposity, and vascular health. **Drug development:** • This research doesn't directly aim to develop new drugs, but rather to understand the mechanisms behind CVD risk in HIV patients. This knowledge could be used to identify new drug targets in the future.
UNIVERSITY OF COLORADO DENVER	CREE, MELANIE G	Impact of GLP-1 on Hepatic Fat and Energy Utilization in Obese Girls with Polycystic Ovarian Syndrome	**Research question:** • Can treatment with a glucagon-like peptide-1 receptor agonist (GLP-1 RA) improve liver function and metabolism in obese adolescent girls with polycystic ovary syndrome (PCOS), independent of weight loss? **Stage:** • In vivo (clinical trial with adolescent girls) **Methods:** • A randomized clinical trial will be conducted with obese adolescent girls with PCOS. • Participants will be divided into two groups: one receiving intensive dietary counseling and the other receiving a GLP-1 RA medication (exenatide) for 16 weeks.

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			• Researchers will measure changes in liver fat content, as well as how the liver processes glucose and fatty acids. • Special techniques will be used to track how the body is making fat and using energy in the liver. **Drug development:** • This research directly tests the effectiveness of a GLP-1 RA drug (exenatide) for treating liver problems in adolescent girls with PCOS. If successful, it could provide a new treatment option for this population.
AUGUSTA UNIVERSITY	BELIN DE CHANTE MELE, ERIC J	Leptin in HIV associated vascular diseases	**Research question:** • How does HIV infection and antiretroviral therapy (cART) affect the risk of cardiovascular disease (CVD) in HIV patients, considering the observed paradox of increased adiposity (fat gain) not leading to higher CVD risk? **Stage:** • In vitro and in vivo (animal models) with some human tissue data **Methods:** • Using animal models of HIV infection and lipoatrophy (fat loss), researchers will investigate the role of leptin signaling and oxidative stress in endothelial dysfunction (a risk factor for CVD). • They will examine the effects of leptin treatment and drugs that target oxidative stress on blood vessel function. • They will compare the effects of HIV infection and cART on body weight, adiposity, and vascular health. **Drug development:** • This research doesn't directly aim to develop new drugs, but rather to understand the mechanisms behind CVD risk in HIV patients. This knowledge could be used to identify new drug targets in the future.
UNIVERSITY OF MICHIGAN AT ANN ARBOR	LIN, JIANDIE D	Metabolic crosstalk through brown fat-enriched	**Research question:** • Do brown fat cells secrete factors that regulate whole body glucose and lipid metabolism, and can these factors be harnessed to treat metabolic syndrome? **Stage:** • In vivo (animal models) **Methods:**

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		secreted factors	• Researchers have identified a specific factor secreted by brown fat cells that appears to regulate metabolism. • They will use genetically modified mice to study how this factor affects whole body metabolism in different conditions (cold exposure, high-fat diet). • They will investigate the mechanisms by which this factor works. **Drug development:** • This research aims to understand how brown fat cells communicate with other tissues to regulate metabolism. If successful, it could lay the groundwork for future development of drugs that target brown fat to treat metabolic syndrome.
UT SOUTHWESTERN MEDICAL CENTER	GUPTA, RANA K	Establishment and Maintenance of Healthy Adipose Tissue in Obesity	**Research question:** • Why does fat tissue expansion in some obese people lead to metabolic problems (insulin resistance, type 2 diabetes) while others are spared these complications? **Stage:** • In vivo (animal models) **Methods:** • Researchers will study the process of fat cell formation (adipogenesis) in different fat depots of mice. • They will focus on a specific signaling pathway involving a protein called HIF alpha (HIFa) that might suppress adipogenesis and promote unhealthy fat tissue remodeling. • By understanding how this pathway functions, they hope to identify potential drug targets. **Drug development:** • This research aims to understand the mechanisms that control how fat tissue expands in different areas of the body. If successful, it could lead to new therapeutic strategies to prevent the development of metabolic problems associated with obesity.
UNIVERSITY OF VIRGINIA	LEITINGER, NORBERT	Pannexin 1 channels in diet-induced metabolic syndrome	**Research question:** • Does a channel protein called pannexin-1 (Panx1) in liver cells play a role in the progression of non-alcoholic fatty liver disease (NAFLD) to fibrosis? **Stage:** • In vivo (animal models) **Methods:**

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			• Researchers will use mice with modified Panx1 genes to see how it affects the development of NAFLD and fibrosis in a high-fat, high-fructose diet model. • They will also investigate if blocking Panx1 function with a liver-specific antisense oligonucleotide (ASO) protects against fibrosis. • Experiments will be conducted to understand how Panx1 might influence both liver cells and scar-forming cells (hepatic stellate cells). **Drug development:** • This research directly aims to develop a new therapeutic approach to combat NAFLD and fibrosis by targeting the Panx1 channel. They will test an ASO therapy specifically designed to block Panx1 in the liver.
MAINEHEALTH	BROWN, AARON CLIFFORD	miR-27 mediated regulation of mitochondrial function in thermogenic adipocytes	**Research question:** • How do microRNAs (miRNAs), specifically miR-27a/b, regulate the function of beige fat cells (beige adipocytes) that burn calories to generate heat? **Stage:** • In vitro (human induced pluripotent stem cells) **Methods:** • Researchers will use human induced pluripotent stem cells (iPSCs) to differentiate and activate beige fat cells. • They will investigate how miR-27a/b affects mitochondrial function in these cells, including protein levels involved in mitochondrial biogenesis and removal (mitophagy). • They will also examine how miR-27a/b levels influence beige fat cell response to cold temperature (which activates thermogenesis) and a high-fat diet. **Drug development:** • This research focuses on understanding how miRNAs regulate beige fat cell function. While not directly developing a drug, these findings could inform future development of therapies to increase beige fat activity and combat obesity.
JAMES A. HALEY VA MEDICAL CENTER	PATEL, NIKETA A.	Adipose stem cells' niche in obesity	**Research question:** • How does a long non-coding RNA (lncRNA) called GAS5 influence the development of obesity and related health problems? **Stage:** • In vitro (human cells) and in vivo (mice) **Methods:**

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			• Researchers will investigate how GAS5 levels affect the function of human fat stem cells (ASC) and mature fat cells (adipocytes) derived from obese and lean individuals. • They will use techniques to manipulate GAS5 levels (increase or decrease) and measure how it affects fat cell metabolism and insulin signaling. • A small molecule drug designed to stabilize GAS5 levels will be tested in obese mice to see if it can improve metabolic health. **Drug development:** • This research directly aims to develop a new drug therapy for obesity by targeting a specific lncRNA (GAS5). The project involves testing a small molecule drug that stabilizes GAS5 levels and improves metabolic function in fat cells.
UNIV OF MASSACHUSETTS MED SCH WORCESTER	GUERTIN, DAVID A	Quantitative and functional analysis of brown fat nutrient fluxes in vivo and its role in organ metabolite exchange	**Research question:** • How does brown adipose tissue (BAT) use glucose and other fuels to generate heat and what are the implications for developing therapies to treat obesity and metabolic syndrome? **Stage:** • In vivo (animals) **Methods:** • Researchers will use advanced techniques involving mass spectrometry and tracers to track how brown fat uses glucose and other metabolites for energy production (thermogenesis) in living animals. • They will investigate how diet, environment, and genetics influence brown fat metabolism. • They will also focus on a specific pathway recently identified in active brown fat. **Drug development:** • This research focuses on understanding how brown fat metabolism works, which is a critical step towards developing therapies to activate brown fat for treatment of obesity and metabolic syndrome. While not directly developing a drug, these findings could inform future development of drugs that target brown fat metabolism.
VA GREATER LOS ANGELES HEALTHCARE SYSTEM	JACOBS, JONATHAN PATRICK	Modulation of the Intestinal Microbiome	**Research question:** • Does a high protein diet work against obesity by changing the gut microbiome, and if so, can these changes be harnessed to develop new treatments? **Stage:**

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		in Obesity by a High Protein Diet	• In vivo (humans and mice) **Methods:** • Researchers will conduct a randomized clinical trial with veterans who are overweight or obese. Participants will be assigned to either a high protein or normal protein diet for 16 weeks. • They will analyze the gut microbiome composition and function in participants throughout the study using various techniques. • They will also investigate how the gut microbiome changes relate to weight loss, body fat, and other health markers. • In a separate experiment, germ-free mice will be colonized with gut microbes from human participants to see if the high protein diet-induced microbiome changes influence weight gain and metabolism. **Drug development:** • This research aims to understand how a high protein diet affects the gut microbiome and whether these changes contribute to its effectiveness for weight loss. By identifying specific microbes or their products that promote fat loss, this study could lead to the development of novel therapies based on gut microbiota manipulation.
TEXAS BIOMEDICAL RESEARCH INSTITUTE	ROSS, CORINNA NICOLE	Microbiome-mediated therapies for aging and healthspan in marmosets	**Research question:** • How does the gut microbiome change with age, and can fecal transplants from younger animals improve health and lifespan in elderly animals? **Stage:** • In vivo (animals) **Methods:** • Researchers will study the gut microbiome of marmoset monkeys as they age to see if it loses diversity. • They will then perform fecal transplants from young marmosets to old marmosets to see if it improves the health and lifespan of the older animals. **Drug development:** • This research explores the connection between gut microbiome, aging, and health. While not directly developing a drug, fecal transplants could be a potential therapy if the study shows they can improve healthspan in marmosets.

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UNIVERSITY OF FLORIDA	ZHAO, JINYING	Gut microbiome, aging and cardiometabolic diseases in American Indians	**Research question:** • How does the gut microbiome differ between American Indians and other populations, and how is it linked to aging and cardiometabolic diseases (CMDs) such as obesity and diabetes? **Stage:** • In vivo (humans) **Methods:** • Researchers will analyze gut microbiomes of American Indian participants in a large, ongoing health study. They will compare the gut microbiome composition of participants with and without CMDs and with different ages. • They will also investigate how various factors including age, genetics, diet, and lifestyle influence the gut microbiome in this population. **Drug development:** • This research aims to understand how the gut microbiome might influence aging and CMDs in American Indians. While not directly developing a drug in this stage, the findings could inform future development of therapies targeting the gut microbiome to improve health and lifespan.
UT SOUTHWESTERN MEDICAL CENTER	GUPTA, RANA K	Establishment and Maintenance of Healthy Adipose Tissue in Obesity	**Research question:** • How does a signaling pathway involving a protein called HIF alpha (HIFa) influence the development of fat tissue in different areas of the body, and can targeting this pathway promote healthy fat expansion and prevent metabolic problems in obesity? **Stage:** • In vivo (animals) **Methods:** • Researchers will investigate the role of HIFa signaling in fat tissue remodeling during obesity. • They will focus on a specific cell population within fat tissue (perivascular PDGFRb+ cells) that can give rise to new fat cells. • They will examine how HIFa signaling affects a protein called PPARg, which is important for fat cell development (adipogenesis). **Drug development:**

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			• This research focuses on understanding how a specific signaling pathway controls fat cell development in different areas of the body. By understanding this pathway, they hope to develop new therapeutic strategies to promote healthy fat tissue expansion and prevent metabolic problems associated with obesity.
YALE UNIVERSITY	JASTREBOFF, ANIA	GLP-1 analogue effects on food cues, stress, motivation for highly palatable foods, and weight	**Research question:** • Can a medication called semaglutide (GLP-1a) reduce cravings, hunger, and food intake in people with obesity, and can it help them lose weight? **Stage:** • In vivo (humans) **Methods:** • Researchers will conduct a randomized, double-blind, placebo-controlled clinical trial with 96 participants who are obese. • Participants will receive either semaglutide or a placebo for 12 weeks. • Researchers will assess food cravings, hunger, and food intake in a laboratory setting and in a real-world setting. • They will also measure metabolic markers and stress hormones. **Drug development:** • This research directly tests the effectiveness of a specific drug (semaglutide) for reducing food intake and promoting weight loss in people with obesity.
UNIVERSITY OF CALIFORNIA, SAN DIEGO	YING, WEI	Mechanisms by which hepatocyte extracellular miRNAs mediate peripheral insulin sensitivity	**Research question:** • How do tiny sacs released by the liver (extracellular vesicles containing microRNAs) influence insulin resistance in obesity, and can specific microRNAs within these sacs be harnessed to develop new treatments for diabetes? **Stage:** • In vivo (animals) **Methods:** • Researchers will investigate how microRNAs contained within liver-derived extracellular vesicles affect insulin sensitivity and function of insulin-producing beta cells in obese mice. • They will explore the mechanisms by which specific microRNAs (e.g., miR-3075-5p) promote insulin sensitivity and others (e.g., miR-434-3p) worsen it. **Drug development:**

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			• This research aims to understand how microRNAs shuttled in liver-derived sacs communicate with other cells and influence insulin sensitivity. By identifying specific microRNAs that improve insulin response, they aim to develop them into potential therapies for treating insulin resistance and pre-diabetes in obese patients. This project focuses on understanding the mechanisms but proposes miR-3075-5p as a potential drug target for future development.
UNIVERSITY OF VIRGINIA	LEITINGER, NORBERT	Pannexin 1 channels in diet-induced metabolic syndrome	**Research question:** • Does a channel protein called Panx1 in liver cells play a role in the development of fatty liver disease (NAFLD) and liver fibrosis, and can blocking this channel be a new therapeutic approach for NAFLD? **Stage:** • In vivo (animals) **Methods:** • Researchers will investigate the function of Panx1 in liver cells of mice fed a high-fat diet. • They will compare mice with normal Panx1 function to mice with genetically modified Panx1 and see how it affects the development of fatty liver disease and fibrosis. • They will also explore how Panx1 might influence scar-forming cells (stellate cells) and liver cell metabolism. **Drug development:** • This research focuses on a specific protein (Panx1) in liver cells and its role in NAFLD progression. By demonstrating that blocking Panx1 protects against liver damage in mice, they propose this as a potential new therapeutic strategy for NAFLD. This project is focused on understanding the mechanisms but suggests Panx1 as a potential drug target for future development.