Metabolic Disease and Microbiome Research at the University of Chicago

April 2017

POLSKY Center for Entrepreneurship and Innovation
THE UNIVERSITY OF CHICAGO

Metabolic Disease and Microbiome

Available Technologies

Available Technologies

Cohen UCHI 2290
Modulation Target, Laminin α4, for the Treatment of Metabolic Diseases

- 600 Million adults are obese worldwide. Obesity leads to rising diabetes, and may be the source of 10% of the healthcare costs in the US.
- The laboratories of Dr. Ron Cohen and Dr. Eric Brey have discovered that an extra cellular protein of adipose tissue may be a powerful, novel target for altering the behavior of white fat cells.
- By modulating this novel target, Laminin α4, the white fat may potentially be induced to behave like brown fat and increase calorie expenditure.
- The team has shown that knockout mice do not gain weight even when on a high fat diet. Additionally, wildtype white fat cells grown on a scaffold with modified Laminin demonstrate characteristics of brown fat cells.
- A PCT patent application is pending.
- We are seeking partners to develop compounds targeting this Laminin α4 or to optimize compounds in development by the team in Chicago.

Alverdy UCHI 2630
Prevention of Anastomotic Leak

- Despite new surgical techniques, expert surgeons still experience anastomotic leaks, one of the most feared post-surgical complications for intestinal surgery.
- Dr. John Alverdy and his team have discovered that opportunistic commensal gut microbes cause anastomatic leaks, but providing certain polyphosphate-containing molecules suppress the microbes' pathogenicity within the gut to prevent anastomatic leaks.
- This therapy would be administered prior to gastrointestinal or esophageal surgery and at the site of anastomosis to prevent leaks.
- In a rat model of anastomotic leak, this therapy suppressed pathogenicity and significantly diminished the rate and severity of anastomotic leakage even in the presence of grossly inadequate surgical technique.
- A US patent application and a provisional patent application are both pending on formulations and methods of treating anastomatic leaks.
- Dr. Alverdy and the University of Chicago are seeking commercial partners to move this technology to the clinic.

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Nagler UCHI 2608
Prevention and treatment of salmonella and other enteric diseases in humans and livestock

- Food contamination is estimated to be a $50B problem in the US alone with Salmonella being one of the main culprits.
- People and discovery: The laboratories of Dr. Gabriel Nunez and Dr. Cathy Nagler have shown in a recent publication in Science that certain commensal species of *Clostridia* inhibit various enteric pathogens including Salmonella.
- By delivering controlled amounts of this beneficial strain to livestock, the Salmonella load may be reduced heading into food processing facilities. Additionally, a formulation could be developed for aiding with human recovery from infection.
- Using multiple mouse models, the investigators found that intragastric administration of Clostridia enhanced resistance to Salmonella infection in mice with competent immune systems as well as those with impaired immune systems.
- IP: A provisional patent application is pending.
- Next steps: We are seeking partners to develop preventative products for livestock as well as partners for developing human therapies.

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Research Programs

Metabolic Disease: Adipocyte Biology

Adipocytes in Diabetes

Dr. Cohen's research explores the relationship between diabetes and adipocyte -- a complex endocrine cell that regulates feeding behavior and insulin sensitivity. Through his research findings, Dr. Cohen is working to develop novel therapies for the treatment of obesity and type 2 diabetes.

A skilled endocrinologist, Ronald Cohen, MD, specializes in the diagnosis and management of thyroid diseases with a particular focus on thyroid cancer. He also has a clinical interest in diabetes, obesity and metabolic disorders

Pollutants and Adipocytes

Dr. Sargis' laboratory is focused on understanding the mechanisms by which certain chemical pollutants (environmental endocrine disrupting chemicals or EDCs) modulate adipocyte physiology in order to understand how synthetic chemicals hijack human metabolism and predispose us to the development of various metabolic diseases.

His recent work has shown the capacity of various EDCs to induce adipocytic insulin resistance, potentially through augmentation of glucocorticoid signaling. They are currently focused on characterizing the molecular mechanisms by which these EDCs modulate insulin signal transduction to specifically understand how these chemicals deleteriously influence adipocyte metabolism and to more broadly appreciate how adipose tissue senses cues from the environment to regulate energy metabolism.

His hope is that these studies will also serve as the foundation for sound public policy to mitigate the impact of environmental pollution on human metabolic health.

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Metabolic Disease: Genetics

Insulin Gene Mutations

Dr. Bell's research focuses on the genetics of diabetes mellitus. Ongoing studies in his laboratory include the genetics of type 2 diabetes in the Mexican American population of Starr County, Texas ; the effect of mutations in the insulin gene on insulin biosynthesis and pancreatic beta-cell function; and the identification of modifiers of proteostasis in a novel Drosophila system expressing a mutant human insulin (INSC96Y) in different tissues.

Monogenetic Diabetes

For more than 25 years, Dr. Philipson has tirelessly explored the biophysical, molecular and genetic aspects of insulin secretion, and the genetics of diabetes. He and his colleagues discovered rare insulin gene mutations that produce beta cell ER stress and, in turn, cause neonatal diabetes. In addition, Dr. Philipson and his colleagues are among the nation's leading experts on monogenic diabetes, following more than 100 patients diagnosed with neonatal diabetes and many others with maturity onset diabetes of the young (MODY) type diabetes.

Gene Regulation and Glucose

Dr. Nobrega's group is interested in dissecting the architecture and function of genes and their regulatory networks. They investigate how the multiple transcriptional enhancers, repressors, and boundary elements connected to a gene interact and orchestrate the precise tissue-specific and temporal-specific expression pattern of that gene. They have shown how alterations in TCF7L2 expression play a role as a key regulator of glucose metabolism.

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Metabolic Disease: Sleep

Sleep Loss and Obesity

Dr. Pannain's clinical and research interests include obesity, metabolic syndrome and related health conditions, such as obstructive sleep apnea and diabetes. She investigates the metabolic and endocrine aspects of chronic partial sleep loss, which is generally considered a risk factor for obesity and insulin resistance. Additionally, she is studying the effects of gastric bypass surgery on metabolism, sleep and hunger.

Circadian Behavior and Insulin Sensitivity

Dr. Brady has a long standing interest in studying adipocyte biology and insulin sensitivity. His lab is primarily focused on two transdisciplinary projects.

The first project explores the impact of altered sleep quality and circadian behavior on cellular and systemic insulin sensitivity in humans. Additionally, the impact of bariatric surgery on circadian behavior and insulin action in fat cells is being examined.

The second project is elucidating the role of chronic social isolation on mammary adipose tissue biology and the progression of triple negative breast cancer in mice in collaboration with researchers from oncology.

Metabolic Disease: Pancreatic Function

Autoimmune Diabetes

Dr. Alex Chervonsky is interested in organ-specific diseases such as autoimmune diabetes. Our studies focus on determining how T cells are initially activated in disease pathogenesis, how they home to the target organs, and how they destroy these organs.

Using a mouse model for autoimmune diabetes, we have started a new project to investigate the involvement of innate Toll-like receptors (TLRs) in autoimmunity. TLRs are involved in responses to infection with pathogens, but also maybe involved in the activation of non-infectious immunity. These studies will help to solve the longstanding riddle of how infection with pathogens is connected to autoimmunity.

Islet Isolation and Transplantation

Dr. Witkowski was instrumental in developing an optimized islet isolation technique that greatly improved success in clinical transplants. Under Dr. Witkowski's leadership, multidisciplinary research teams at the University of Chicago are conducting studies designed to improve quality and outcomes in islet cell transplantation in patients with type 1 diabetes.

Beta Cell Lineages

Dr. Horb's lab is focused on identifying the signaling networks leading to the specification of the various pancreas lineages. In particular they seek to define the lineage map of how each individual cell type is specified. They recently completed a microarray analysis identifying downstream targets of the pancreatic endocrine transcription factor Ngn3 and showed that it is possible to promote specific endocrine lineages over others. Specifically they showed that short activation of Ngn3 is sufficient to promote beta and delta cell lineages over alpha cell lineages. They have now identified several factors specific to one lineage over another and are now examining their function.

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Microbiome: Microbiome and Human Disease

Intestinal Microbes

Dr. Eugene Chang's group studies the factors involved in the selection and assembly of intestinal microbes and how to reshape the enteric microbiome to prevent and treat disease. They focus on the study of host-microbe interactions in human and mammalian systems and the bidirectional signaling processes that mediate these interactions. They employ cutting edge approaches that include cultivation-dependent and –independent technologies for microbial analysis, genetic and gnotobiotic mouse models, metabolic and functional measurements, and bioinformatic tools to investigate the host and the microbiome to address these questions.

Inflammatory Bowel Disease

Dr. David Rubin performs clinical research related to outcomes in inflammatory bowel diseases, with particular interest in prevention of cancer associated with these diseases. He is also interested in new therapies for inflammatory bowel diseases, better screening tools for colorectal cancer, and the genetics of inflammatory bowel diseases.

Environmental Regulation of Virulence

The Alverdy lab seeks to better understand the regulation of virulence expression among potential pathogens through investigating the characteristics of the microbial context, molecular machinery that senses that context, and ultimately the lethal combinations of virulence expression that leads to disease. They've focused on the sense and response virulence mechanisms of Pseudomonas aeruginosa, a well characterized and clinically important pathogen, and shown a remarkable potential for this organisms to respond to host environmental cues related to stress, ischemia, immune activation and nutrient depletion. With this core model of environmental regulation of virulence expression, they are pursuing applications in intestinal transplantation, anastomotic and radiation physiology, necrotizing enterocolitis and ischemia/reperfusion injury. He has developed several anti-infective polymer-based compounds that can attenuate the virulence of several multi-drug resistant pathogens that cause life threatening infections in surgical patients.

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Microbiome: Environment and Allergies

Food Allergy

Dr. Nagler and her group are exploring how immune cells in the intestinal mucosa distinguish innocuous dietary antigens and trillions of commensal bacteria from pathogenic microbes and mount an appropriate response to each. They are pursuing several different, but complementary, lines of research aimed at examining the mechanisms regulating non-responsiveness to these stimuli in healthy individuals and its abrogation in food allergy. Their murine disease models will provide the pre-clinical basis for future translational studies aimed ultimately at the development of novel immunotherapeutic modalities.

Microbial Communities

Dr. Sogin investigates the diversity and evolution of single-cell organisms and produced the reference framework for understanding the evolution of microbial eukaryotes. His group pioneered the first use of next generation DNA sequencing to characterize complex microbial communities which led to discovery of the rare biosphere.

Microbial Ecosystem

Dr. Jack Gilbert's lab is focused on the ecology, evolution and metabolic dynamics of microbial ecosystems. Leveraging next-generation sensor technology, they are creating networked grids of automated microbial detection platforms to capture microbial ecosystem dynamics in air- and water-based environments. These cloud system enabled sensor arrays to provide real-time feedback on how environmental changes affect microbial processes to create built environments considering microbial ecology, and improve the health and productivity of these environments. This is enabling a revolution in forensic techniques that leverage the unique microbial fingerprint of every individual to track their movement and activity in built ecosystems.

Marine Ecosystems

Dr. David Mark Welch investigates patterns of microbial diversity in marine ecosystems and the human body, to monitor changes that reveal ecosystem health and the limits of environmental resiliency.

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Microbiome: Clinical Research

Preterm Infants

Dr. Erika Claud specializes in neonatology, providing care to critically ill infants. She has an interest in the diagnosis and treatment of preterm infants and conditions of the immature digestive tract. Dr. Claud's research focuses on intestinal epithelial biology as it relates to neonatal necrotizing enterocolitis (NEC), a life-threatening inflammatory bowel disorder of unknown cause that afflicts premature infants.

Inflammatory Bowel Diseases

Dr. Stacy Kahn specializes in the evaluation and treatment of digestive diseases in children and adolescents. She has a particular interest in inflammatory bowel diseases (IBD) including Crohn's disease and ulcerative colitis. Dr. Kahn's research focuses on new treatments for Crohn's disease and ulcerative colitis. Specifically she is studying microbiome-based therapies for inflammatory bowel disease, as well as the important ethical issues associated with this innovative treatment. Her other research interests include the underlying causes of IBD, novel diagnostic tools in IBD, and clinical and research ethics.

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Startup Companies

Gusto Global

Microbiome drug discovery and development company focusing on next generation immune-modulation therapies.

Technology: Proprietary supercomputing bioinformatics and predictive modelling platform, informs Gusto's lead program development. Lead programs include the development of multi-strain synthetic consortia for targeted indications.

JACK GILBERT
Founding Scientific Advisor
Faculty Director, The Microbiome Center
Professor, Department of Surgery
University of Chicago

Co-Founders: John Fennebresque, Jr., Daniel van der Lelie, Safiyh Taghavi, Mark Spizer

Strategic Advisors: John Alverdy (University Chicago), Christopher Henry (ANL), Nikos Kyrpides (JGI)

More Information:
John Fennebresque
Co-Founder and CEO
jfennebresque@gustoglobal.com

Non-Confidential Deck

Business Model:
Develop and enable differentiated therapeutics with our leading Gust+ development technology platform. Our mission is to create differentiated, innovative products by applying our platform technologies to novel live biotherapeutic medicines in collaboration with pharmaceutical and biotechnology companies and to our own proprietary product candidates.

Stage: Pilot project with leading, global pharmaceutical company. Series A capital raise.

IP: Licensed IP for food allergy and surgical site infection indications through UCGo program. Other company provisionals filed.

Next Steps: Management and support team build-out; making key hires within the first 3 to 6 months, including an immunologist; filing for patent protection around foundational concepts for synthetic community engineering and performance optimization.

BACK

CLOSTRABIO

ClostraBio has participated in many Polsky and affiliated programs:

- iCorps; Collaboratorium; Polsky Exchange
- Innovation Fund, New Venture Challenge
- Chicago Innovation Mentors (sponsored by Polsky);
- Polsky Exchange Mentors; PROPEL (through iBIO)

Developing therapeutics for life-threatening food allergies

Technology: Novel, synthetic pharmaceuticals have been identified to prevent and treat life-threatening food allergies. This drug candidate, to be taken orally, replicates the function of certain gut bacteria that have been shown to prevent or reduce allergic reactions to food. In early dosing studies, the drug reduces the presence of the proteins and antibodies responsible for allergic reaction by 80-90%. The drug candidates are screened in a humanized mouse developed specifically to identify therapeutics for food allergy and elucidate their mechanism of action. The model gives greater insight into allergic sensitivity, leading to better treatments.

Cathryn Nagler, PhD
President
Co-founder

Jeffrey Hubbell, PhD
Co-founder
Member of the Board

Bruce Hamaker, PhD
Co-founder

John Colson, PhD,
Director of Operations

More Information:
john.w.colson@clostrabio.com
www.clostrabio.com

Markets/Business Model: We are a research intensive pharmaceutical company actively seeking partners for clinical development. Initial target indications are peanut and cow's milk allergy, the two most prevalent food allergies. We aim to expand to treat all of the roughly 15 million Americans with food allergies. Our drugs may also have therapeutic benefits in IBD and this therapeutic area will be explored in later development.

Stage: Preclinical discovery and optimization. The first drug candidate has been dosed In animal models and completely prevents physical symptoms of an allergic reaction to peanuts. Dose optimization and comparisons of monotherapy to existing treatments are ongoing. Cow's milk allergy will follow in 3-4 months. Have completed seed round of funding for these studies.

IP: The University of Chicago has filed provisional application for compositions of matter and methods to treat human disease. ClostraBio has an option to license this patent.

Next Steps: Complete financing of $1-1.5M for preclinical efficacy and mechanism studies. Follow on financing of $9M to complete preclinical safety/toxicology studies for Phase 1 clinical trials, complete the executive team, and identify / secure development partner. A subsequent financing of $15-20M is expected to launch Phase 1 trials and expand the pipeline

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AVnovum

AVnovum is participating in Polsky's Innovation Fund

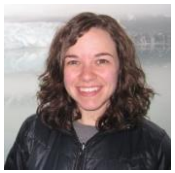
Preventing Fungal Disease

Technology: Novel, highly specific peptides have been designed to target the virulent form of fungi. These peptides are based on a naturally occurring peptide which has been shown to maintain fungal commensalism by deterring virulence. Unlike other anti-fungal and antibiotic agents, these peptides can be used prophylactically to prevent fungal disease in high-risk patients.

Gene Chang
Scientific Lead

Myles Minter
Business Lead

Joe Pierre
Post-doc



Katie Harris
Post-doc

For More Information Contact:
mminter@uchicago.edu

Markets/Business Model: Fungal infection and dysbiosis especially affects patients who are immunocompromised or diabetic. There are over 5M immunocompromised individuals in the US and 30M with diabetes.

Stage: Preclinical. The naturally occurring peptide has been shown to inhibit yeast infection in mouse models and to prevent expression of virulence factors through *in vitro* tests.

IP: A provisional patent application is being prepared through the university.

Next Steps: High throughput screen of additional compounds and selection of leads for *in vivo* validation. Initiate discussions with potential future investors and development partners.

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UChicago: Kovler Diabetes Center

Lou Philipson, MD, PhD

Director of Kovler Diabetes Center & Professor of Medicine

Leading authority on difficult to treat and monogenic diabetes. Regular consultant and advisor to companies. Principle Investigator on more than 10 clinical trials. Co-director of the Human Islet Transplantation project.

New state-of-the-art clinical and research center

Graeme Bell, PhD

Louis Block Distinguished Professor of Medicine & Human Genetics

World leader in genetics and regulation of glucose metabolism. Director of the University of Chicago Diabetes Research and Training Center.

THE UNIVERSITY OF CHICAGO MEDICINE
Kovler Diabetes Center

- > 100 years of advancing diabetes research
- >120 scientists and clinicians
- Multidisciplinary teams conducting early discovery and clinical studies
- Leading monogenic diabetes registry

SMAHC
SLEEP • METABOLISM AND HEALTH CENTER

THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

THE UNIVERSITY OF CHICAGO
DIABETES RESEARCH AND TRAINING CENTER

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UChicago Microbiome Center

the microbiome center
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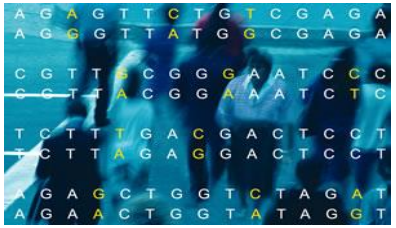
Unique Research Facilities:

- Gnotobiotic Core animal facilities
- True microorganism-free conditions
- One of select few facilities in the US

Computational & Analytical Expertise:



- State-of-the-art high-throughput sequencing and genotyping facilities
- Big data management

Clinical Expertise:

- New state-of-the-art clinical and research center
- Performed fecal/microbiota transplant in youngest patient to date

THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

Argonne NATIONAL LABORATORY

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UChicago: Select Microbiome Projects

Earth Microbiome Project:
- Led by Jack Gilbert
- Analyze 200,000 samples
- Reconstruct 500,000 microbial genomes
- Generate global Gene Atlas

http://www.earthmicrobiome.org/

Hospital Microbiome Project:
- Led by Jack Gilbert, John Alverdy, other
- Analyze microbial samples from surfaces, air, staff, and patients from the UC new hospital
- Characterize bacterial population development in healthcare setting

http://hospitalmicrobiome.com/

Home Microbiome Project:
- Led by Jack Gilbert
- Sponsored by Alfred P. Sloan Foundation
- Analyze microbial samples from human environment
- Completed analysis of microbial diversity of cell phones and shoes

http://www.homemicrobiome.com/

How to Partner with the University of Chicago

Contact the Polsky Center for Entrepreneurship and Innovation Technology Commercialization and Licensing team and speak to anyone on the project management team.

Matthew Martin, PhD
Assistant Director
Phone: 773-234-5515
mmartin@tech.uchicago.edu

Subscribe to our University of Chicago Technology Commercialization team newsletter here.