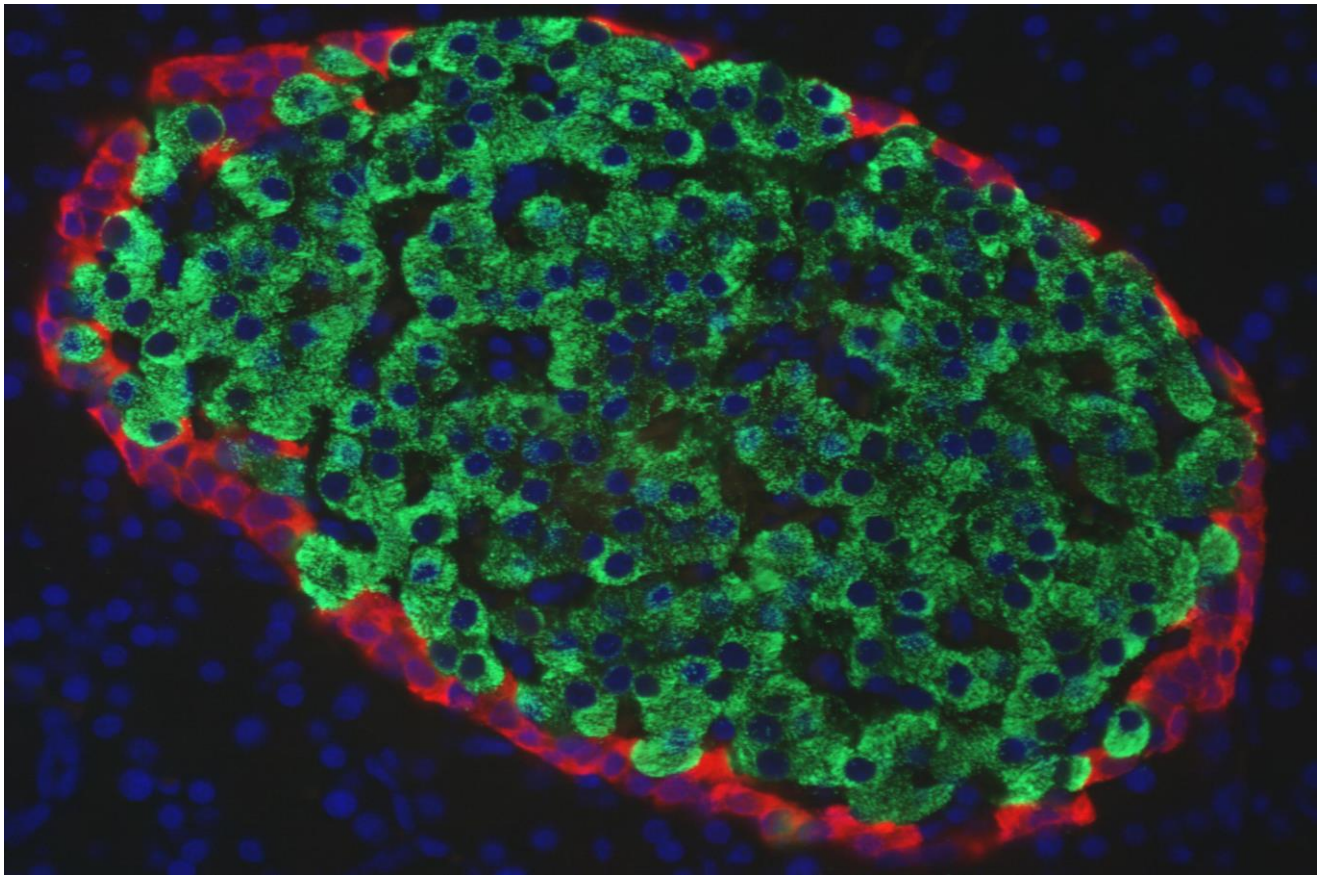
White Paper—2016 Workshop

Organized by the Connecticut Center for Metabolic Disease Research (CCMDR) and the Weizmann Institute of Science

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WORKSHOP OVERVIEW

A research workshop dedicated to metabolic disease research, with a specific emphasis on diabetes (T1D and T2D) and obesity, was held at The University of Connecticut, Department for Cell and Genome Sciences in Farmington, Connecticut, on April 11-12, 2016. The event was co-sponsored by The Jackson Laboratory (JAX), Yale University and the University of Connecticut (UConn) and included scientists from the Weizmann Institute of Science. This was the third annual workshop held for the purpose of sharing research advances on the study of metabolic disease among speakers with a diverse range of expertise. Researchers from the Weizmann Institute contributed not only to the larger scientific discussion, but also provided insight into the formation of the Center for Metabolism and Metabolic Disorders within their own institution. This workshop represents the continued dedication of researchers in Connecticut and in Israel to the goals of the CCMDR, which are to form a multi-institutional collaborative effort to foster innovation and research breakthroughs in the area of metabolic diseases with an emphasis on T1D, T2D and obesity research. Creation of the CCMDR is spearheaded by Dr. Milton Wallack, Founder of the Connecticut Stem Cell Coalition and former President of the New Haven chapter of the Juvenile Diabetes Research Foundation (JDRF). Joining his efforts are key biomedical leaders from Connecticut's premier research institutions, including Dr. Kevan Herold and Dr. Robert Sherwin of Yale University, Dr. Marc Lalande from UConn and Dr. Charles Lee from JAX-GM. In addition to the research participants and administrative leaders from the aforementioned institutions, CT State Representative Lonnie Reed, co-chair of the bipartisan life sciences caucus, stressed that CT legislators are committed to supporting the life sciences.

SCOPE OF PROBLEM AND STATEMENT OF INTENT

The need for a better understanding of the mechanisms that drive obesity and diabetes has never been more apparent. Changes in average body mass index (BMI) calculations, from 1975 to 2014 in 200 countries across the globe, were recently compiled by the NCD Risk Factor Collaboration and published in the *Lancet*. The authors calculated a steady increase in the average global BMI in both women and

men, from approximately 21.9 kg/m^2 in 1975 to 24.3 kg/m^2 in 2014[1]. The prevalence of obesity increased from 3.2% in 1975 to 10.8% in 2014 in men, and from 6.4% to 14.9% in women. Further, the authors conclude that if the post-2000 trend in BMI increases continue, the probability of meeting the global obesity target—stagnation at 2010 levels by 2025—is virtually zero. Since high BMI is an important risk factor for diabetes, it stands to reason that the globe will experience similar increases in diabetes diagnoses in adults, in line with current trends.

Even more troubling is the increased rate of obesity rate in children. In the US, 33% of children between the ages of 2 and 19 are overweight and 17% or obese, according to data analyzed from the NHANES study[2]. Importantly, these data suggest that over 4.5 million U.S. children and adolescents have severe obesity[2]. The substantial contribution of severe childhood obesity to the prevalence of diabetes and the costly burden of severe obesity in adults emphasizes the urgency with which we must develop programs to understand and address severe obesity in children and adolescents.

The prevalence of diabetes in Connecticut has remained relatively stable over the last three years—9.3% in 2013[3] and 8.9% in 2016[4]—with an estimated 83,000 diabetics remaining undiagnosed[4]. Predictions suggest >930,000 adults in Connecticut have pre-diabetes, a health condition that predisposes individuals to T2D, heart disease and stroke[5]. The direct (health care) and indirect (disability, premature mortality) costs of diabetes-related care in Connecticut are estimated at $2.92 billion[5]. Not surprisingly, concurrent increases in obesity, a major risk factor for developing T2D, have also been observed, with nearly two-thirds of Connecticut' s adult population being overweight or obese[5].

These numbers reflect similar trends occurring at the national level. In the U.S., approximately 29.1 million adults (9.3% of total population) suffer from diabetes—of which 90-95% have T2D and ~5% have T1D—and more than one-third are classified as obese[6,7]. As of 2014, one in nine US health care dollars is spent on diabetes, with total 2014 expenditures reaching US $612 billion[8]. The health care costs of

obesity were recently shown to be responsible today for nearly 21% of total health care spending in the US[9]; even by more conservative estimates, total health care costs of obesity are projected to reach 16-18% by 2030[10]. Combining these estimates, it is clear that the US is on track to exceed the trillion-dollar mark for diabetes and obesity-related costs in the near future.

Similar progressions are being observed globally. Diabetes incidence is growing rapidly in other countries, including India, China, Mexico, Brazil, the United Kingdom and across the Middle East. Recent reports suggest that, worldwide, ~387 million adults have diabetes, and by 2035 over half a billion people will suffer from both diabetes and obesity[9]. Health systems in many of the low- and middle-income countries seeing these increases in incidence are often not designed to cope with the challenges of chronic disease[11,12]; thus, the risk for economic challenges and even collapse due to both direct and indirect costs of diabetes and obesity are high.

Metabolic diseases such as diabetes and obesity have clearly reached epidemic proportions, yet national and global responses to this public health crisis have been insufficient, with relatively few advances being made towards disease prevention, treatment or cure despite the many billions of federal, foundational and biotech/pharmaceutical dollars being spent to understand diabetes and identify new therapeutic strategies. As such, suffering from these diseases continues to grow exponentially, placing tremendous burdens on health care systems and society as a whole. There is thus an urgent need for new approaches to address these issues.

The primary objective of the CCMDR is to fill a research void that exists in the area of metabolic diseases—specifically, the relative paucity of coherent and unified partnerships among biomedical institutions, especially those with multidisciplinary capabilities aimed at direct clinical impact. The CCMDR is attempting to mobilize a unique array of world-class researchers working in Connecticut and abroad and blend their efforts into a focused endeavor to solve problems pertaining to diabetes and

obesity. The CCMDR is hoping to partner with the Weizmann Institute and harness their expertise in metabolic research, as well as their experience in developing the Center for Metabolism and Metabolic Disorders (CMMD) of the Weizmann Institute. Like the CMMD, the CCMDR will promote innovative opportunities in terms of translational science and entrepreneurship. This will entail a novel approach, coordinating both existing and new expertise across four major research areas—cell biology, immunology, genetics and genomics, and the microbiome—together with expertise in metabolism, computational biology and bioinformatics. The combined clinical and scientific resources at Yale, UConn and JAX and the Weizmann Institute offer the depth and breadth of expertise needed in each of these areas to create an appealing infrastructure for synergism and collaboration, which could also include Connecticut biotech, pharmaceutical and life science companies. While the CCMDR will initially focus on diabetes and obesity, it will eventually pursue solutions to other metabolic disease entities while always seeking the development of new treatment options and commercial opportunities.

WORKSHOP—THE SCIENCE

This year's CCMDR Workshop saw a significant expansion of shared science over the 2015 Workshop, due in part to the integration of the Weizmann Institute and increased participation among investigators from Yale, the University of Connecticut and The Jackson Laboratory. Twenty-two research talks were presented, on topics ranging from basic mechanisms of insulin resistance to how psychology of reward can be leveraged to improve patient behaviors.

After an introductory overview of metabolic research at the Weizmann presented by Dr. Alon Chen, the morning of Monday, April 11th saw five talks from Weizmann and Yale participants. Dr. Kevan Herold of Yale first discussed his research using humanized mice to investigate the mechanisms by which anti-CD3 antibodies treat Type 1 Diabetes (T1D). Dr. Herold presented evidence that microbes in the gut are required for anti-CD3 treatment to be effective. Next, Dr. Hugh Taylor, also from Yale, showed that stem cells from the uterus can be used to create a variety of differentiated cell types, including islet-like cells

that produce insulin. Uterine stem cells are an attractive source of pluripotent cells, owning to the fact that they plentiful, regularly replenished and easily extracted, as compared to other stem cell sources such as bone marrow or cord blood. The second session of the first morning was kicked off by Dr. Atan Gross from the Weizmann Institute, who presented studies of MTCH2, which Dr. Gross suggested may act as a metabolic sensor that links mitochondrial function with diet-induced obesity. Dr. Robert Sherwin (Yale) next discussed his work investigating the Brain–Diabetes connection, primarily focusing on the function of glucose-excited and -inhibited neurons in the ventromedial nucleus of the hypothalamus. He showed that altered regulation of this circuitry in obese individuals causes disruption of reward-motivation pathways that may lead increased desire for and consumption of high-calorie foods. For the final Monday morning talk, Dr. Gerald Shulman (Yale) presented his work on the molecular mechanisms of insulin resistance, examining signaling pathways in the liver and muscle. A major theme of Dr. Shulman's talk was that insulin resistance is not so much a consequence of total fat abundance but of fat distribution, and one promising therapeutic strategy will be to specifically target ectopic fat, e.g., with a liver-targeted mitochondrial protonophore. Drs. Shulman's interest in targeting mitochondrial metabolism as a potential therapeutic strategy resonated with Dr. Gross's talk earlier in the session.

Nine scientific talks were presented on Monday afternoon over three sessions, featuring speakers from Weizmann, The Jackson Laboratory, Yale and the University of Connecticut. Dr. Sigalit Boura-Halfon (Weizmann) started Session Three with her talk on the control brown adipose tissue innervation by macrophages, showing that this relationship is important for maintaining steady-state energy expenditure. Next, Dr. David Serreze of The Jackson Laboratory in Bar Harbor, Maine presented work on mouse models of T1D, specifically those that express a humanized T1D gene variant, the HLA-A2.1 allele. These mice are being used to identify the autoantigens that contribute to T1D in patients that harbor that allele, and Dr. Serreze discussed potential avenues for using identification of these antigens to develop clinical interventions. Dr. Vishwa Deep Dixit (Yale) next talked about the effects of metabolic processes on aging, focusing particularly on the impact of calorie restriction on health span. He showed

that calorie restriction lowers inflammation and macrophage activation in adipose tissue and identified possible drug targets and calorie-restriction mimetics for enhancing health and lifespan.

Session Four began with a presentation by Dr. Michael Walker of the Weizmann Institute, who discussed the role of short chain fatty acids (SCFAs) in the function of pancreatic beta cells, and how this relationship affects the link between obesity and Type 2 Diabetes (T2D). He presented a study on the SCFA receptor GPR41 that suggested SCFAs play a major role on maintaining glucose homeostasis. Dr. Sonia Caprio (Yale) followed with a talk on obesity and T2D in youth that covered the epidemiology of these conditions as well as clinical studies of obese adolescents. Key points from Dr. Caprio's talk were that obese children progress to T2D much more quickly than adults, and that T2D prevention in obese youth should start very early, targeting both insulin resistance and beta cell dysfunction. Dr. Caprio also found that fatty liver was associated with impaired insulin action independent of visceral fat, reflecting Dr. Shulman's earlier findings. The final talk of the session was by Dr. Maria Luz Fernandez from the University of Connecticut, who presented work toward resolving the controversy over the effects of egg consumption on the health of diabetics. Dr. Fernandez performed a randomized clinical trial that showed that eggs produced no increase in heart disease risk compared to oatmeal but instead have beneficial effects on liver enzymes and inflammatory markers.

Dr. Yael Kuperman (Weizmann) gave the first talk of Session Five, in which she discussed the role of the corticotrophin-releasing factor system in the neurobiology of stress. She showed that CRF reduces the excitability of the Agouti-related peptide system, linking CRF to the transition form the anabolic to catabolic state. Next, Shangqin Guo of Yale presented her work on induced pluripotent stem cells, specifically focusing on fast-cycling, "privileged" somatic cells that are more amenable to cell fate transitions than cells with a slower cell cycle. Although conversion of privileged cells to insulin-producing cells is still a technical challenge, Dr. Guo discussed her success in converting cells from the gut and cord to insulin-secreting cells. Dr. Michael Stitzel, from The Jackson Laboratory for Genomic

Medicine, gave the final presentation of the day. Dr. Stitzel presented his work on T2D, in which he has been resolving the specific transcriptional effects of causative loci identified by genome-wide association studies. He has been able to show that a T2D variant at the C2CD4A gene affects binding of the transcription factor NFAT, leading to disrupted regulation of C2CD4A (and perhaps C2CD4B).

The second morning of talks began with a presentation by Dr. Yehiel Zick (Weizmann), who discussed his work identifying genes involved in programmed cell death of beta cells. He has discovered a nuclear-localized G protein–coupled receptor, TM7, as a key player in maintaining beta cells, showing that it may be involved in regulating alternative splicing due to stress. Next, Dr. Anthony Vela of the University of Connecticut School of Medicine presented his work toward harnessing T cell costimulation to target tumors; this costimulation is necessary for T cells to effectively compete for energy in the metabolic environment of a tumor. Dr. Vela showed that CD134 and CD137 work very well to costimulate CD8 T cells and presented the genomic effects of costimulation. Dr. George Weinstock (JAX-GM) presented next, giving an overview of his work on the second phase of the Human Microbiome Project, in which has been collaborating with Dr. Michael Snyder's group at Stanford. Drs. Weinstock and Snyder have been taking an integrative approach toward understanding the role of the microbiome in T2D onset. He presented a cross section of integrative data that included an examination of the effects of a "junk food" diet on the microbiome. Dr. Weinstock specifically noted the need for integrating microbial and metabolic research and suggested approaching the NIH with proposed CCMDR-initiated collaborations to integrate into the Human Microbiome Project. Dr. Martin Kriegel (Yale) also gave a microbiome-themed presentation for the final talk of the first Tuesday morning session. Dr. Kriegal showed that microbial orthologs (e.g., from *P. propionicum*) of the Ro60 autoantigen—which may be the primordial antigen in lupus—can stimulate the production of anti-Ro60 antibodies in the absence of human-derived Ro60. He proposed that such crosstalk could occur when bacteria breach the gut barrier, and showed that such breaches might be reduced through dietary means.

The final session of the workshop began with a talk by Dr. Ari Elson (Weizmann), who presented his research on the roles of protein tyrosine phosphatases (PTPs) in metabolic regulation. He focused on two orphan receptors, PTPα and PTPε, which he showed regulate leptin signaling via Jak2. Dr. Elson also discussed plans to use mutant mice to better understand these receptors. Dr. Alison Kohan (University of Connecticut) next presented on the role of the intestine in metabolic disease. She discussed her work on a mouse model that overexpresses human Apolipoprotein C-III, showing that increased APOC3 leads to higher fasting triglyceride levels, thus creating a model of hypertriglyceridemia. She showed abnormal intestinal fat absorption in these mice, and presented a novel culture system for studying intestinal tissues. Dr. Nancy Petry (UConn Health) next presented her behavioral psychology research using incentives, rewards and reinforcers to improve patient behaviors. She showed high efficacy of these methods when applied to substance abuse treatment and showed how they could also be highly effective in improving the health of overweight and obese patients, e.g., by increasing exercise. Dr. Janie Merkel, Director of the industry-inspired Yale Center for Molecular Discovery, gave the final scientific talk on the Program in Innovative Therapeutics for Connecticut's Health (PITCH; http://pitch.yale.edu/). PITCH is a collaborative endeavor that gives eligible scientists the opportunity to apply the small-molecule screening capacity of the Center for Molecular Discovery toward their own research questions.

WORKSHOP—UPDATES FROM 2015

The addition of the Weizmann Institute researchers to the CCMDR workshop proved to be highly productive to both the dialogue surrounding the Center, as well as finding synergies between potential collaborators. Importantly, discussions are underway for a memorandum of agreement between the CCMDR sponsor institutions and the Weizmann Institute to create an international, multi-purpose collaboration focused on Metabolism and Metabolic Disease, with an initial emphasis on diabetes (T1D and T2D) and obesity ("The Metabolic Research Alliance" or "MRA"). This collaboration will be based on an open, non-exclusive sharing of assets, capabilities, academic, science and business interests and opportunities between participants. Participants hope to share specific assets and know-how in the field,

such as research topics, pre-clinical studies, innovative technologies, research and clinical initiatives and funding sources, to further the scientific goals of developing improved treatments and cures for metabolic diseases.

There were several complimentary assets identified from scientific talks, and researchers at the workshop were eager to develop new avenues of research that play to each other's strengths. High-level themes for which each institution adds significant value to the collaborative effort are summarized below.

Complementary Strengths and Research Programs

Yale University

Yale Center for Clinical Investigation (YCCI) and NIH Clinical and Translational Science (CTSA) Award

- Clinical-patient population (T1D and T2D), with ability to collect human tissues-samples
- Bariatric surgery cohort (stool and small bowel samples for microbiome study)

Immunology & Immunobiology Program fits with microbiome (e.g., dendritic cells)

Pancreatic Beta Cell Program

Stem Cell Center—basic and translational resources

Clinical Endocrinology and Metabolism - Gerald Shulman, M.D., Ph.D.

Human Genetics & Genomics - Richard Lifton, M.D., Ph.D.

CRISPR technology

*Unique patient cohorts (ethnically diverse, adolescent, adult) to identify disease mechanisms

University of Connecticut

Lipids & Lipid Metabolism Program

Pancreatic Beta Cell Biology Program

Stem Cell Program

Global Affairs

*Unique patient cohorts (ethnically diverse, adult) to identify disease mechanisms

JAX

Genetics & Genomics Technologies and Resources

- CRISPR technology — test genetic variants on a rolling basis and much more quickly
- Long-read sequencing technologies to identify metabolic-diseases associated isoforms.
- Humanized mice for T1D/T2D — powerful model for looking at disease over time and compiling complex genetic models

Microbiome Program

- Yale bariatric surgeries for small bowel samples jejunum (area that interacts with immune system)
- Bariatric Surgery (Hartford Hospital) in conjunction with Microbiome Program
- In vitro models for investigating beta cell function, epigenomics

*Unique patient cohorts to identify disease mechanisms

Weizmann Institute

Center for Metabolism and Metabolic Disorders (CMMD).

In addition to the research expertise outlined previously, the CMMD has additional foci outlined below.

- Cellular metabolism and development – Ayelet Erez, M.D., Ph.D., Yaqub Hanna, M.D., Ph.D., Eran Hornstein, M.D., Ph.D.
- Microbiome – Eran Elinav M.D., Ph.D.
- Systems Biology – Eran Segal, Ph.D., Shalev Itzkovitz, Ph.D.
- The Metabolic Research Forum

*Unique patient cohorts to identify disease mechanisms

SUMMARY

For the third straight year, the CCMDR Workshop promoted an innovative and progressive approach to fill the need for focused, translational research efforts related to metabolic disease. The addition of the Weizmann Institute, and the memorandum of agreement between the Weizmann and CCMDR-participating institutions, greatly increased the scientific scope, the number of potential collaborations,

and funding opportunities. The resulting arrangement is expected function as a collaborative and fully integrated undertaking that will strive to coordinate the scientific and clinical resources of Yale, UConn and JAX, with those of the Weizmann Institute. The CCMDR, with the participation of the Weizmann Institute, will promote synergistic activities that will allow for new discoveries and clinical approaches for those suffering from diabetes and obesity, while also creating new entrepreneurial opportunities.

PLANNING COMMITTEE, SPECIAL INVITEES AND RESEARCHERS

Planning Committee

- Kevan Herold, M.D. — Professor of Immunobiology and of Medicine, Yale School of Medicine
- Marc E. Lalande, Ph.D. — Health Net Professor and Chairman, Department of Genetics and Genome Sciences, University of Connecticut School of Medicine
- Charles Lee, Ph.D., FACMG — Scientific Director and Professor, The Jackson Laboratory for Genomic Medicine
- Ophir Shahaf, LL.B., MBA — Health Care Innovations, Israel Partnerships, Office of Global Affairs, University of Connecticut
- Robert S. Sherwin, M.D. — C.N.H. Long Professor of Medicine, Yale School of Medicine
- Dr. Milton Wallack — Founder of the CT Stem Cell Coalition
- Daniel Weiner, Ph.D. — Vice Provost for Global Affairs, University of Connecticut

Special Invitees

- Bruce Liang, M.D. — Dean, University of Connecticut School of Medicine
- Edison Liu, Ph.D. — President and CEO, The Jackson Laboratory
- Malavi Madireddi, Ph.D — Senior Director, Translational Development for JDRF
- Lonnie Reed — CT State Representative, Co-chair Governor' s Bipartisan Life Sciences Caucus
- Jeffrey Seeman, Ph.D — Vice President for Research, University of Connecticut
- Laurel Sweet — Pharmaceutical Research and Development, Pfizer and Bayer

Research Participants

Yale University

- Sonia Caprio, M.D. — Hormonal mechanisms driving childhood obesity and T2D
- Vishwa Deep Dixit, DVM, Ph.D — Harnessing immune-metabolic interaction to enhance healthspan
- Shangqin Guo, Ph.D. — Privileged stems cells and cell fate in diabetes
- Kevan Herold, M.D. — Role of microflora in regulating tolerance and immune responses

- Martin Kriegel, M.D., Ph.D. — Microbiota in systemic autoimmunity
- Janie Merkel, Ph.D. — Screening with PITCH at Yale Center for Molecular Discovery
- Robert Sherwin, M.D. — Role of the brain in regulating glucose metabolism
- Gerald Shulman, M.D., Ph.D. — Mechanisms driving insulin resistance in T2D
- Hugh Taylor, M.D. — Endometrial stem cells for use in regenerative medicine

University of Connecticut

- Maria Luz Fernandez, Ph.D. — Relationship between diet and chronic disease in T2D
- Alison Kohan, Ph.D. — Mouse model of hypertriglyceridemia and intestinal enteroid culture system
- Nancy Petry, Ph.D. — Reinforcement to improve diabetes management
- Anthony Vella, Ph.D. — T-cell biology and the impact of inflammation on the immune system

The Jackson Laboratory (JAX and JAX-GM)

- Dave Serreze, Ph.D. — Immune tolerance defects in T1D
- Michael Stitzel, Ph.D. — Epigenetics and enhancers in islet cells
- George Weinstock, Ph.D. — Human Microbiome Project

The Weizmann Institute

- Sigalit Boura-Halfon, Ph.D. — Macrophage control of brown adipose tissue innervation
- Alon Chen, Ph.D — Weizmann Institute metabolic disease research overview
- Ari Elson, Ph.D. — Protein tyrosine phosphatases and leptin receptor signaling
- Atan Gross, Ph.D — Role of mitochondrial MTCH2 in energy utilization
- Yael Kuperman, Ph.D— AgRP neuron regulation of sympathetic nervous system
- Michael Walker, Ph.D. — Short chain fatty acids in beta cell function
- Yehiel Zick, Ph.D — Cytokine-induced death of beta cells

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