“One always finds one’s burden again.”

Albert Camus
This fourth year of the Sabri Ülker Center for Nutrient, Genetic, and Metabolic Research has been an exciting one with scholarly accomplishments of our members, publication of several important studies, and advancing our scientific goals on several fronts to get one step closer to producing translational opportunities.

Work in the Center continues to focus on advancing basic mechanistic research to address the cellular and molecular mechanisms underlying common chronic metabolic diseases, which pose the greatest threats to global human health.

This year we have discovered key mechanisms that protect the critical metabolic organs against stress, advanced our work in the area of immunometabolism to explain the reasons behind metabolic inflammation that occurs in obesity and sets the stage for diabetes, uncovered the biological effects of a naturally occurring molecule that is found in common foods and tested this concept in humans, and achieved important progress toward understanding the structural changes that our cells undergo in response to fluctuations in nutrients. We utilized our technology platforms through the Sabri Ülker Imaging Lab and through collaborations with the world’s most advanced groups to achieve a stunning resolution in mapping the three-dimensional organization of liver cells and how these subcellular structures are altered in obesity. We are committed to training the next generation of scientists. Six of our current fellows received prestigious honors and fellowships for their work and three of them moved on to build their independent groups. Finally, we have completed our second Symposium at Harvard with the support of the Sabri Ülker Foundation with resounding success. You will find the details of the “Metabolism and Life Symposium” in the pages of this report.
Unceasing struggle is a reward,...
...an opportunity to contribute to humanity.
Resolutely pressing on...
...no matter how difficult the task is.
Unlocking the mysteries of metabolic biology...
...by pushing the scientific frontier.
“To understand the root causes of a health problem so common, one has to look back into our developmental history to understand the reasons behind this alarming development. Maybe our biological infrastructure is in a mismatch with the current chapter of human life and exposes us to metabolic diseases. Our goal is to find the mechanisms underlying these vulnerabilities at the molecular level and help people to overcome them.”

Gökhan Hotamışlıgil, MD, PhD
Director of the Sabri Ulker Center for Nutrient, Genetic, and Metabolic Research, Chair, Department of Genetics and Complex Diseases and James S. Simmons Chair of Genetics and Metabolism at the Harvard T.H. Chan School of Public Health
Dear Friends,

This year was marked by important scientific progress in multiple areas in our Center. We made progress towards our long-term interest in understanding specific energetic mechanisms that are altered in obesity, as well as specific structural changes subsequent to metabolic alterations. We found these structural alterations to be associated with calcium dysregulation in specific compartments of the liver cells, illustrating a fundamental imbalance in metabolic diseases. We also found a molecular mechanism that impairs calcium flux into the endoplasmic reticulum in obesity. We completed a project focused on understanding how a short-chain fatty acid that is present in common foods can alter metabolic regulation and how it affects human health directly in a proof-of-principle clinical study. This year was also marked by the publication of our discovery that an adaptive program that controls protein quality is essential for thermogenesis and metabolic function in the brown adipose tissue, disruption of which causes inflammation and diabetes. In yet unpublished work, we are unraveling an exciting molecular mechanism of obesity-associated asthma with clinical implications and also a component of the adaptive response in immune cells that is critical for inflammation resolution, with repercussions for the development of metabolic disease. We also discovered a molecular mechanism that is critical for the digestive functions of the pancreas. Finally, we are also discovering the mechanisms involved in the secretion of an adipocyte-born hormone that we have previously reported on and its role in diabetes through actions on different organs, such as liver and pancreas.

These and previous important discoveries by our group of scientists caused general excitement in our field, as they have deepened our comprehension of physiological and pathological metabolic regulation. I am very grateful for being part of these contributions and having them recognized with the 2018 EASD–Novo Nordisk Foundation Diabetes Prize for Excellence, another important mark of this year.

In addition, an invigorating atmosphere has caught hold of our days, as we have started planning our Third Symposium on Metabolism and Life, which will be held in Istanbul in 2020. We are organizing a unique program with international leaders in the metabolism field, which will certainly provide an outstanding opportunity for celebrating science.

I hope you enjoy reading about our efforts and accomplishments.

Sincerely,

Gökhan S. Hotamışlıgil, MD, PhD
Sabri Ülker Center Symposium
Harvard University, Cambridge, Massachusetts
May 29–30, 2018
Amalgam of Science and Art: The 2018 Symposium “Metabolism and Life”

The symposium “Metabolism and Life,” organized by the Sabri Ülker Center at Harvard T.H. Chan School of Public Health, was a perfect synesthetic experience. The symposium, held at Harvard’s Memorial Hall on May 29–30, featured a program of highly innovative research about metabolism, the chemical processes that occur in living organisms to maintain life. The event was opened by a musical performance by Turkey’s classical guitar virtuoso Ahmet Kanneçi, followed by an inspiring speech by Center Director Gökhan S. Hotamışlıgil who reminded us that research means going into the unknown, in the words of Albert Szent-Györgyi. Trying to predict your path and results are, in Szent-Györgyi’s words, “like telling Michelangelo or Renoir that he must tell you in advance how many reds and how many blues he will buy, and exactly how he will put those colors together,” stated Dr. Hotamışlıgil about unraveling the mysteries of Science in analogy to artistic creations. “The Sabri Ülker Center allows us to pursue new, unexpected research alleys.”

Representing hardship in every worthwhile pursuit in life, sculptures by Turkish master sculptor Cem Sağbil entitled “Sisyphos and Life” expanded on the commonalities between Science and Art – both require great devotion and reflect privilege in regards to freely exploring life’s inquiries.
Amalgam of Science and Art: The 2018 Symposium “Metabolism and Life”
The Sabri Ülker Symposium

1. Gökhan Hotamışlıgil, MD, PhD. Director of the Sabri Ulker Center and James S. Simmons Chair of Genetics and Metabolism
2. Ali Ülker, Vice Chairman of Yıldız Holding and pladis
3. Michelle A. Williams, Dean of Harvard T.H. Chan School of Public Health
4. Alan M. Garber, Provost of Harvard University
Harvard Provost Alan Garber and Dean of Harvard Chan School Michelle Williams highlighted the powerful roles of basic science and metabolic research, dissecting the paths that science and research can open and contribute to global health.

With an impassioned speech, Ali Ülker took the stage and shared the story about the starting point of the Sabri Ülker Foundation. It was delivered in loving memory of his grandfather, who was a baker and became one of the greatest entrepreneurs in Turkey. The joy reflected on children’s faces from receiving delicious treats produced by his bakery at that time, explained Mr. Ülker, was the driving force for his grandfather to expand his business.

With this affectionate recollection, the Foundation and the Center were created with the purpose of perpetuating happiness for the younger generations and bridging global efforts to solve the threatening epidemics of metabolic diseases.
The Decade of Discovery

Generations of Scientists Sharing Their Passions

The intent of perpetuating joy can be achieved in different ways. Pursuing curiosities about how life works is certainly a gratifying one and holds the promise of helping others improve their health. This is a motivation that is carried on across different stages of a scientific career.

The symposium organized scientific panels that began with the younger generation of scientists, “Rising Stars,” and continued with talks by those who have risen to great heights. Speakers discussed essential pillars of metabolic regulation in contexts such as immune response, aging, neuronal circuitry, energy expenditure, protein homeostasis, and lipid regulation. Nobel laureates Michael Brown and Joseph Goldstein of the University of Texas Southwestern Medical Center, illustrated a 45-year partnership that resulted in fundamental discoveries about the complex pathways that regulate cholesterol and laid the groundwork for the use of statins to prevent cardiovascular disease. Before discussing their new findings about two cholesterol pathway molecules that have great relevance for metabolism, Dr. Brown acknowledged the Sabri Ülker Foundation for its contributions to research: “When you are supporting work in an established laboratory, you are not only supporting those discoveries, you are supporting the creation of the next generation of scientists,” he said.

The evening ended with energizing closing remarks by Mark Elliot, Vice Provost for International Affairs at Harvard University, who acclaimed the recent discoveries accomplished at Harvard as a result of the Ülker family’s gift and Dr. Hotamışlıgil’s leadership. He also delighted the audience with his new developing skills in the Turkish language.
“It is an honor to speak at the Sabri Ülker Symposium. I deeply admire Gökhan’s love for Turkey and his desire to encourage Turkish scientists at home and abroad. The Center is off to a great start.”

Michael S. Brown

“Thanks go to Gökhan for orchestrating such a “scholarly feast,” as he so aptly described the event. It is truly a wonderful celebration of science in a temple of science.”

Joseph L. Goldstein
Keynote Speakers:
Dr. Joseph Goldstein and Dr. Michael Brown

Joseph L. Goldstein received an MD degree from Southwestern Medical School of the University of Texas Health Science Center in Dallas and is currently the Chair of the Department of Molecular Genetics at the medical school. In 1985, he was named Regental Professor of the University of Texas. He also holds the Paul J. Thomas Chair in Medicine and the Julie and Louis A. Beecherl Distinguished Chair in Biomedical Science.

Michael S. Brown received an MD degree from the University of Pennsylvania. He was an intern and resident at the Massachusetts General Hospital, and a postdoctoral fellow with Earl Stadtman at the National Institutes of Health. He is currently Paul J. Thomas Professor of Molecular Genetics and Director of the Jonsson Center for Molecular Genetics at the University of Texas Southwestern Medical School in Dallas.

Joseph Goldstein and his colleague, Michael S. Brown, discovered the low-density lipoprotein (LDL) receptor and worked out how these receptors control cholesterol in blood and in cells. They showed that mutations in this receptor cause Familial Hypercholesterolemia, a disorder that leads to premature heart attacks. For this discovery, they applied the techniques of cell culture and enzymology to first develop an assay for a key enzyme involved in making cholesterol in human cells. In skin cells from healthy people, the enzyme’s activity was suppressed by the presence of LDL in the culture medium. In contrast, no suppression occurred in skin cells from the FH patients. At the basic level, this work opened the field of receptor-mediated endocytosis, and at the clinical level, it helped lay the conceptual groundwork for the development of drugs called statins that lower blood LDL cholesterol and prevent heart attacks. Drs. Brown and Goldstein shared many awards for this work, including the Lasker Award in Basic Medical Research, Nobel Prize in Physiology or Medicine, and National Medal of Science. They are both members of the US National Academy of Sciences and Foreign Members of the Royal Society. Dr. Brown served for 16 years on the Board of Directors of Pfizer, and he is currently a Director of Regeneron Pharmaceuticals. Dr. Goldstein serves as the Chairman of the Albert Lasker Medical Research Award Jury and is a member of the Boards of Trustees of the Howard Hughes Medical Institute and The Rockefeller University (Life Trustee). More recently, Drs. Brown and Goldstein received the Albany Medical Center Prize in Medicine and Biomedical Research (2003) and the Rolf Luft Award (2016).

In more recent work, Drs. Brown and Goldstein discovered the sterol regulatory element-binding proteins (SREBP) family of transcription factors and showed how these membrane-bound molecules control the synthesis of cholesterol and fatty acids through a newly described process of Regulated Intramembrane Proteolysis. Different from other transcription factors, the SREBPs are synthesized as intrinsic membrane-bound proteins of the endoplasmic reticulum (ER). After synthesis, the SREBPs form a complex with a membrane-embedded escort protein called SCAP. In lipid-depleted cells, SCAP facilitates the incorporation of SREBPs into vesicles that bud from the ER and move to the Golgi apparatus, where the SREBPs are processed sequentially by two membrane-bound proteases. When cholesterol accumulates in ER membranes, SCAP undergoes a conformational change that causes it to bind to one of two ER retention proteins called Insig-1 and Insig-2. This binding prevents SCAP from escorting SREBPs to the Golgi, thereby abrogating the proteolytic processing of SREBPs. This feedback inhibition is essential for the maintenance of cholesterol homeostasis in animals.
Dr. Ömer Yılmaz is an Assistant Professor of Biology at the Koch Institute for Integrative Cancer Research at MIT and a gastrointestinal pathologist at the Massachusetts General Hospital and Harvard Medical School. His laboratory focuses on understanding the mechanisms by which adult stem cells and their microenvironment adapt to different diets and signals of tissue regeneration, cancer and aging.

Since intestinal stem cells (ISCs) possess the ability to self-renew and the capacity for differentiating into tissue-specific cell types, they likely play an important role in remodeling the intestine in response to diet-induced physiologies. Most ISCs express the G-protein-coupled receptor 5 (Lgr5) and reside at the bottom of intestinal crypts nestled between Paneth cells. Dr. Yılmaz’s group is interested in unraveling the molecular mechanisms related to the interactions between ISCs and Paneth cells in conditions of caloric restriction and obesity. This knowledge will provide deeper understanding of intestine physiology, adaptation to different diets and pathological conditions, such as colon tumorigenesis and have important implications in determining healthy dietary components. Recently, his group has shown that a 24-hour fasting improves intestinal stem cell function in young and aged mice by inducing fatty acid oxidation, highlighting the role of this process in mediating regenerative effects through fasting in intestinal biology. These results may represent a viable strategy for increasing intestinal regeneration and generating preventive measures against chronic diseases.
Sabri Ülker Symposium Speakers

Dr. Yasemin Sancak is an Assistant Professor at the Department of Pharmacology, University of Washington. Her laboratory is interested in understanding how diverse mitochondrial functions are regulated and coordinated, with a focus on calcium signaling. Her ultimate goal is to mechanistically understand rare and common diseases that are caused by mitochondrial dysfunction. Mitochondria are known to have the ability to take up and store large amounts of calcium, but very little is understood about the mitochondrial calcium uptake machinery. Dr. Sancak’s group has put effort into uncovering this particular aspect of mitochondrial regulation using loss-of-function studies in cells and animal models. In addition, their interest is to understand how this complex machinery is regulated at the transcriptional and post-transcriptional level. Dr. Sancak identified key molecular components of this complex machinery, such as the EMRE protein, and characterized its function. Recently, her group has shown that a mitochondrial uniporter’s regulatory subunit called MICU1 plays an important role in ion specificity, allowing it to distinguish between calcium and manganese. This finding may have relevant implications for human neurodegenerative diseases such as sporadic forms of Parkinson’s disease, which have been shown by epidemiological studies to be associated with manganese exposure. Since proper function of mitochondria is a critical determinant of cellular metabolism and function, these observations have important implications for health and disease, including many metabolic diseases.

Dr. Ali D. Güler is an Assistant Professor of Biology at the University of Virginia. His group is interested in understanding how the mammalian nervous system integrates and processes environmental and peripheral signals for proper behavioral responses. It is known that feeding, sleeping and reproductive patterns are assigned to multiple brain regions and are differentially gated. In order to understand how the brain weighs stimuli to shape behavioral output, Dr. Güler’s group uses genetic tools that allow precise control of neural activity, combined with electrophysiology and behavioral assays. In addition, his laboratory is interested in elucidating the role of genetically defined populations of neurons within the hypothalamus and midbrain during behaviors associated with feeding and thermoregulation. To achieve these goals, his team has generated a novel combination of viral and genomic constructs that allow manipulation of both endogenous and exogenous genes in anatomical, genetic and temporal space. Recently, his group has focused on a very interesting aspect of dopamine neurotransmission mediated by Drd1 within the suprachiasmatic nucleus, demonstrating that Drd1 is a key component that determines the rate of entrainment following changes in the light cycle. These findings suggest a role for dopamine input to the circadian clock, highlighting a highly conserved relationship between the circadian system and neuromodulatory circuits that control motivational behaviors. These findings have important implications for understanding feeding behavior and energy expenditure and conditions that predispose or promote obesity.
Dr. Shizuo Akira described exciting and groundbreaking studies from his laboratory that sought to identify these cells. They observed that mice lacking the transcription factor C/EBPβ became resistant to development of fibrosis. Based on these observations, they then employed careful characterization of differences in innate immune cell populations in these experimental models to identify key cells involved. This resulted in the discovery of a particular subtype of monocytes, which they termed segregated-nucleus-containing atypical monocytes (SatMs). Transfer of SatMs into mice lacking C/EBPβ was sufficient to alter sensitivity to fibrosis. Dr. Akira reported that SatMs induce fibrotic responses including osteopontin expression in the target cells, fibroblasts. He went on to describe extensive studies of signaling pathways in these cells that are key to the induction of fibrosis, including chemokine signals that are required for the recruitment of SatMs to sites of inflammation and fibrosis. These findings suggest promising new targets for therapeutic approaches to reducing fibrosis, as effective clinical treatments for this dangerous pathology are currently lacking.

Dr. Elçin Ünal is an Assistant Professor in the Molecular and Cell Biology Department at the University of California, Berkeley. Her laboratory is interested in investigating the regulatory mechanisms of meiotic differentiation, a process known as gametogenesis, with the goal of understanding fundamental mechanisms of degeneration and aging. Upon commitment, a progenitor cell undergoes DNA replication and recombination followed by two meiotic divisions and cellular remodeling to form haploid gametes. Dr. Ünal’s group focuses on understanding how the fitness of gametes is maintained during their production to keep the appropriate nuclear and cytoplasmic content to make healthy progeny. For this purpose, they study gametogenesis during aging, as well as gene expression program control of specialized events such as chromosome segregation during meiosis. Recently, her group has focused its interest on regulatory components of chromosome separation during meiosis, specifically the kinetochore. At the beginning of meiosis, the kinetochores are inactive, preventing chromosomes from separating too soon. This regulation is achieved by controlling the levels of a protein called Ndc80. In yeast, her group has demonstrated that two mRNAs carrying the same protein-coding message (but one containing an extension that inhibits it from being translated into protein) are key to regulate the levels of Ndc80, and one of them is only produced in early meiosis. Importantly, the key components found in the regulation of Ndc80 during meiosis are found in a myriad of organisms, from yeast to humans, suggesting that these mechanisms may be similar to control proteins involved in other cellular processes.
Sabri Ülker Symposium Speakers

Dr. Ronald M. Evans described studies continuing a career-long effort devoted to understanding the functions of nuclear hormone receptors, a family of transcriptional mediators of the potent effects of many endocrine factors including steroid and reproductive hormones. These receptors are also well-established targets of widely used and effective drugs as well as naturally occurring endogenous and exogenous molecules, including lipids and nutrients. In this talk, Dr. Evans reported novel roles of the vitamin D receptor (VDR) in altering the tumor environment in pancreatic cancer. Considering cancer “the wound that never heals,” factors that contribute to aberrant remodeling of the tissue environment of tumors (analogous to constant healing) are of great interest. In particular, the dense desmoplastic stroma that is a hallmark of pancreatic cancer contributes to resistance to chemotherapy as well as resistance to attack by the patient’s endogenous immune system. This effect is mediated in part by the activation of pancreatic stellate cells. Dr. Evans reported striking results showing that the VDR suppresses this activation, acting as a transcriptional brake to the program induced by transforming growth factor β (TGFβ). TGFβ is well known to drive dysfunctional tissue remodeling including fibrosis in a number of pathological conditions. VDR activation antagonizes the TGFβ-mediated transcriptional program via its association with nuclear proteins that remodel chromatin. Dr. Evans reported beneficial effects of VDR agonists in promoting immune cell access to pancreatic tumors and improved response to other therapies. VDR agonists may also be effective in reducing β-cell failure in diabetes, illustrating the powerful possibilities of addressing metabolism in many different contexts to generate creative solutions for disease.

One of the mechanisms that connect obesity to many metabolic dysfunctions including insulin resistance and diabetes is lipotoxicity, or the deleterious effects of lipid overload on normal cellular processes. Dr. Jean Schaffer’s laboratory has developed novel models of diabetic cardiomyopathy and used genetic screens in cultured mammalian cells to identify loci that are critical determinants of tissue responses to lipid overload. She described a genetic screen to identify mutations that protected cells from the deleterious effects of exposure to high glucose levels and toxic fatty acids. The lab identified a protective mutant that blocked expression of the ribosomal protein Rpl13a, but found that re-expression of that protein failed to reverse the effects. Instead, they discovered that the same locus also encodes several small nucleolar RNAs (snoRNAs) within intron sequences of the gene encoding Rpl13a. They went on to show that deletion of these snoRNAs was responsible for the protection from lipotoxicity. In follow-up studies, Dr. Schaffer’s lab developed an animal model and showed that the same deletions improved glucose metabolism in this experimental model. These results demonstrated an interesting effect of snoRNAs on systemic metabolism and perhaps as mediators of lipotoxic signals that disrupt metabolic homeostasis. Dr. Schaffer’s group is continuing to explore the mechanisms behind this effect and have pinpointed alterations in mitochondrial function and reactive oxygen species production in response to lipid exposure as a major target. Thus the snoRNAs provide a novel target for improving cellular and systemic metabolism to provide protection from the effects of lipotoxicity.
Dr. Vamsi Mootha's lab applies state-of-the-art systems biology approaches including genomics, proteomics and genome-wide Crispr-based screens to understand the details of mitochondrial function. One major goal of this approach is to improve the understanding of mitochondrial diseases of humans. Dr. Mootha's work strives to develop diagnostics and, ultimately, therapies for these diseases. Dr. Mootha described a recent genetic screen designed to identify factors that enable cells to survive and grow despite inhibition of mitochondrial oxidative phosphorylation. This screen produced a single strong hit, the Von Hippel Lindau (VHL) protein, an enzyme key to the response of cells to hypoxia. Under normal oxygen conditions, VHL mediates degradation of Hif1a, a transcription factor that regulates many genes required for response to low oxygen. In low oxygen, or absence of VHL, Hif1a and the hypoxic response are active. Reasoning that moderate hypoxia might mimic absence of VHL, Dr. Mootha's lab obtained a mouse model of Leigh's syndrome, a rare but severe mitochondrial disease of humans that results in early onset of profound neurological deficits that culminate in death in early childhood. The mouse model, which is defective in a component of the mitochondrial respiratory chain, exhibits neurological deficits and early death similar to Leigh's syndrome. Dr. Mootha's group exposed this experimental model to modest hypoxia, replicating atmospheric conditions in high altitudes with human populations. Treatment of the mice with moderate hypoxia resulted in remarkable protection from lethality and development of neurological deficits. These results suggest that hypoxia could be a relatively simple therapy for Leigh's syndrome and clinical trials.

Dr. Brenda A. Schulman's lab studies how proteins are regulated by becoming covalently linked to the small protein ubiquitin or to structurally related ubiquitin-like proteins (UBLs). Ubiquitination is a fundamental and widespread mechanism controlling timing, subcellular location, assembly, conformation, and activity of thousands of different human proteins and macromolecules, which is central for proper function and survival of cells. Defects in ubiquitin and UBL pathways have been associated with numerous diseases, including cancers, neurodegenerative disorders, and viral infections. Thus, understanding mechanisms underlying regulation by ubiquitin and UBLs is of broad importance for understanding signaling pathways and targeting those pathways in diseases. Dr. Schulman described ongoing work unveiling details of the structure and function of the remarkable molecular machines that catalyze the conjugation of ubiquitin to its substrates, ubiquitin ligases, and how these interactions determine the fate of proteins. Dr. Schulman's group is using structural methods like cryo-electron microscopy to determine the structure of these complexes as well as biochemical methodologies to explore how the ligases identify substrates, find ubiquitination sites and finally catalyze the ligation reaction. Another area of interest being pursued by Dr. Schulman's lab is whether similar interactions could be described for the metabolism of lipids and how these influence the impact of lipids on cellular and metabolic processes.
Dr. Leslie B. Vosshall is a molecular neurobiologist who studies how behaviors emerge from the integration of sensory input with internal physiological states. She reported fascinating studies on the mosquito *Aedes aegypti*. *Ae. aegypti* is historically best known as the carrier of the yellow fever virus but is also a vector species for emerging pathogens such as dengue, chikungunya and zika viruses. Dr. Vosshall is investigating neural mechanisms that drive host-seeking and feeding behaviors in this insect, with an eye toward reducing transmission of these significant diseases via human blood feeding. Females of the species require blood feeding for production of eggs, but host-seeking behavior is strongly suppressed after a single meal until eggs develop. Dr. Vosshall's group followed up on previous work which suggested that members of a neuropeptide family, NPY, could be responsible for this feeding behavior. NPY is conserved in many species and in mammals is related to satiety and feeding behavior responses in the hypothalamus of mammals. Dr. Vosshall described successful efforts to identify a small molecule NPY receptor agonist that could mimic the effects of feeding and suppress host-seeking behavior in non-fed mosquitos. Her group also identified NPY receptor candidates in a newly produced *Ae. aegypti* genome and identified a specific molecule, NPYLR7, that mediated the effect of the agonist on feeding behavior. Mosquitoes with genetic ablation of this specific receptor resulted in resistance to the effects of the agonist. These results shed new light on the behavioral circuitry of this important pest and also might suggest novel approaches to suppressing or controlling feeding behavior to reduce diseases.

Dr. Michael P. Czech has a long-standing interest in the functions of lipid biosynthetic pathways in adipose tissue, originating with papers he published decades ago suggesting that impaired de novo lipogenesis in adipocytes is a significant defect in obesity. To elucidate the role of de novo lipogenesis in obese mouse models, Dr. Czech’s group created a mouse strain in which the gene encoding fatty acid synthase (FASN), the key enzyme in fatty acid synthesis, could be inducibly deleted in adult mouse adipose tissue. The expectation was that this inducible enzyme deletion would mimic the reduction in de novo lipogenesis observed in obese mice as well as humans. Surprisingly, deletion of FASN in high-fat diet fed, obese mice actually improved insulin sensitivity and glucose metabolism. This intriguing result could be attributed to the induction of thermogenic beige adipocytes in white fat depots of the knockout animals. Dr. Czech went on to describe experiments that determined that this was not a cell-autonomous phenomenon, i.e., that deletion of FASN in adipocytes did not directly result in conversion to the thermogenic phenotype. Rather, deletion of FASN in vivo resulted in increased sympathtic innervation of the white adipose tissue and local production of catecholamines, well known as drivers of thermogenic responses in adipocytes. A possible mechanism for this phenomenon is increased production of neurotrophic factors by adipocytes with ablation of FASN. Further work by Dr. Czech’s group suggests that the effect of FASN deletion is not due to reduced fatty acid synthesis per se, but rather by accumulation of FASN substrates like acetyl-CoA and malonyl-CoA, which serve as signaling molecules in addition to their roles as metabolic intermediates.
Sabri Ülker Symposium Speakers

Dr. Gerald I. Shulman
Yale University Medical School
Professor of Medicine, Cellular and Molecular Physiology and Physiological Chemistry

Dr. Bruce Spiegelman
Harvard University
Professor of Cell Biology and Medicine

Dr. Gerald Shulman’s lab has focused on mechanisms of insulin resistance in mouse models and human patients. He has emphasized the need for a new line of diabetes therapies that improve insulin sensitivity and are currently lacking in the clinical toolkit for treatment of type 2 diabetes. In his presentation, Dr. Schulman summarized work from his lab that employed novel, noninvasive methodologies for measurement of metabolism in human subjects, a necessary complement to the studies of mouse models to enhance translational opportunities. Dr. Schulman’s work confirms that muscle glucose transport is a key defect in impaired overall glucose homeostasis and he discussed signaling pathways that mediate insulin resistance in response to accumulation of fat in muscle. A dominant concept in the field has been that liver insulin resistance, specifically the ability of insulin to suppress glucose production, is exerted mainly at the level of transcriptional control of enzymes involved in the gluconeogenic pathway. Dr. Schulman argued that this might contribute to chronic regulation, but it cannot explain rapid responses to lipid overload. Rather, he discussed results from his and other labs that suggest that acute regulation of hepatic glucose metabolism is achieved through a complex set of changes in protein phosphorylation, substrate availability, allosteric regulation of enzymes, and redox state of liver cells. Based on this, liver-independent phenomena such as failed suppression of adipose tissue lipolysis, increased substrate (fatty acid and glycerol) delivery to the liver and inflammation may also be considered as contributors to excess liver glucose output in diabetes.

Dr. Bruce Spiegelman reminded listeners of the thermodynamic principle that energy can be expended in the form of work or dissipated as heat. There has been much interest recently in classical adaptive thermogenesis which involves mitochondrial electron transport uncoupled from ATP production. This uncoupled mitochondrial electron transport is carried out in specialized brown or beige adipose tissue depots that express the uncoupling protein UCP1, which enables electron flow without ATP generation. This permits heat-generating electron flow to continue as ATP accumulation normally inhibits respiratory electron flow. However, a paradox emerged from genetic manipulations that ablated expression of UCP1 in mice: such mice are still able to maintain normal body temperature when exposed to cold, suggesting that there must be alternative mechanisms of heat generation. Dr. Spiegelman’s lab discovered that brown and beige fat responsible for heat generation expressed high levels of enzymes involved in the ATP/creatine cycle, a well-known mechanism for maintaining high energy phosphate levels in active muscle and heart tissue. In brown and beige adipose tissue, the ATP/creatine pathway functions as a futile metabolic cycle that consumes ATP and regenerates ADP, which permits high respiratory chain activity and generation of heat without the need for dissipating the proton gradient by uncoupling. Strikingly, ablation of expression of GATM, a key enzyme in the creatine biosynthetic pathway, impaired ability to adapt to cold temperature. Enhancement of this futile cycle or other nonclassical means of thermogenesis could constitute new approaches to treat obesity.
The endoplasmic reticulum (ER) is a vast tubular network in cells responsible for protein synthesis, folding, quality control and disposal. When this organelle is unable to cope with demands, the ER experiences stress and mounts an adaptive response to establish equilibrium. Dr. Peter Walter has pioneered the efforts that revealed mechanisms of protein quality control in the endoplasmic reticulum’s response to stress. His key discoveries describe the molecular basis of the ER's adaptation to stress which include mechanisms underlying the unfolded protein response (UPR), a coordinated cellular response to an excess of improperly folded proteins in the endoplasmic reticulum. Misregulation of this pathway and accumulation of misfolded proteins contributes to many diseases including cancer and neurodegenerative diseases. Despite these critical roles, it has been difficult to develop drugs targeting the function of the endoplasmic reticulum. In his talk, Dr. Walter described new pharmacological approaches to modulating key components of the UPR in an effort to treat such diseases. His group identified small molecule modulators of the UPR, including ISRIB (an acronym for Integrated Stress Response Inhibitor). ISRIB is an experimental drug which reverses the effects of eIF2α phosphorylation, one of the key targets of the UPR. Dr. Walter summarized recent studies showing effectiveness of ISRIB in preclinical models of cancer and neurodegenerative diseases. Remarkably, ISRIB also improves cognitive deficits in a mouse model of traumatic brain injury, and even enhances cognitive ability and long-term memory in normal mice. These results further support the key role of the UPR in many diseases and provide promising new avenues toward clinical therapies.

Dr. Linda Partridge described work in several model systems, including mice and fruit flies, aimed at understanding mechanisms behind the phenomenon of lifespan extension as a result of restriction of dietary caloric intake. She described work investigating the ability of dietary restriction to improve lifespan and “healthspan,” or the duration of healthy life, asking the question of whether beginning caloric restriction (CR) later in life could produce benefits similar to lifelong CR. Instead, Dr. Partridge reported that mice appear to develop resistance to effects of caloric restriction as they age. However, animals placed on a calorie restricted diet early in life for a relatively short period showed increased healthspan and lifespan. These results point to a “memory” mechanism that maintains the effects of dietary restriction early in life. To discover this mechanism, Dr. Partridge’s lab undertook an analysis of gene expression in liver and adipose tissue and found a transcriptional signature mainly in adipose tissue with significant changes in mitochondrial biogenesis as well as lipid metabolism pathways, suggesting that adipose tissue adapted to safe lipid storage contributes to longevity. In complementary studies in fruit flies, Dr. Partridge’s lab studied mechanisms by which the mTOR signaling pathway influences lifespan. They find that induction of autophagy in cells of the flies’ gut protects the flies from age-related deterioration. Similar to CR in mice, rapamycin treatment in early life extends lifespan even if treatment is stopped. The long-term goal of Dr. Partridge’s work is to identify key biological pathways like these memory mechanisms that can ultimately be modulated in humans to improve life and healthspan independent of dietary intervention.
Intestinal cells showing the secreted granules into the lumen of the colon.
Where are you from?
I was born and raised in Thessaloniki, Greece, and also studied there for my undergraduate degree at the Aristotle University. I then spent 6 years in Germany for my graduate studies before I moved to Boston to join the Sabri Ülker Center. So I would say I feel European or even a global citizen. Having worked in very international environments for the last decade, I believe that scientists end up being an exciting mix of cultures and influences.

What were you doing before you joined the Sabri Ülker Center?
I completed my PhD degree in Cologne, Germany. I was doing research on how the central nervous system regulates energy homeostasis to impact obesity and diabetes. Excitingly, I also studied how the sense of smell may impact our body weight and metabolic health.

What compelled you to join the Center?
I wanted to deepen my understanding and expertise on immunometabolism, a field of research that Dr. Hotamışlıgil pioneered almost 3 decades ago, which has now become a vibrant and broad area of study in many labs. I was already working on the effect of hypothalamic inflammation on metabolism and aging and I believe that the Sabri Ülker Center is the right place to expand my knowledge and prepare me for an independent academic career. The Sabri Ülker Center offers a vigorous, high-paced, stimulating and inspiring international environment with high-end technologies and facilities at Harvard University to tackle difficult questions.

Could you describe your main project?
I am trying to dissect, in molecular detail, the role of a protein that integrates immune and metabolic responses that are important for metabolic disease. It is an interesting molecule as it was initially discovered and recognized for its role in viral defense but then was demonstrated to also be essential in nutrient sensing. What is fascinating is that this protein called PKR is the only protein known not only to possess a kinase function but also binds to double-stranded RNA. I am trying to identify mechanisms of activation of this molecule and how it affects metabolism. I am very grateful to have received an American Heart Association fellowship to pursue this project.

What do you hope will emerge from your project?
Curiosity is my main drive in science. I hope that our discoveries will give rise to even more thrilling questions and novel projects. Basic research is a never-ending trip to the unknown. Eventually, our observations can be translated into useful applications and drugs that will improve the health of people suffering from obesity-associated diseases, such as cardiovascular diseases, type 2 diabetes and multiple types of cancer.

What role does the Sabri Ülker Center play in your career path?
The Sabri Ülker Center is a place where we, as scientists, are given the opportunity to freely explore and ask intriguing questions which advance our fundamental understanding of biology and eventually expand knowledge. In a uniquely stimulating and supportive atmosphere where curiosity is reinforced, we are given the opportunity to mature scientifically and pursue our long-term academic goals.
Where are you from?
I was born and raised in Istanbul, Turkey. I completed my undergraduate studies at the Sabancı University combining biology and engineering.

What were you doing before you joined the Sabri Ülker Center?
After my undergraduate education, I worked briefly and came to Harvard to pursue my PhD degree under the mentorship of Professor Hotamışlıgil. At the end of my PhD work, we discovered a new metabolic hormone with extremely exciting biology and therapeutic prospects. I decided to stay in the Sabri Ülker Center to pursue the biology of this hormone and how it can be turned into a therapeutic.

What compelled you to join the Center?
I joined the center for the people in it and its unique atmosphere. You can always find interesting projects to work on, but the people that make up the lab is what makes the environment productive and enjoyable to work in. Professor Hotamışlıgil has created an extremely stimulating and supportive environment where one can freely pursue unconventional ideas and collaborate. I am also excited to pursue paths that may one day help people with metabolic disease.

Could you describe your main project?
Right now I am working on how adipose tissue communicates with the liver to regulate energy production during fasting. Our group has identified FABP4 to be a major secreted endocrine factor from adipocytes during fasting. My project has focused on how it functions on hepatocytes to establish communication between adipocytes and the liver. We are finding that FABP4 is essential for the action of other well-known endocrine factors to function on the liver. Moreover, we can intervene on this pathway and prevent excess hepatic glucose production seen in obesity and diabetes. One other aspect that we have found over the years is that some commonly consumed food ingredients increase secretion of these hormones and signal the liver to make more glucose even after having a meal. We think chronic exposure to these food components and excess hepatic glucose production may set a base for pathogenesis of obesity and diabetes.

What do you hope will emerge from your project?
Understanding how a disease manifests itself and the underlying pathological mechanisms helps us design better treatment options. And those treatment options are sometimes pharmaceutical approaches and sometimes rather simple lifestyle changes. I am hoping we can understand the disease and how it becomes problematic to the body so we can recommend some options (dietary and lifestyle choices) that will prevent the disease in the first place or may treat it after it emerges.

What role does the Sabri Ülker Center play in your career path?
It has been a tremendous opportunity to work with a wonderful group of people, scientifically, intellectually and personally, and I will be looking for equally engaging and challenging work environments from now on. It will be a hard task to match, but once you get infected with the excitement of this community, it is hard to settle for anything less.
Next Generation of Scientists

Where are you from?
I was born in Hamburg, Germany, and also spent my first years in science there at University Medical Center Hamburg-Eppendorf. I am a biochemist by training and was always fascinated by the basic principles of metabolism and how metabolism is essential for life and impacts human health and well-being.

What were you doing before you joined the Sabri Ülker Center?
Science – just like art – is a universal profession that reaches beyond the barriers of language, religion or nationality. The Center is a place where these ideals of science have materialized, and people are working every day to gain new knowledge to ultimately foster human progress. The Center offers a unique international environment, a very high level of scientific freedom and benefits from Professor Hotamişligil’s outstanding leadership. I was told that Boston is the capital of the scientific universe and as such, one of the working environments you should experience as a scientist – and it is true!

Where are you now?
Very recently I became a principal investigator at Ludwig Maximilian University of Munich, Germany, where I am leading a small research team – as we have just started, we are still recruiting and expanding! Metabolic research is strong in Munich and there are many translational and collaborative centers for obesity and cardiovascular diseases.

Could you describe your main project?
Metabolic adaptation, the ability of our cells to respond to and manage different states of energy availability and demand, is a key mechanism to prevent cellular stress and is often disturbed in metabolic diseases like diabetes and atherosclerosis. We have recently discovered that protein waste management of cellular components is an important aspect of fat cell biology carried out by the Nfe2L1 gene, also referred to as the NRF1 gene, and linked to metabolic dysfunction. This finding opened new avenues to pursue so we are now learning more about the nature of the waste, who brings the trash for pickup and how these programs are coordinated within the cells. Hopefully, this will allow us to find new molecular clues as to how these cells keep themselves healthy.

What do you hope will emerge from your project?
Even though we are primarily using cell and animal models in the lab, I think we should never lose sight of our ultimate goal, which is finding novel cures for human disease. We are now establishing strong clinical partnerships in Munich to obtain human samples ranging from adipose biopsies to heart tissue, in order to learn more about the translational potential of our findings. There is a great deal more to learn about human disease and I am confident that we can fill in one or two pieces of the puzzle. Eventually the road to new cardiometabolic therapies will become clearer than we can now imagine.

What role does the Sabri Ülker Center play in your career path?
We are sometimes limited by our fears and anxieties to fail in our projects and careers, so we make small steps along the path in front of us. The Center with its generous support, excellent facilities, long-term vision and exceptional scientific environment has taught me that it sometimes requires a step into the dark to really find new paths and potentially groundbreaking discoveries.
Gökhan Hotamışlıgil received the 2018 EASD-Novodisk Foundation Diabetes Prize for Excellence. This tremendous honor celebrates over 25 years of Dr. Hotamışlıgil’s research contributions, many of which have significantly increased our knowledge of diabetes, its disease mechanisms, and its complications.

Gökhan Hotamışlıgil says: “I am tremendously humbled to receive this most prestigious award for excellence in diabetes research. There is nothing as valuable as the recognition by peers in one’s scientific career. I would like to accept this momentous honor on behalf of my students and fellows; without their dedication and diligence, none of the cited accomplishments would have been possible. I am grateful to the great teachers and mentors, from elementary school onwards, I had the immense fortune to encounter and to those who have supported our work over the past 25 years for their generosity. My deepest gratitude goes to my family for their endless and invaluable love, support and patience. I hope that one day our work will make a small contribution to the quality of human life, especially among those influenced by metabolic diseases.”
Sabri Ülker Center
Achievement Highlights

We are proud to report that six members of the Center were the recipients of prestigious awards, including:

Alex Bartelt, PhD
*Friedmund Neumann Prize*
For studies of the novel mechanisms involved in preservation and function of brown adipose tissue in physiology and during metabolic stress and disease

Furkan Burak, MD
*Charles A. King Trust Fellowship*
For studies of the mechanisms underlying obesity-related asthma and exploring the underlying molecular and cellular mechanisms

MinDian Li, PhD
*Glenn Foundation Fellowship*
For studies of the impact of aP2-Fabp4 and lipid metabolism in aging and metabolic homeostasis and the underlying molecular mechanisms

Kacey Prentice, PhD
*Juvenile Diabetes Research Foundation Fellowship*
For studies of novel mechanisms and treatment strategies against type 1 diabetes through preservation of beta cell function and survival

Jani Saksi, PhD
*Sigrid Juselius Foundation Fellowship*
For studies of the mechanisms of action of the newly discovered hormone aP2-Fabp4 and its biological functions

Eva Tsaousidou, PhD
*American Heart Association Fellowship*
For studies of the molecular mechanisms underlying immunometabolic abnormalities in obesity and diabetes and activation pathways of PKR
Cells expressing “colorful cell” plasmid, which targets the following organelles: Mitochondria – Green, ER – Red, Peroxisome – Far Red, Nucleus – Blue.
Selected Publications

We are pleased to share a sample listing of the Department of Genetics and Complex Diseases high-impact 2018 publications:

Defective STIM-Mediated Store Operated Ca\(^{2+}\) Entry in Hepatocytes Leads to Metabolic Dysfunction in Obesity.

Arnuda AP, Perez AM, Porta-Gil G, Gurney L, Goh T, Cagampang E, Lee GY, Goncalves RL, Hotamisligil GS. eLife, December 2017

Brown Adipose Tissue Thermogenic Adaptation Requires Nrf1-Mediated Proteasomal Activity.


A Common Food Preservative Increases Post-Prandial Hepatic Glucose Production.


TACI-Deficient Macrophages Protect Mice Against Metastamification and Obesity-Induced Dysregulation of Glucose Homeostasis.


Deregulation of CRTCs in Aging and Age-Related Disease Risk.

Squires CC, Silva-Garcia CG, Mair WB. Trends in Genetics, April 2018

Low-Fat vs Low-Carbohydrate Diets and Weight Loss. A Randomized Controlled Trial.

Qi L, Bray GA, Sacks FM. Journal of the American Medical Association, July 2018

Apolipoproteins E and CII Interact to Regulate HDL Metabolism and Coronary Heart Disease Risk. Impaired HDL Subspecies Defined by Presence of Apolipoprotein C-III and Incident Coronary Heart Disease in Four Cohorts.


High-Density Lipoprotein Subspecies Defined by Presence of Apolipoprotein C-III and Incident Coronary Heart Disease in Four Cohorts.


ARMMs as a Versatile Platform for Intracellular Delivery of Macromolecules.


The Sabri Ülker Center has provided us with the unique opportunity to pursue solutions for one of the greatest epidemics of our modern world – metabolic disease – in an uninterrupted and free manner. We are honored to have the privilege to carry on this mission with the highest standards of scholarship and utilize the cutting-edge technology platforms such as those at the Sabri Ülker Imaging Center and at the Harvard University campus and beyond.

This mission fills us with joy and gratification as we guide our trainees in their scientific development. While acquiring new technical skills and unfolding their scientific thought to address the most challenging metabolic biology questions, they bring to light surprising discoveries about physiological and pathological processes that will pave the way to prevent and expand treatments for metabolic diseases. In this annual report, we have presented a brief summary of their achievements as well as the research and training activities of our Center. We are grateful to the Ülker family for making it possible for us to pursue our scientific passions and make tangible progress toward improving human health.
Liver cells expressing “colorful cell” plasmid, which targets the following organelles: Mitochondria - Green, Golgi - Yellow, ER - Red, Peroxisome - Far Red, Nucleus - Blue.