

*for* Nutrient, Genetic, and Metabolic Research

The Decade of Discovery 2017 Annual Report



HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

This third year of the Sabri Ülker Center for Nutrient, Genetic, and Metabolic Research has been marked by excellent progress on multiple fronts, including personal accomplishments of our trainees, publication of studies that were years in the making, and surprising scientific findings that challenge established dogma. Work in the Center is focused on advancing basic research to address the cellular and molecular mechanisms that underlie chronic metabolic diseases. which pose the greatest threats to global human health. This year we have developed new screening platforms for the identification of novel molecules and mechanisms that modulate cell stress response systems, and have utilized technology available through the Sabri Ülker Imaging Lab and the Harvard community to uncover the structural changes that our cells undergo in response to fluctuations in energy supply. We look forward to pursuing these lines of investigation as paths toward our ultimate goal of understanding how our cells manage nutrients and energy, and developing new approaches to treat and prevent metabolic disease. Lastly, we continue our commitment to training the next generation of scientists.

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# WE CONTRIBUTE





"The Sabri Ülker Center for Nutrient, Genetic, and Metabolic Research is dedicated to promoting scientific advancement in understanding the underlying mechanisms of chronic metabolic diseases, as well as identifying preventive measures and novel therapeutic avenues to combat these greatest threats to global health."

#### Gökhan Hotamışlıgil, MD, PhD

Director of the Sabri Ülker Center for Nutrient, Genetic, and Metabolic Research, Chair, Department of Genetics and Complex Diseases and James S. Simmons Professor of Genetics and Metabolism at the Harvard T.H. Chan School of Public Health

# It is with great pride that I provide you with this update about the 2017 accomplishments of the Sabri Ülker Center.

This year was marked by important scientific progress in multiple areas. We made exciting advances in our understanding of how liver cells respond to the stress of cholesterol overload, and how protein turnover affects the cells that help our bodies maintain their temperature. Importantly, this work has identified key signaling nodes that could be used as targets to design new therapeutic interventions to combat the metabolic decline associated with aging and obesity. Utilizing cutting-edge imaging techniques available through the Sabri Ülker Imaging Center and at Harvard, our researchers made unexpected observations regarding how cells alter their structure in response to fluctuations in nutrient availability, and characterized the molecular machinery that controls the balance of ions within cellular compartments. We completed a study that provided surprising insights into the connection between aging and metabolic health and revealed unexpected effects of a common food preservative on metabolic health. These are some emerging new areas of inquiry that we will continue to explore and advance utilizing our technology platforms.

Most excitingly, we are actively involved in planning the Second International Symposium on Metabolism and Life, which will be held next May in Boston. We have engaged an unparalleled lineup of speakers, featuring Nobel Prize laureates and international leaders in the field, as well as an impressive group of young investigators who constitute our Rising Star presenters. I have no doubt that this event will be a success, honoring our goal of promoting global scientific development and providing our trainees and junior scientists with outstanding opportunities to network, establish collaborations, and hear from groundbreaking scientists.

I hope you enjoy reading about our efforts and accomplishments.

Sincerely,

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GÖKHAN S. HOTAMIŞLIGIL, MD, PhD

# WE PROVIDE EXTRAORDINARY







Cos-7 cells, a monkey kidney cell line, showing mitochondria in red and endoplasmic reticulum in blue/ green/yellow. These cells are very flat and commonly used in the field of cell biology to study the structure of organelles. These cells are typically 30 microns wide and 1-2 microns thick

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During the past year, we have been pleased to witness the completion and publication of several exciting and innovative studies led by members of the Sabri Ülker Center.

We feel that these new insights into the interfaces between nutrient sensing and metabolism, cellular function, and ultimately human diseases have not only furthered our scientific knowledge of these areas but have suggested new pathways for potential therapeutic interventions.

The highlight of the year was a groundbreaking study led by postdoctoral fellow Scott Widenmaier that added an entirely new view to our understanding of the regulation of metabolism of cholesterol, one of the key molecules involved in cellular function as well as whole-body metabolism. Because of its significant role in major maladies like cardiovascular and metabolic disease, cholesterol metabolism has long been a focus of intensive study, yet our results reveal for the first time a mechanism by which cells respond to high intracellular cholesterol levels and complement a long-standing paradigm of cholesterol regulation.

Another critical study revealed a previously unknown function of molecular quality control systems in determining the metabolic function of adipose tissue that has been recently appreciated as a key contributor to whole-body energy balance and a potential target of treatments for obesity and metabolic diseases. We also published a study providing a novel view of the relationships among nutrient intake and metabolism in determining health and lifespan in aging animals illustrating a path to extend metabolic health throughout life.

These and several other publications including important collaborative studies continue our track record of contributions to the science of metabolism as it relates to human disease.

"Yin-Yang of Cholesterol Management"

#### Nrf1 Is an ER Membrane Sensor That Is Central to Cholesterol Homeostasis

Widenmaier SB, Snyder NA, Nguyen TB, Arduini A, Lee GY, Arruda AP, Saksi J, Bartelt A, Hotamışlıgil GS *Cell, November 2017* 



Cholesterol is an essential component of cellular membranes, and its concentration has profound effects on membrane properties, cellular processes, and organismal function. Cholesterol is highly responsive to nutrients and genetic factors in humans, and dysregulated levels are a strong risk factor for cardiovascular disease and other maladies.

While the harmful effects of cholesterol have been predominantly linked to its increased levels in the circulation, it is within the cells that many critical processes take place and the metabolism of cholesterol must be tightly controlled for proper function. A well-established paradigm in cell biology is the system by which cells respond to low cholesterol levels. The transcription factor serum response element-binding protein-2 (SREBP2) is synthesized as an inactive precursor form that is associated with the ER membrane. Under conditions of low cholesterol concentration in the

endoplasmic reticulum (ER) membrane, SREBP undergoes proteolytic cleavage allowing the transcription activation domain of the protein to be translocated to the nucleus where it promotes expression of enzymes required for cholesterol synthesis, thus restoring cholesterol concentrations.

However, parallel mechanisms that respond to high cholesterol content in the cells have not been previously elucidated. In our earlier work, we have identified a critical role for ER in metabolic regulation beyond its classic function in protein quality control and trafficking. Interestingly, the ER in all cells contains the lowest amount of cholesterol, hence rendering this membrane structure the potential to serve as a sensor of cholesterol. Since it is paramount that cells must be protected from excess cholesterol, which is highly toxic, we envisioned that a response system to protect against the rise in cellular cholesterol must exist and may reside in the ER. This study describes the discovery of a novel mechanism for such sensing and ameliorating high cholesterol levels in cells and protection against the damage due to its accumulation. We demonstrate that the transcription factor nuclear factor erythroid factor-2, like-1 (Nfe2I1, also known as Nrf1) is localized in the ER and contains structural elements to recognize cholesterol. Interestingly, Nrf1 protein levels are greatly increased by exposure of cells to cholesterol, as well as by feeding animals a high cholesterol diet. Most strikingly, livers of mice with a specific deletion of hepatic Nrf1 expression (Nrf1<sup>L-KO</sup> mice) accumulated massive amounts of lipids, primarily cholesterol-derived species, when fed a high cholesterol diet. This striking metabolic abnormality could be reversed by replenishing Nrf1 in deficient livers strongly implicating Nrf1 as a key regulator to restrain cholesterol accumulation and related damage.

These observations raised the question of how Nrf1 senses and responds to cholesterol levels. Our results show that Nrf1 directly senses ER cholesterol via binding to a specific domain in the protein, an essential feature that regulates multiple aspects of Nrf1 behavior and function including its translocation to the nucleus. In the presence of elevated cholesterol, Nrf1 is excluded from the nucleus, which unleashes the defensive countermeasures program to defend against cholesterol excess. We also identified the immunometabolic components of this adaptive response and identified a candidate molecule directly targeted by Nrf1.

Taken together, these results suggest that Nrf1 is a sensor for high cholesterol that functions in a complementary, opposite way to low cholesterol sensing by the SREBP2 system. These counterbalancing systems permit fine-tuning of cholesterol levels, critical to normal cellular functions. We believe these critical observations fill an important gap in understanding cholesterol metabolism and the cellular- or organ-based adaptive responses to nutrient fluctuations. Targeting of these built-in adaptive responses, such as the case with Nrf1, could provide a novel approach to ameliorate pathologies related to cholesterol accumulation and improve treatment of metabolic diseases.

We believe these critical observations fill an important gap in understanding cholesterol metabolism and the cellular or organ based adaptive responses to nutrient fluctuations.

"Lifelong Metabolic Health"

# Uncoupling of Metabolic Health from Longevity through Genetic Alteration of Adipose Tissue Lipid Binding Proteins

Charles KN, Li M-D, Engin F, Arruda AP, Inouye K, Hotamışlıgil GS *Cell Reports, October 2017* 



Evolutionarily conserved pathways that impact longevity and aging (such as insulin and insulin-like growth factor pathways) overlap with systems that respond to nutrients and regulate metabolism. Furthermore, many studies have confirmed clear connections between energy balance, metabolic health, and longevity: overnutrition and obesity are associated with impaired metabolic health and reduced longevity whereas caloric restriction (CR) promotes metabolic health and increased longevity. However, even among "healthy" weight individuals, risk of metabolic dysfunctions increases with age. Furthermore, while it is well known that inflammation appears and metabolic health typically deteriorates with age, it is unclear whether these problems could be prevented throughout life and if such an intervention would extend healthspan and/or lifespan.

In this study, led by joint first authors Khanichi Charles and Min-Dian Li, we first demonstrate that mice that are deficient in fatty acid binding proteins FABP4 (aP2) and FABP5 (mal1) are markedly resistant to age-related obesity, inflammation, insulin resistance, diabetes, fatty liver disease, and brown adipose tissue degeneration. This preservation of metabolic health was evident even after long-term exposure to a high-fat, high-calorie diet. From earlier studies, we also know that deficiency of FABP4 and FABP5 also protects against atherosclerosis and extends survival in apolipoprotein E-deficient mice. This finding demonstrates that lipid binding proteins are control regulators of metabolic health and do so in a sustained manner. Thus, the FABP-deficient mice provide a useful model to address the question of whether preservation of metabolic health contributes to the extension of lifespan.

Interestingly, we also discovered that FABP deficiency mimics several features of long-term caloric restriction. However, we were surprised to discover that despite the metabolic similarities to the CR regimen, and a remarkable preservation of metabolic health, FABP deficiency did not result in extension of lifespan in mice. Furthermore, FABP deficiency did not result in improvements in measures of cardiac, muscle, or cognitive features of aging mice. FABP deficiency, therefore, represents a unique model in which longevity and most measures of aging are uncoupled from metabolic health. This work may inform future work seeking therapies for metabolic diseases as well as other conditions associated with aging in humans. The ability to extend the number of years that people are healthy would be a highly impactful achievement from a public health perspective. Identification of a potential mechanism and simple interventions to target this mechanism may help us get closer to attaining this goal. FABPs present one attractive target for interventions to preserve metabolic health throughout life.

Survival of Tissue-Resident Memory T Cells Requires Exogenous Lipid Uptake and Metabolism Pan Y, Tian T, Park CO, Lofftus SY, Mei S, Liu X, Luo C, O'Malley JT, Gehad A, Teague JE, Divito SJ, Fuhlbrigge R, Puigserver P, Krueger JG, Hotamışlıgil GS, Clark RA, Kupper TS *Nature, March 2017* 



In recent years, it has been recognized that alterations in metabolism in innate and adaptive immune cells occur concomitantly with activation or alterations of the inflammatory phenotype of those cells. This includes alteration in fatty acid metabolism, and our group has a continuing interest in exploring the roles of fatty acid binding proteins including FABP4 (aP2) and FABP5 (mal1) in modulating metabolism in a variety of cell and organ contexts.

In this collaboration with colleagues at the Dana-Farber Cancer Center, Brigham and Women's Hospital, and others, the functions of FABP4 and FABP5 as regulators of the properties of tissue-resident memory T ( $T_{RM}$ ) cells of skin were explored. These cells, which are critical for resistance to infection by various pathogens, express high levels of FABP4 and FABP5 following an infection challenge. Further, it is demonstrated that  $T_{RM}$  cells derived from double-knockout mice that lack expression of both FABP4 and FABP5 are defective in protection from an infection challenge due to impaired survival of the resident T cells. These cells were also defective in utilizing exogenously supplied fatty acids as a fuel source via mitochondrial oxidation, suggesting that fatty acid uptake and oxidation are critical to the long-term survival of the T\_{RM} cells.

Increased FABP4 and FABP5 expression and enhanced extracellular fatty acid uptake were also demonstrated in human  $T_{RM}$  cells. The functions of these cells are important in effective vaccine responses, but also contribute to autoimmune pathologies, thus understanding of these key metabolic pathways may inform both of these areas of human medicine and pave the way for new therapeutic approaches.

#### The Cold-Induced Lipokine 12,13 diHOME Promotes Fatty Acid Transport into Brown Adipose Tissue

Lynes MD, Leiria LO, Lundh M, Bartelt A, Shamsi F, Huang TL, Takahashi H, Hirshman MF, Schlein C, Lee A, Baer LA, May FJ, Gao F, Narain NR, Chen EY, Kiebish MA, Cypess AM, Blüher M, Goodyear LJ, Hotamışlıgil GS, Stanford KI, Tseng Y-H *Nature Medicine, May 2017* 



Along with its vital metabolic functions, adipose tissue has been recognized as a rich source of endocrine factors including peptide hormones that have profound effects on whole-body energy homeostasis, affecting diverse properties such as food seeking and satiety as well as insulin sensitivity of other organs such as the liver. Our lab and others also discovered that lipid synthesis in adipose tissue is a source of potent lipid species, termed lipokines, which constitute a new class of metabolic hormones and affect remote tissues.

This paper reports results of a study carried out in collaboration with colleagues at the Joslin Diabetes Center of the Harvard Medical School and others. The objective was to identify additional novel lipokines that might be involved in the regulation of brown adipose tissue (BAT) function. BAT is a specialized form of adipose tissue that is adapted to consume lipids and other fuels to produce heat to maintain body temperature in cold-exposed animals. The enormous capacity of BAT to utilize caloric energy makes it an attractive target for treatment of obesity and related metabolic disorders.

This study employed liquid chromatography–tandem mass spectrometry (LC–MS/MS) to identify and quantify lipid species whose abundance was altered by cold exposure of mice, a treatment known to activate BAT and increase its metabolic activity. This approach identified 12,13-diHOME (12,13-dihydroxy-9Z-octadecenoic acid) as a species significantly increased in blood samples of cold-exposed mice. It was also confirmed that the same lipid molecule increased in abundance in blood samples taken from several cold-exposed human subjects. Treatment of mice with 12,13-diHOME led to increased BAT metabolic activity and improved resistance to cold exposure in mice. Mechanistically, one of the functions of 12,13-diHOME is to increase fatty acid uptake via enhancing the activity of fatty acid transporter proteins, consistent with promoting increased availability of a major fuel for thermogenesis. Identification of lipid mediators of thermogenesis like 12,13-diHOME might provide novel and simple approaches to activation of BAT as a potential therapy for obesity.

#### Inflammation, Metaflammation and Immunometabolic Disorders

Hotamışlıgil GS *Nature, February 2017* 



It is now well recognized that close interactions between immune responses and metabolism are required for health and underlie the pathology of many chronic diseases such as obesity and diabetes. This comprehensive analysis provides a synthesis of the field and covers advances in understanding the details of these interactions. Also discussed is emerging human genetics linked to susceptibility to immunometabolic disorders, as well as the exciting translational paths and recent trials of novel pharmaceutical interventions in these disorders.

#### The Foundations of Immunometabolism and Implications for Health and Disease Hotamişligil GS

Immunity, September 2017



This review provides a historical background and timeline as well as a description of recent advances that have led to a better understanding of the complex interactions between immune responses and metabolism, especially in situations of chronic nutrient excess. Also discussed is the impact of nutritional and metabolic status on the functional programming of immune cells. Immunometabolic interactions underlie the pathology of many significant diseases including obesity, diabetes, and cardiovascular disease, thus continued investigation in this area is vital to the development of novel therapeutic approaches.

#### **ER Stress Promotes Inflammation through Re-Wired Macrophages in Obesity**

Garfinkel BP and Hotamışlıgil GS *Molecular Cell, June 2017* 



It is well established that inflammation and ER stress are hallmarks of obesity and diabetes and contribute strongly to the pathogenesis of these diseases. Work in our lab and many others has also established endoplasmic reticulum (ER) stress as a major pathway that contributes to the pathology of metabolic diseases. In this Preview, we comment on work by Shan, et al. (*Molecular Cell, June 2017*) that sheds new light on a molecular mechanism by which ER stress contributes to inflammation and causes cellular and physiological dysfunction associated with obesity. This study showed that activation of the ER stress sensor IRE1 $\alpha$  in macrophages associated with adipose tissue in obesity shifts their population toward a pro-inflammatory M1 phenotype. This study reveals that ER stress in immune cells, in addition to adipocytes, compounds the inflammatory state of obese adipose tissue.

#### **Immune Cell Intolerance for Excess Cholesterol**

Widenmaier SB and Hotamışlıgil GS *Immunity, December 2016* 



The intricate relationship between metabolism and the immune system is critical in health and disease. In this Preview, we comment on recent findings by Ito, et al. (*Immunity, December 2016*) that describe a new connection between defects in cholesterol metabolism in immune cells and defects in immune response that might contribute to the pathology of autoimmune diseases. It is demonstrated that dysregulated cholesterol levels affect the function of CD11c<sup>+</sup> cells (antigen-presenting cells that activate T- and B-cells critical in immune responses). Excess cholesterol accumulation in CD11c<sup>+</sup> cells leads to activation of T-cells and production of antibodies that recognize self-antigens, a hallmark of autoimmune diseases. These findings suggest that treatments that normalize cholesterol control in CD11c<sup>+</sup> cells could be effective therapies for many common diseases that result from autoimmune responses.

#### Type I Interferons Interfere with Liver Glucose Metabolism

Parlakgül G and Hotamışlıgil GS *Cell Metabolism, June 2017* 



Glucose production by the liver is normally suppressed by insulin when it is secreted in response to feeding. Failure of this response is a major contributor to excess blood glucose levels in diabetes. In this Preview, we comment on recent work by Ghazarian, et al. (*Cell Metabolism, June 2017*) that proposes a novel connection between obesity, inflammation in the liver, and consequent failure to respond to insulin. These observations suggest that alterations in gut bacteria trigger production of inflammatory mediators including type I interferon by immune cells in the liver, which in turn cause insulin resistance. This paper adds to a body of recent work implicating alterations in gut microbiota in the pathology of metabolic diseases.

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Cos7 cells, expressing "Colorful Cell" plasmid that targets the following organelles: Mitochondria – green, ER – red, Peroxisome – far red, Nucleus – blue

# WE INVEST IN TRAINING FOR THE





#### **NEXT GENERATION OF SCIENTISTS**



#### a. Where are you from?

I'm from Oshawa, Ontario, Canada; a city just outside of Toronto. I completed both my bachelor's and PhD training at the University of Toronto. During my time at the university, I also produced commissioned paintings for individual clients to help pay my tuition and living expenses as I pursued my science degree. I still paint occasionally, though now it is mostly for pleasure. Most of my artistic skills are now used for scientific illustrations, presentation, and figures.

#### a. What were you doing before you joined the Center?

Before joining the Hotamışlıgil lab I completed my PhD in the lab of Dr. Michael Wheeler in the Physiology Department at the University of Toronto, Canada. There I worked primarily on insulin-producing pancreatic beta cells, examining how circulating factors affect insulin biosynthesis and secretion to contribute to the development of Gestational and Type 2 Diabetes.

## a. Why did you decide to join the Center for your postdoc?

First and foremost, I was attracted to the diversity of basic science and translational research taking place in the lab. After finishing my PhD I wanted to continue with research in metabolic disease and diabetes while expanding my breadth of knowledge from beta cells to other tissue types. The Hotamışlıgil lab provided the perfect opportunity to diversify my skill set and develop a new perspective on investigating metabolic diseases. In addition, the lab's industry collaborations and the opportunity to work on a project with direct potential for translation to humans was a significant contributing factor to my decision, as ultimately I hope my work can make a difference in the lives of patients.

KACEY PRENTICE, PhD Postdoctoral Fellow 2015–present

# a. Can you tell us a little about your main project?

I am working on a protein called aP2 that is secreted from fat cells into circulation during periods of fasting and obesity. Previous work from our group and others has shown that reducing aP2 levels, both in humans and rodent models, prevents the development of a wide array of diseases including diabetes and cardiovascular disease. I am currently working to understand how aP2 regulates signaling in diverse tissue types, including beta cells and the liver, to induce metabolic dysfunction, and how we can therapeutically target this signaling.

## a. What is most challenging about your work?

The most challenging part of working in the Hotamışlıgil lab is staying focused on one specific question. In the lab we are incredibly fortunate to have the intellectual freedom and resources to pursue any direction of research we choose within our projects. This facilitates creativity and discovery, but it can also be difficult to focus on one line of questioning when there are so many exciting options, leading to many long days (and nights!).

## a. Where do you see yourself in 5 years?

In 5 years I hope to have an independent faculty position at an academic institution. My goal is to have my own research group investigating circulating factors that affect beta cell function and insulin secretion in health and disease. I hope to gain a greater understanding of nutritional and inter-organ regulation of insulin secretion and identify potential biomarkers and novel therapeutic targets that can help in the prevention and treatment of diabetes.

#### **NEXT GENERATION OF SCIENTISTS**



#### a. Where are you from?

I am from Turkey, and graduated from Kocaeli University Medical School.

## a. What were you doing before you joined the Center?

I started my professional career in the Sabri Ülker Center right after my graduation. During my medical studies, I carried out research on metabolism of NASH (non-alcoholic steatohepatitis) patients.

#### Why did you decide to join this Center?

I wished to develop my critical and analytical thinking skills, and apply these as a physician-scientist to contribute to human health. I had followed the work of the Hotamışlıgil lab during my studies and was inspired by their work in the area of metabolism. I visited the lab and was really impressed by the lab members' motivation and joy for science. Dr. Hotamışlıgil was very warm and supportive to lab members. I chose to follow this path and was lucky to be able to join in 2011 as a postdoctoral fellow.

#### Can you tell us a little about your main project?

While in the lab, I was involved in the exciting discovery of a new hormone called aP2. This hormone is released by fat cells and increases glucose production in liver contributing to hyperglycemia in diabetes. This finding added to our understanding of obesity-related diabetes and suggested that aP2 could be a novel therapeutic target. We produced antibodies against aP2, and discovered one that decreased fasting blood glucose, improved insulin sensitivity, and decreased fat accumulation in the liver in high fat dietinduced obesity. This finding gave us tremendous hope for translational applications to treat diabetes and fatty liver disease. M. FURKAN BURAK, MD Postdoctoral Fellow 2011–2014 Visiting Scientist 2014–present

# a. What surprised you when you joined the Center?

I was nicely surprised by the collegiality in the lab. It was a great opportunity to work in an environment where I had the luxury to make mistakes, to be independent, to learn without limits, and to contribute to human health. As I progressed through my clinical years, I have continued to work with the Sabri Ülker Center, which has significantly enhanced my career. The collaborative culture in the lab made it possible for me to grow and continue my research.

In our discussions, Gökhan always encouraged me and kept saying: the sky is the limit! Then I realized that every contribution one makes to human health through a scientific discovery will become a little star in the sky that enlightens our world.

## a. Where did you go after you left the Center?

Due to my deep interest in seeing the translational effects of my bench work at the bedside, I started an internal medicine residency at Mount Auburn Hospital, Harvard Medical School. After graduation from residency, I started an endocrinology fellowship at Brigham and Women's Hospital, where I have continued both my clinical practice and research in the lab. I am always thankful to Gökhan Hotamışlıgil for this great opportunity and the Ülker family for their generous contributions to our research.

## Where do you see yourself in 5 years?

I treat diabetic patients on a daily basis but the Center gave me the opportunity to have an impact both on my individual patients and hopefully more broadly through drug discovery and improved medical therapeutics. I would like to follow my passion and apply the things that I learned from the Center in my own research group, fighting against diabetes and obesity and establishing a clinical metabolic wellness center to translate our discoveries to patients.

#### NEXT GENERATION OF SCIENTISTS



# a. Where are you from?

I was raised on a grain farm in the province of Saskatchewan, part of the prairie lands of Canada.

#### What were you doing before you joined the Center?

I was living in Vancouver, Canada, earning a PhD in Physiology at the University of British Columbia. I was studying the mechanism of action of gut-derived hormones called incretins. These hormones have emerged as a powerful class of therapeutics for people with Type 2 diabetes.

#### a. Why did you decide to join this Center for your postdoc?

One of the reasons I choose the Hotamışlıgil group was because it comprises people with expertise ranging from clinical medicine to basic molecular biology as well as people coming from around 12 different countries and 4 different continents. I enjoy and benefit from being in this kind of intellectually diverse environment. But I think the tipping point for me occurred in a private conversation with Dr. Hotamışlıgil, in which I felt confident that he would be willing to support me pursuing a new line of research rather than expanding upon ongoing projects. I had a strong desire to pursue this more open-ended kind of project.

#### Can you tell us a little about your main project?

My interest is in understanding how defense systems in humans and other mammals protect against excess consumption of food, and whether we can make these systems work better to treat disease. In my main project, SCOTT WIDENMAIER, PhD Postdoctoral Fellow, 2010–present

my colleagues and I are studying how a metabolic factory within the cell, called the endoplasmic reticulum, senses when too much cholesterol has been ingested and how this sensing triggers a set of molecular responses causing cholesterol to be removed from the cell. One exciting aspect of this newly identified defense mechanism is that it seems to be present in all cell types, so we are hopeful that it will have therapeutic implications for a multitude of diseases caused by cholesterol overload.

## a. What surprised you when you joined the Center?

One of my first surprises in the lab was the wealth of access to intellectual and material resources. For many of us who came from labs with limited resources, it is initially quite challenging to know how to take full advantage of this blessing for maximizing scientific progress. Another surprise for me was the degree to which members within the lab were choosing to team up and collaborate in order to solve questions that could not otherwise have been solved by any one individual.

## Where do you see yourself in 5 years?

I envision I will be leading an independent research group that is focused on solving important and fundamentally profound biological questions, which nobody else had even thought to ask, and inspiring other scientists to do the same. I hope that I will continue my work in science to make an impact on human life.

Hepa1-6 cells, expressing "Colorful Cell" plasmid that targets the following organelles: Mitochondria - green, Golgi - yellow, ER - red, Peroxisome - far red, Nucleus -blue

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# WE ADVANCE KNOWLEDGE THROUGH IMPACTFUL









Live cell showing the tubular structure of mitochondria in green and nucleus in blue

# GENETICS AND COMPLEX DISEASES

Faculty members within the Department of Genetics and Complex Diseases are recognized for their unique and impactful contributions to the science of metabolic biology. These achievements highlight the ongoing quest to gain insight into complex human diseases through basic research. These include:



#### Robert V. Farese, Jr., MD

Professor of Genetics and Complex Diseases Department of Genetics and Complex Diseases Harvard T.H. Chan School of Public Health Professor of Cell Biology, Harvard Medical School

The Endocrine Society awarded Dr. Farese the prestigious Roy O. Greep Award for Outstanding Research. This award was bestowed in recognition of Dr. Farese's seminal contributions to the understanding of cellular lipid metabolism.



#### William Mair, PhD

Associate Professor of Genetics and Complex Diseases Department of Genetics and Complex Diseases Harvard T.H. Chan School of Public Health

The American Federation for Aging Research awarded Dr. Mair the Breakthrough in Gerontology (BIG) Award for his cutting-edge research in the biology of aging.



#### Gökhan Hotamışlıgil, MD, PhD

Chair, Department of Genetics and Complex Diseases James S. Simmons Professor of Genetics and Metabolism Harvard T.H. Chan School of Public Health

The National Institute of Environmental Health Sciences (NIEHS) awarded Dr. Hotamışlıgil the prestigious Hans L. Falk Lectureship for his paradigmshifting work in understanding the important role of immunometabolism in complex diseases such as obesity, diabetes, and atherosclerosis.

#### **PUBLICATIONS**

2017 was a banner year for publications within the Department of Genetics and Complex Diseases. A summary of our faculty's high-impact publications is listed below:

Triglyceride Synthesis by DGAT1 Protects Adipocytes from Lipid-Induced ER Stress during Lipolysis. Chitraju C, Mejhert N, Haas JT, Diaz-Ramirez LG, Grueter CA, Imbriglio JE, Pinto S, Koliwad SK, Walther TC, Farese RV Jr. **Cell Metabolism, August 2017** 

Identification and Characterization of a Novel DGAT1 Missense Mutation Associated with Congenital Diarrhea. Gluchowski NL, Chitraju C, Picoraro JA, Mejhert N, Pinto S, Xin W, Kamin DS, Winter HS, Chung WK, Walther TC, Farese RV Jr. Journal of Lipid Research, June 2017

Mice Lacking Lipid Droplet-Associated Hydrolase, a Gene Linked to Human Prostate Cancer, Have Normal Cholesterol Ester Metabolism. Kory N, Grond S, Kamat SS, Li Z, Krahmer N, Chitraju C, Zhou P, Fröhlich F, Semova I, Ejsing C, Zechner R, Cravatt BF, Farese RV Jr, Walther TC.

Journal of Lipid Research, January 2017

The mTORC1 Signaling Network Senses Changes in Cellular Purine Nucleotide Levels.

Hoxhaj G, Hughes-Hallett J, Timson RC, Ilagan E, Yuan M, Asara JM, Ben-Sahra I, Manning BD.

Cell Reports, October 2017

mTORC1 Couples Nucleotide Synthesis to Nucleotide Demand Resulting in a Targetable Metabolic Vulnerability. Valvezan AJ, Turner M, Belaid A, Lam HC, Miller SK, McNamara MC, Baglini C, Housden BE, Perrimon N, Kwiatkowski DJ, Asara JM, Henske EP, Manning BD. Cancer Cell, November 2017

AKT/PKB Signaling: Navigating the Network. Manning BD, Toker A. Cell, April 2017

Metformin Inhibits Hepatic mTORC1 Signaling via Dose-Dependent Mechanisms Involving AMPK and the TSC Complex. Howell JJ, Hellberg K, Turner M, Talbott G, Kolar MJ, Ross DS, Hoxhaj G, Saghatelian A, Shaw RJ, Manning BD. *Cell Metabolism, February 2017* 

Dietary Restriction and AMPK Increase Lifespan via Mitochondrial Network and Peroxisome Remodeling. Weir HJ, Yao P, Huynh FK, Escoubas CC, Goncalves RL, Burkewitz K, Laboy R, Hirschey MD, Mair WB. *Cell Metabolism, December 2017* 

Mono-Unsaturated Fatty Acids Link H3K4me3 Modifiers to C. elegans Lifespan. Han S, Schroeder EA, Silva-García CG, Hebestreit K, Mair WB, Brunet A. *Nature, April 2017* 

Splicing Factor 1 Modulates Dietary Restriction and TORC1 Pathway Longevity in C. elegans.

Heintz C, Doktor TK, Lanjuin A, Escoubas C, Zhang Y, Weir HJ, Dutta S, Silva-García CG, Bruun GH, Morantte I, Hoxhaj G, Manning BD, Andresen BS, Mair WB.

Nature, January 2017

Hypothalamic-Pituitary Axis Regulates Hydrogen Sulfide Production. Hine C, Kim HJ, Zhu Y, Harputlugil E, Longchamp A, Matos MS, Ramadoss P, Bauerle K, Brace L, Asara JM, Ozaki CK, Cheng SY, Singha S, Ahn KH, Kimmelman A, Fisher FM, Pissios P, Withers DJ, Selman C, Wang R, Yen K, Longo VD, Cohen P, Bartke A, Kopchick JJ, Miller R, Hollenberg AN, Mitchell JR. *Cell Metabolism, June 2017* 

STING Senses Microbial Viability to Orchestrate Stress-Mediated Autophagy of the Endoplasmic Reticulum. Moretti J, Roy S, Bozec D, Martinez J, Chapman JR, Ueberheide B, Lamming DW, Chen ZJ, Horng T, Yeretssian G, Green DR, Blander JM. *Cell, November 2017* 

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"I believe deeply that bringing together the brightest minds from across the world allows us to build a stronger platform for excellence in scholarship and research."

#### Mark C. Elliott, PhD

Vice Provost of International Affairs at Harvard University Mark Schwartz Professor of Chinese and Inner Asian History in the Department of East Asian Languages and Civilizations and in the Department of History in the Faculty of Arts and Sciences

## **COMMITMENT TO DIVERSITY**





# Harvard is a globally engaged university, committed to being a welcoming, international community.

I believe deeply that bringing together the brightest minds from across the world allows us to build a stronger platform for excellence in scholarship and research. As Vice Provost for International Affairs, I oversee international academic initiatives, facilitate international research opportunities, and help build relationships to bring international scholars to Harvard. In this vein, I am immensely grateful to the Ülker family for their support of the Ülker fellowship program, which enables young international scientists to pursue their postdoctoral training in an outstanding Harvard laboratory. I also look forward to working with the family to host Turkish and other international students at the Ülker Symposium to be held in Boston in 2018, and helping to show them all of the resources and opportunities that Harvard University has to offer.

Sincerely,

Mark Enit

MARK ELLIOTT, PhD



"The Center's work to address the expanding global health threats of chronic and complex diseases, including diabetes and cardiovascular disease, is a critically important component of the School's life sciences research program."

Michelle A. Williams, ScD Dean of the Faculty Harvard T.H. Chan School of Public Health

#### A MESSAGE FROM THE DEAN

![](_page_36_Picture_1.jpeg)

The Sabri Ülker Center for Nutrient, Genetic, and Metabolic Research is a jewel among the School's rich array of basic science laboratories and research centers.

The Center's work to address the expanding global health threats of chronic and complex diseases, including diabetes and cardiovascular disease, is a critically important component of the School's life sciences research program.

The School is proud to partner with the Ülker Foundation to advance the Center's vital public health mission. The Center's approach to scientific training, coupled with breakthrough nutrient and metabolic research, widely promoted through major publications, educational opportunities, and far-reaching events such as the Ülker Symposium, is a model for high-impact science in the public health sphere.

I applaud the Ülker Center for another productive year and look forward to further accomplishments in the year ahead.

Sincerely,

MICHELLE A. WILLIAMS, ScD

#### LOOKING FORWARD

![](_page_37_Picture_1.jpeg)

# I am exceedingly proud of our efforts in this third year of the Ülker Center, and as I look forward to 2018, I anticipate continued excitement and endurance as we promote scientific progress.

Our researchers are inspired to achieve the highest standard of scholarship with the ultimate goal of making discoveries that will expand scientific knowledge. We hope that one day these discoveries will inform public policy, human behavior, and therapeutic efforts to improve human health. We are incredibly fortunate to have access to cutting-edge technologies such as those available at the Sabri Ülker Imaging Center and the Harvard University campus. These resources enable our work at the Ülker Center to be at the global forefront of metabolic research. More broadly, we enjoy the rich intellectual environment of the Harvard community and the city of Boston.

As our group grows and changes, it is a tremendous honor to watch over the scientific development of our trainees. During their years here they hone their technical skills, improve their scientific thinking and communication, and eventually take steps to become independent researchers. As you have glimpsed in these pages, their efforts also produce important insights into physiological and pathological processes that are guiding strategies to treat and prevent diseases.

Lastly, I am also looking forward to our next Symposium on Metabolism and Life, to be held May 29–30, 2018, in the historic Memorial Hall, adjacent to the Harvard University undergraduate campus. Our guests will be treated to presentations from the leading stars of metabolism research. It is sure to be a most memorable event for our trainees and fellows, an unmatched opportunity to hear directly from their scientific heroes!

I am so grateful to the Ülker family for making it possible for us to pursue our scientific passions and make tangible progress toward improving human health.

![](_page_38_Picture_0.jpeg)

![](_page_39_Picture_0.jpeg)

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