



*for Nutrient, Genetic,
and Metabolic Research*

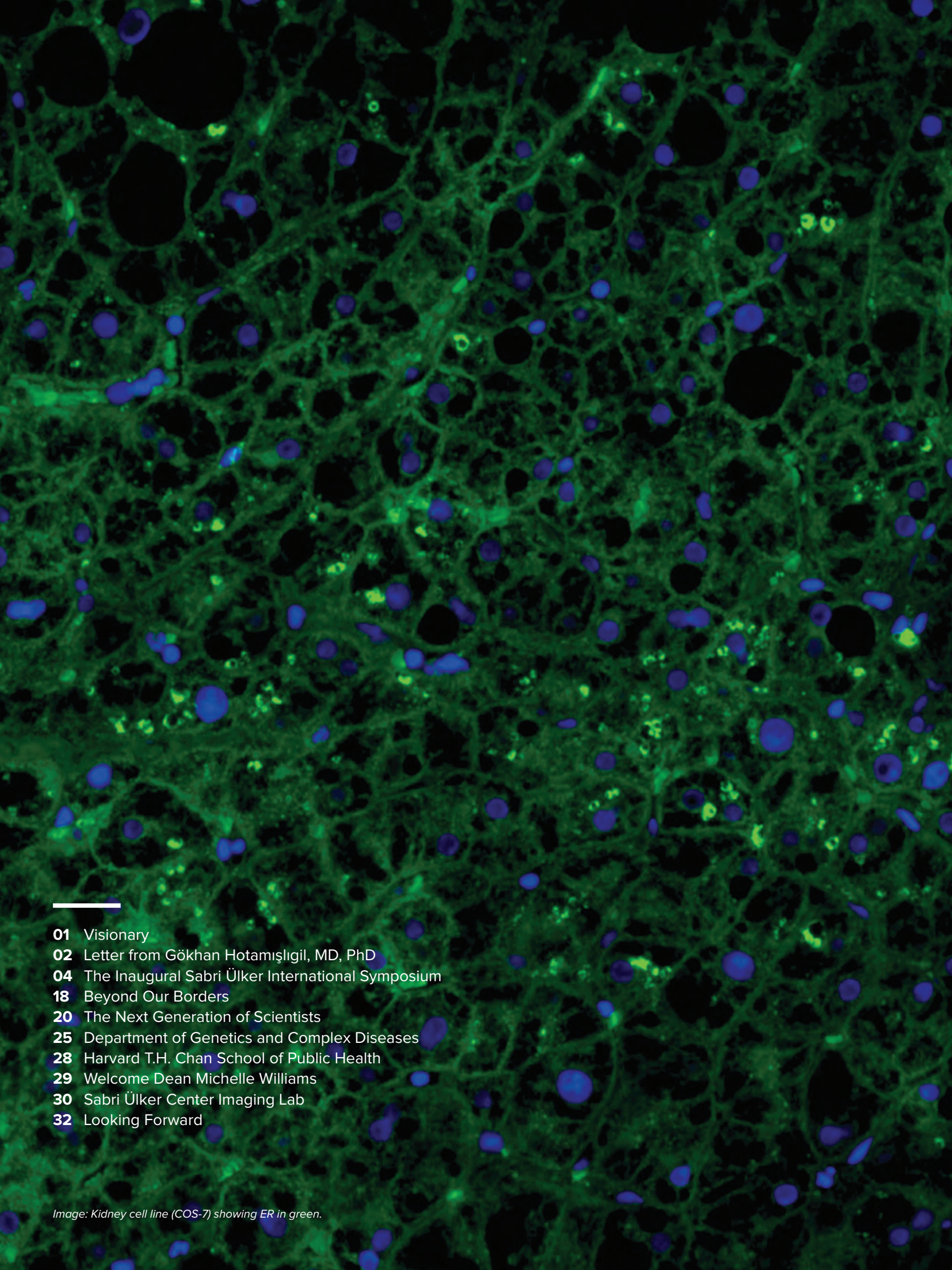
*The Decade of Discovery
2016 Annual Report*



DEPARTMENT OF
**GENETICS AND
COMPLEX DISEASES**



HARVARD T.H. CHAN
SCHOOL OF PUBLIC HEALTH



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Image: Kidney cell line (COS-7) showing ER in green.

Visionary

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.

This second year of the center has seen remarkable progress in several fronts, as our scientists have been able to follow their passion for discovery, develop new platforms for investigation, and make use of cutting-edge technologies to tackle challenging questions. Most importantly, this year was marked by the inaugural Sabri Ülker Symposium on Metabolism and Life, which was hosted in İstanbul by the Sabri Ülker Foundation and featured leading researchers from around the globe. Bringing the highest level of science to an audience of emerging local and regional scientists and students was a tangible extension of the mission of the Ülker Center to promote scientific education and intellectual development throughout the world.

Seeing the Invisible



“The Sabri Ülker Center Imaging Lab will allow us to continue and expand our discovery of the cellular and sub-cellular processes that contribute to metabolic disease.”

Gökhan Hotamışlıgil, MD, PhD

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

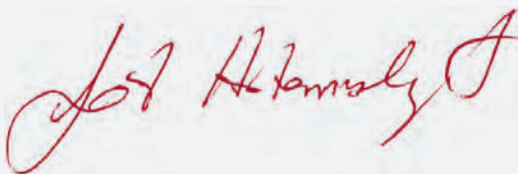
Dear Friends,

It is with great pleasure that I provide you with this update about the activities and accomplishments of the Sabri Ülker Center in 2016.

This year many of our researchers reached important milestones in their careers, completing their doctoral or postdoctoral work, progressing to independent careers, and preparing manuscripts describing discoveries that have resulted from their hard work and devotion. These discoveries and reports reveal some of our important findings regarding the effects of food preservatives, the mechanisms that enable our cells to adapt to nutrient overload, and surprising signaling pathways that connect adipose tissue action with systemic metabolism. One very exciting development, as detailed in these pages, was the opening of the Sabri Ülker Center Imaging Lab this autumn, outfitted with world-class imaging systems and analysis capability, which will allow us to examine cells in fine detail and continue to expand our ability to explore the cellular and sub-cellular processes that contribute to nutrient responses as they relate to metabolic disease. Importantly, this platform, equipped with confocal and other advanced microscopes, will also be an extremely valuable resource for other research groups within our community and will facilitate collaborative studies.

Most memorably, this year we organized an international symposium on Metabolism and Life that took place in İstanbul. We were able to attract outstanding speakers from different continents, who shared their groundbreaking work with an audience comprising both fellow scientists and many young Turkish and regional students and researchers. The event also featured Rising Star presentations from remarkable Turkish junior scientists and faculty, highlighting their outstanding contributions and illustrating their paths to success. Finally, the Sabri Ülker International Science Award recognized an exceptionally promising early stage scientist in the broad field of metabolism. This event was an unquestionable success, and our hosts at Sabri Ülker Foundation were absolutely terrific in every detail, setting a high bar for our future gatherings!

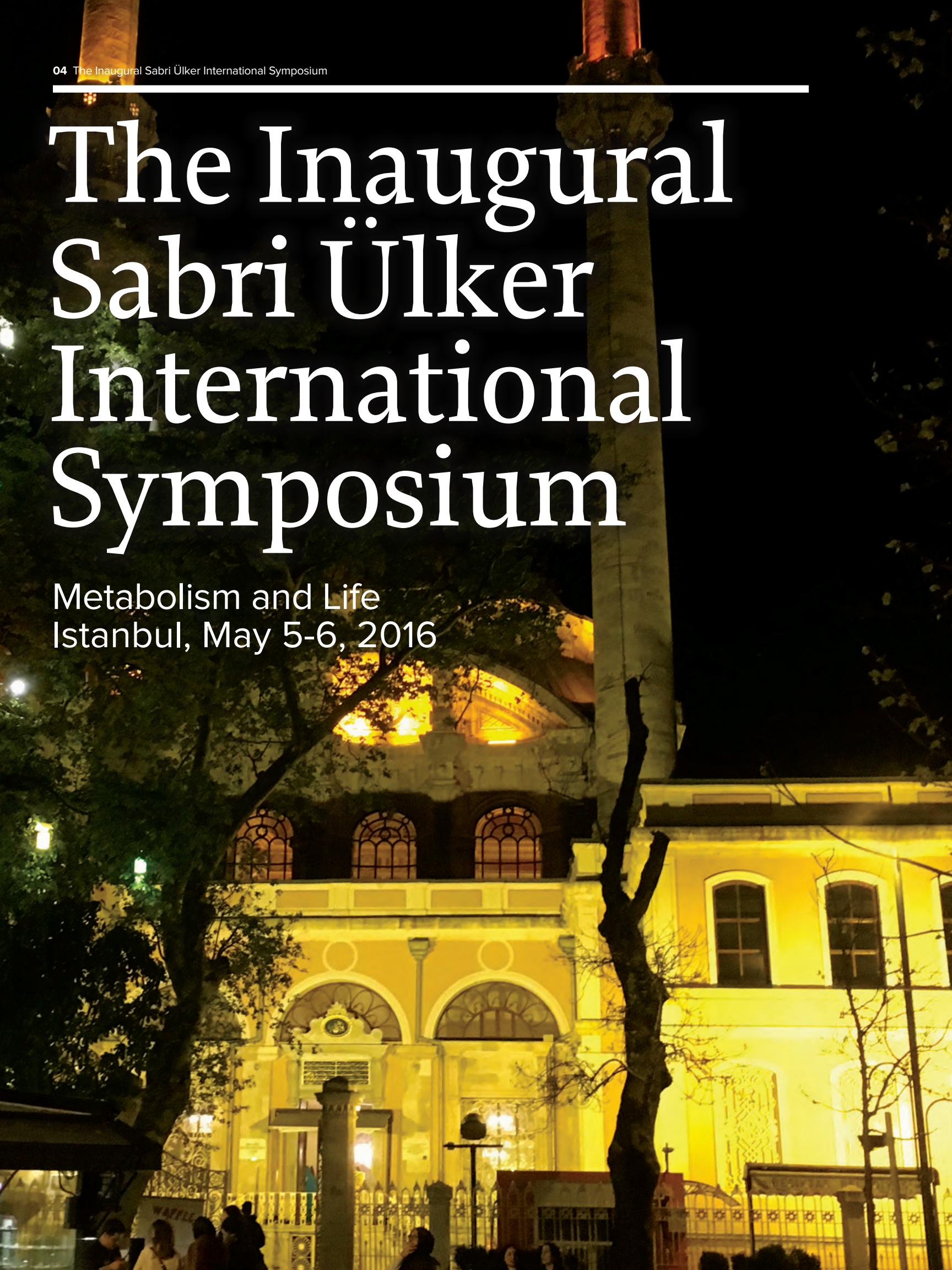
Sincerely,



Gökhan Hotamışlıgil, MD, PhD

The Inaugural Sabri Ülker International Symposium

Metabolism and Life
Istanbul, May 5-6, 2016





Keynote Lecture with Brian Kobilka

The inaugural Sabri Ülker Symposium, which took place May 5-6 in İstanbul, was designed to bring together world leaders in metabolism research to present their work before an audience of Turkish scientists and students.

The meeting fostered communication and collaboration, as scientists shared their unpublished work and made new connections across disciplines. In addition, the symposium highlighted the work of young Turkish scholars who are just beginning to make their mark in the field. Taken together, it was a rare and special opportunity to showcase groundbreaking science and promote investigation of the molecular underpinnings of metabolism, its interaction with nutrients, and its dysregulation in chronic disease.

Dr. Brian Kobilka, professor at Stanford University and winner of the 2012 Nobel Prize in Chemistry gave the keynote address of the evening. Dr. Kobilka's talk was focused on the use of structural methods to aid drug discovery, specifically how understanding the minute details of protein conformation can guide the development of new and groundbreaking therapeutics. Dr. Kobilka's career has been centered on elucidating the structure of G protein coupled receptors (GPCRs), which are responsible for receiving signals from hormones and neurotransmitters and conveying their intracellular effects. Many critical metabolic pathways operate through these receptors. Dr. Kobilka described how GPCRs transmit signals by pairing with intracellular G proteins and also act through an alternative pathway involving molecules called arrestins, which can result in differential effects. For example, pharmaceutically activating the opiod receptor can provide robust pain relief, but through arrestin-mediated signaling, the opiod receptor suppresses respiration and activates reward pathways, putting patients at risk for dependency. By capturing the tiny structural changes that differentiate GPCRs bound to G proteins from those bound to arrestins, scientists are now able to screen for drug candidates that preferentially act through one of those pathways, which will enable the discovery of drugs with fewer side effects.





The Inaugural Sabri Ülker International Symposium

“An unparalleled opportunity for attendees to engage with globally recognized leading scholars in the field of metabolism.”

Sabri Ülker International Science Award Winner



Dr. Kivanç Birsoy, a newly independent investigator and assistant professor at Rockefeller University, was one of the rising stars featured at the symposium and the winner of the inaugural Sabri Ülker International Science Award.

Dr. Birsoy described his work using systematic approaches to study cellular metabolism, particularly the pathways that are active in cancer cells. Although it is well known that cancer cells undergo a radical shift in their metabolic program to become more dependent on glycolysis to produce energy from sugar breakdown (a phenomenon known as the Warburg effect), many continue to also undergo aerobic respiration, which utilizes oxygen to produce energy. Dr. Birsoy explained his hypothesis that the continued reliance on aerobic respiration may indicate that byproducts of that pathway – rather than the energy generated – are important to support cellular proliferation. To explore this biology Dr. Birsoy is performing a screen to identify genes that are required for cell growth when processes that generate energy from nutrients in the mitochondria are mildly inhibited. The findings from this research may have far-reaching implications, as abnormal mitochondrial function is characteristic of many diseases including obesity, diabetes, neurodegeneration, ischemia, and cancer.

Sabri Ülker Symposium Speakers



Dr. Peter Tontonoz

*Professor, Pathology and
Laboratory Medicine University
of California, Los Angeles;
Investigator, Howard Hughes
Medical Institute*

Dr. Peter Tontonoz is a professor at the University of California Los Angeles School of Medicine and an investigator of the Howard Hughes Medical Institute. Dr. Tontonoz described his recent work on how different lipids influence cell function, as well as approaches to alter the lipid make-up of membranes for therapeutic opportunities against metabolic disease. He focused on the lysophosphatidylcholine acyltransferase (Lpcat) enzymes, which are the proteins that remodel phospholipids, important structural building blocks of cell membranes. The relative saturation of phospholipid chains is a major determinant of membrane fluidity as well as cellular function. Dr. Tontonoz's laboratory studies the function of LPCAT3, which drives the inclusion of unsaturated chains in phospholipids and is the major LPCAT enzyme in the brain, liver, intestine, and adipose tissue. Importantly, using tissue-specific deletion models, Dr. Tontonoz has made important discoveries including that LPCAT3 in the intestine is important for the uptake of lipids from the diet, while LPCAT3 in the liver is important for proper synthesis of lipoprotein particles and may be connected to cholesterol metabolism. Furthermore, this work has also revealed that LPCAT3, by regulating the phospholipid composition of the endoplasmic reticulum (ER) membrane, can control lipogenesis, with consequences for systemic metabolic and inflammatory phenotypes. These findings indicate that membrane composition generally, and LPCAT3 specifically, are promising potential therapeutic targets in combatting metabolic disease.



Dr. Susanne Mandrup

*Professor, Biochemistry
and Molecular Biology
University of Southern
Denmark*

Dr. Susanne Mandrup, a professor at the University of Southern Denmark and member of the Royal Danish Academy of Sciences and Letters, described in her talk how glucose-induced changes in gene expression influence beta cells. Beta cells in pancreatic islets produce insulin, making them critical determinants of systemic glucose homeostasis and important players in the development of diabetes. Dr. Mandrup's group is utilizing a combination of unbiased approaches to identify genes in beta cells that are acutely regulated in response to high levels of glucose. Notably, Dr. Mandrup described a novel method dubbed "iRNASeq", which summarizes the intron reads from RNA sequence analysis and normalizes to read length, to give a superior approximation of induced transcriptional changes. In addition, she is also using advanced methods such as chromatin immunoprecipitation coupled with sequencing and gain and loss of function of known players in this biology, such as the glucose-sensing transcription factor ChREBP, to finely map the regulation of glucose-induced genes. In doing so, Dr. Mandrup hopes to advance our understanding of how beta cells respond to environmental stimuli including glucose and gain insight into critical functional nodes that may be targets for the prevention or treatment of diabetes.

Sabri Ülker Symposium Speakers



Dr. Lale Ozcan

*Assistant Professor,
Department of Medicine
Columbia University
Medical Center*

Rising Star

Dr. Lale Ozcan, an assistant professor at Columbia University, was a rising star presenter. Due to the increased prevalence of cardiovascular disease in individuals with type 2 diabetes, all new diabetes therapeutics must be evaluated for their potential to influence cardiovascular risk. It has been shown that dysregulation of glucagon signaling is a major contributor to hyperglycemia in type 2 diabetes, but approaches that directly antagonize glucagon signaling have the unfortunate side effect of increasing plasma lipid levels and hence the risk of cardiac events. As Dr. Ozcan described, glucagon signaling increases cytosolic calcium levels, which activate a calcium-sensing enzyme called CaMKII. CaMKII, in turn, promotes hepatic glucose production and interferes with insulin signaling in hepatocytes. Dr. Ozcan's work suggests that targeting the signaling intermediates in this pathway may enable the development of metabolic disease therapies that avoid inducing undesired lipid phenotypes. In addition, she described her interest and preliminary investigation into the pathways that link glucagon signaling to altered lipid homeostasis, in the hope that this may reveal new points for metabolic disease intervention.



Dr. Alan Attie

*Jack Gorski Professor
of Biochemistry,
University of Wisconsin*

Dr. Alan Attie, a professor at the University of Wisconsin and a leading geneticist, spoke about the genetic architecture of insulin secretion and new platforms for identifying genes responsible for complex phenotypes in metabolism. Human studies suggest that many of the major genetic contributors to diabetes susceptibility are the genes that determine the capacity of beta cells to secrete insulin. Dr. Attie described a comprehensive and powerful screening method to discover new genes involved in this biology, utilizing a cross of eight mouse strains with different metabolic properties to recapitulate complex human genetics. This approach enables the identification of loci that modulate the insulin secretory response to various drugs and secretagogues, and has led to surprising insights into beta cell function. For example, Dr. Attie's group discovered that *Sorcs1*, a vacuolar sorting protein, is involved in the formation of insulin secretory granules, and showed that the prostaglandin E receptor 3 (EP3) is induced by glucose but antagonizes GLP-1 signaling. Interestingly, many of the loci identified in the screen so far are intronic, suggesting that their effects on insulin secretion may be difficult to unravel because they involve effects that are more nuanced than simply genetic loss of function. Furthermore, Dr. Attie speculated that by correlating multiple physiological and biochemical readouts with genetic markers, this type of analysis could allow for genetic mapping of other complex phenotypes, such as understanding the role of host genetics on the composition of the microbiome. The use of this platform combined with human genetic studies facilitates discovery of genes that may otherwise be overlooked. Dr. Attie invited other scientists to take advantage of this important open resource to facilitate their research efforts.

Sabri Ülker Symposium Speakers



Dr. Robert V. Farese, Jr.

*Professor, Genetics and
Complex Diseases
Harvard T.H. Chan School
of Public Health*

Dr. Robert V. Farese, Jr., delivered an eloquent and visually stunning talk about the mechanisms by which all cells store energy in the form of triglycerides within lipid droplets. Dr. Farese is a professor at the Harvard T.H. Chan School of Public Health, where he and his scientific partner Dr. Tobias Walther, an investigator of the Howard Hughes Medical Institute, co-direct a lab studying lipid storage, membrane biology and neurodegenerative disease in the department of Genetics and Complex Diseases. All cells must have measures to manage lipids, and lipid storage in the form of droplets is a fundamental process vital for survival and function. As Dr. Farese described, the diglyceride acyl transferase (DGAT) enzymes catalyze the last step in triglyceride synthesis, and work from his lab has been fundamental to the understanding of how DGAT proteins control the formation of lipid droplets. Interestingly, cells have two types of lipid droplets, initial (iLDs) and expanding (eLDs), and while DGAT1 appears to be most important for the formation of iLDs, DGAT2 localizes to the membrane of eLDs to synthesize new triglycerides and allow them to grow. Utilizing remarkable imaging techniques, Dr. Farese's group has been able to define the processes that lead to the formation of lipid droplets and understand how these are essential for cells to respond to normal fluctuations in nutrient availability and how they are dysregulated in metabolic disease.



Dr. Emilie Marcus

*CEO of Cell Press and
Editor of Cell*

The lunch break featured Dr. Emilie Marcus, a talented scientist who trained in neuroscience at Yale University and the Salk Institute before joining the scientific publishing world. Dr. Marcus' hard work and broad scientific interests resulted in a rapid rise to her current position as the CEO of Cell Press and Editor-in-Chief of the journal *Cell*. As the leader of this preeminent publication, Dr. Marcus has launched multiple initiatives to engage the readership in scholarly debate, provide scientists and students with opportunities to interact with editorial staff, and feature the personal stories of researchers that underlie their major discoveries. In her presentation, Dr. Marcus shed light on the sometimes mysterious biomedical publishing process and gave invaluable advice regarding how to optimally craft scientific manuscripts. Dr. Marcus also provided insight into the current fraud and reproducibility issues facing the biomedical science community, and stressed the importance of honesty and integrity in the preparation of figures and analysis of data, as well as the measures that need to be in place for its preservation. This discussion was highly informative for young students and scientists and was received with great enthusiasm. There was also a lively Q&A session and discussion following the presentation.

Sabri Ülker Symposium Speakers



Dr. Deniz Atasoy

*Assistant Professor, Physiology,
School of Medicine
Istanbul Medipol University*

Rising Star

Dr. Deniz Atasoy, a rising star presenter and an assistant professor at Istanbul Medipol University School of Medicine, spoke about his work studying the neuronal circuits that control feeding behavior. It has long been known that two neuronal populations in the hypothalamus coordinate appetite and food intake in mammals: while neurons that express the molecule POMC suppress feeding, neighboring cells that express AGRP promote feeding. Dr. Atasoy has utilized a novel and powerful technique called optogenetics, which involves using light to control the activity of specific neurons in the brain, to investigate the action of AGRP-expressing neurons. Remarkably, stimulating AGRP neurons using this approach is sufficient to induce voracious feeding behavior, even in experimental models that are already well-fed. Dr. Atasoy explained that he is now exploring the higher brain regions that control this behavior and how such behaviors could be manipulated experimentally. He is also using genetic markers to label and identify AGRP axon projections and synapses with electron microscopy to characterize the long-range connections from these neurons. By using these innovative approaches to shed light on the complex circuits that control our feeding behavior, Dr. Atasoy hopes to understand how they might be manipulated and managed to help fight the obesity epidemic and related health problems.



Dr. Laurie Glimcher

*President and CEO of
Dana-Farber Cancer Institute*

Dr. Laurie Glimcher, CEO and President of the Dana-Farber Cancer Institute and previously the Dean of Weill Cornell Medical College, provided a history of the field of cancer immunotherapy and shared recent insights from her own work on the subject. For more than a century, there have been hints that by activating the immune system it may be possible to direct the body to kill and eliminate tumor cells, and in the last five years, we have witnessed the development of therapies that activate T cells to drive them to attack tumor cells. However, as Dr. Glimcher described, a major obstacle in the cancer immunotherapy field is the micro-environment surrounding tumors, which often contains immunosuppressive cells that block T cell infiltration. Dr. Glimcher's lab has demonstrated that a stress response pathway emanating from the endoplasmic reticulum which includes the protein XBP-1 is highly activated in the dendritic cells that surround ovarian tumors, and that signaling through this pathway interferes with the ability of dendritic cells to recruit T cells. Remarkably, Dr. Glimcher and her group found that delivering nanoparticles that deplete XBP-1 in dendritic cells decreased tumor growth and increased survival in a mouse model of metastatic cancer. This highly promising pre-clinical work provides hope that similar strategies may be adopted to treat cancer patients and also illustrates the intricate links between immunity, metabolism, and tumorigenesis.

Sabri Ülker Symposium Speakers



Dr. Ira Tabas

*Vice-Chairman of Research,
Department of Medicine,
Columbia University; Professor of
Medicine and Anatomy & Cell Biology,
Columbia University College of
Physicians and Surgeons*

Dr. Ira Tabas, professor and vice chair of research at Columbia University, delivered his presentation on hepatocyte calcium signaling and endoplasmic reticulum (ER) stress in obesity and type 2 diabetes. Dr. Tabas is interested in finding the common signaling pathways that underlie the connection between type 2 diabetes and cardiovascular disease and developing ways to prevent or treat these common pathologies. Work from his group has shown that disordered calcium signaling leads to ER stress and defective insulin signaling both in the macrophages that reside in atherosclerotic plaques and in hepatocytes. He described the connections of this biological response to the actions of an enzyme that responds to calcium, CAMKII, and explained that genetic deletion of CAMKII in obese mice restores ER homeostasis and improves glucose homeostasis. Similarly, suppressing the activity of this enzyme alleviates ER stress in macrophages of atherosclerotic lesions, related to preferential formation of the anti-inflammatory leukotriene LTA4. Dr. Tabas's current work is focused on identifying additional downstream mediators of this pathway, in the hope that they may represent feasible therapeutic targets.



Dr. Ebru Erbay

*Assistant Professor,
Molecular Biology and Genetics
Bilkent University*

Rising Star

Dr. Ebru Erbay is an assistant professor at Bilkent University and also a rising star presenter. Dr. Erbay's research focus is on finding points for potential therapeutic intervention in atherosclerosis, particularly by exploiting biologically active nutrients. She and others have clearly demonstrated that lipid-induced ER stress in macrophages contributes to the formation and persistence of atherosclerotic lesions, and she has defined the molecular mechanisms that underlie the harmful effects of toxic lipids. Remarkably, she has shown that in a mouse model of atherosclerosis, treatment with a chemical compound that improves ER function reduced ER stress and macrophage apoptosis within lesions. She described her recent studies using a lipid hormone to reduce inflammation and to treat cardiovascular disease in experimental models. This discovery opens the way to simple and effective preventive measures which can be tested in humans. Dr. Erbay is currently exploring additional methods to alter ER stress signaling or improve ER function, and evaluating their effect on atherosclerotic plaque formation and inflammation. Dr. Erbay hopes to understand how these pathways can be manipulated and managed to address the epidemic of metabolic disease.

Sabri Ülker Symposium Speakers



Dr. Ruslan Medzhitov

David W. Wallace Professor of Immunobiology, Yale School of Medicine; Investigator, Howard Hughes Medical Institute

Dr. Ruslan Medzhitov, a professor at Yale University School of Medicine and an investigator of the Howard Hughes Medical Institute, presented his perspective on the regulation of immune responses, and how this is integrated with metabolic pathways. As Dr. Medzhitov described, specific metabolic programs are required within immune cells to support their inflammatory or anti-inflammatory states. For example, when macrophages are exposed to lipopolysaccharide, a bacterial toxin, they undergo a pro-inflammatory transformation that requires increased glycolytic flux. In addition, Dr. Medzhitov is interested in understanding the feedback mechanisms that control the resolution of inflammation and how the failure of resolution can lead to chronic disease states including diabetes and obesity. In this vein, his previous work focused on IL-10, which is a negative regulator of inflammation and is encoded by a gene that is commonly mutated in human colitis patients. IL-10 inhibits the production of other cytokines such as TNF and interferon, and Dr. Medzhitov is now interested in understanding how its production is integrated with metabolic pathways within immune cells.



Dr. Gökhan Hotamışlıgil

James S. Simmons Professor of Genetics & Metabolism; Chair, Department of Genetics and Complex Diseases, Sabri Ülker Center for Metabolic Research; Associate Member, Harvard-MIT Broad Institute, Harvard Stem Cell Institute

The final presentation of the Symposium was given by Dr. Gökhan Hotamışlıgil, the chair of the Department of Genetics and Complex Diseases and the Sabri Ülker Center at the Harvard T.H. Chan School of Public Health. The underlying theme of Dr. Hotamışlıgil's talk was his group's effort to understand why modern humans develop diabetes, and why it occurs so frequently. As Dr. Hotamışlıgil emphasized, episodes of high glucose (hyperglycemia) are generally not life threatening and were likely rare events over the course of human history. Conversely, episodes of low blood glucose (hypoglycemia) can be acutely life threatening, and accordingly mammals have developed robust and redundant counterregulatory mechanisms to prevent their occurrence. However, in the modern era with abundant food supply and lifestyles characterized by reduced physical activity, it is the dysregulation of these counterregulatory mechanisms that leads to development of metabolic disease. From this perspective, the signals that connect energy storage depots like fat tissue to hepatic glucose production could be promising therapeutic targets, but many of these remain unknown. Dr. Hotamışlıgil then described a recent discovery of one such novel hormone, the fatty acid binding protein aP2, which is produced from the adipose tissue and instructs the liver to produce glucose. As the level of this hormone progressively increases in obesity and diabetes, it causes abnormal glucose metabolism. Dr. Hotamışlıgil and his group have shown that neutralizing the protein with a monoclonal antibody improves glucose tolerance and reduces fatty liver in obese mice. Further understanding this biology could reveal new mechanisms and new molecular targets for metabolic disease treatment.

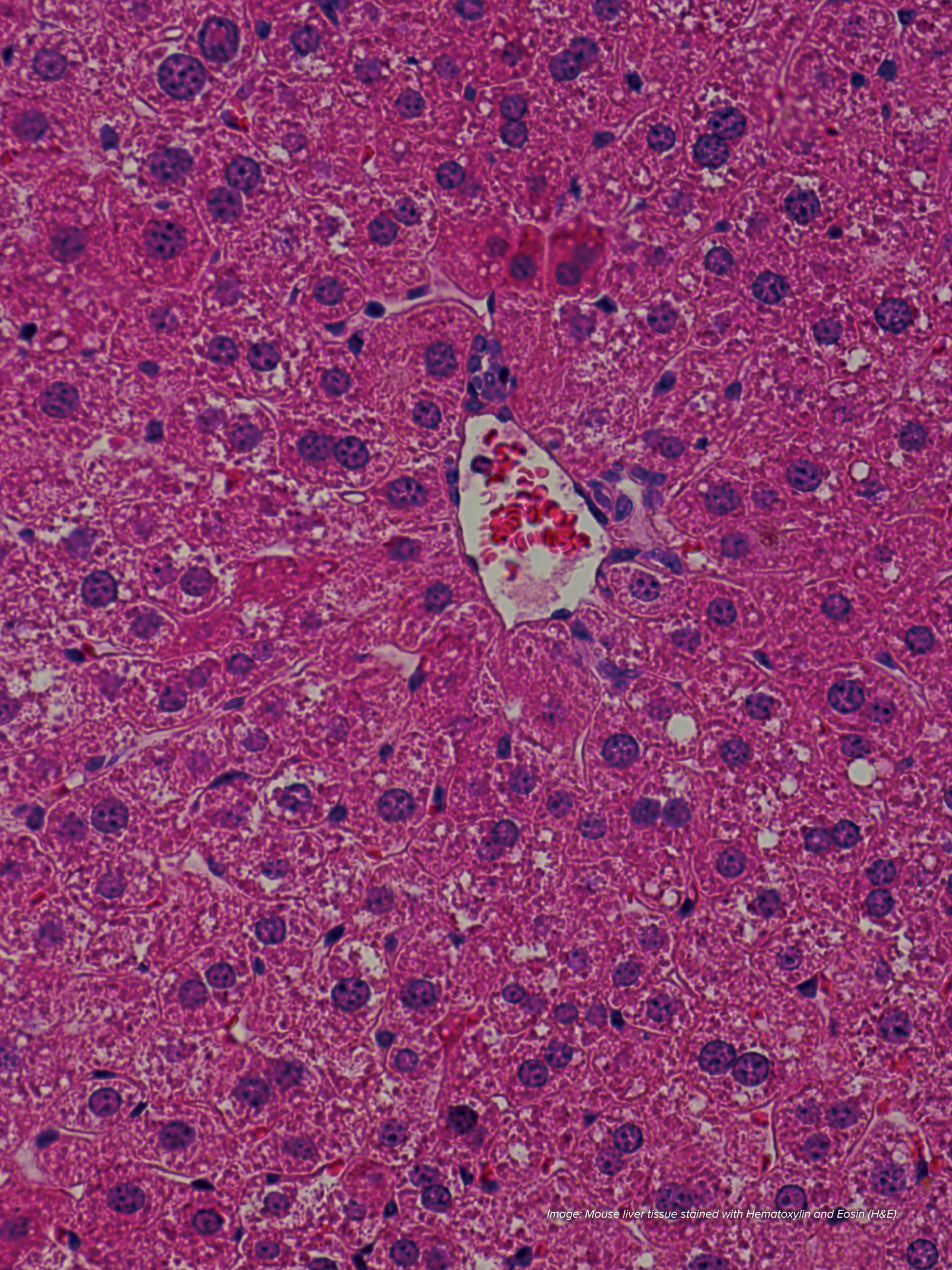
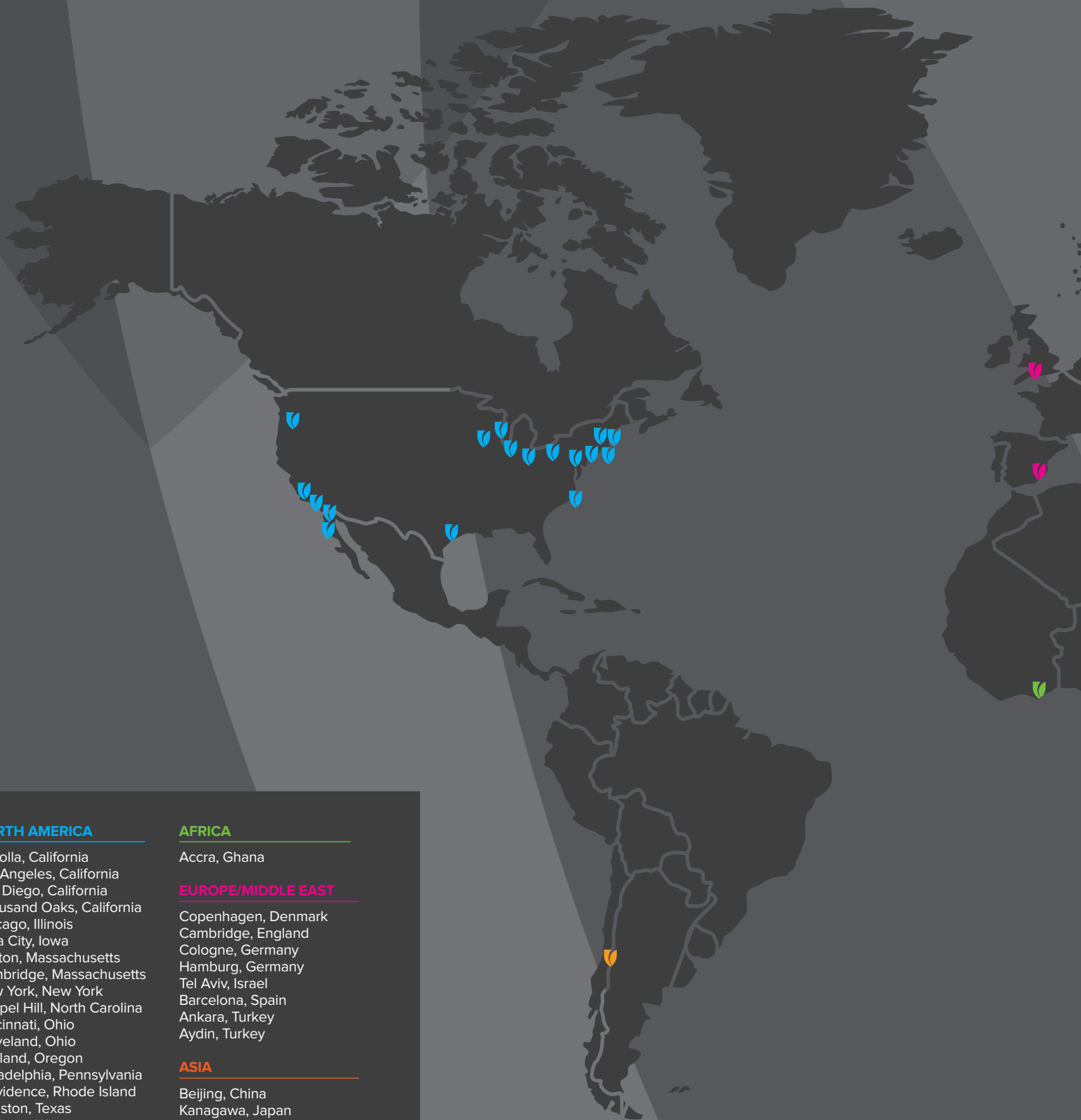


Image: Mouse liver tissue stained with Hematoxylin and Eosin (H&E).

Beyond Our Borders



NORTH AMERICA

La Jolla, California
Los Angeles, California
San Diego, California
Thousand Oaks, California
Chicago, Illinois
Iowa City, Iowa
Boston, Massachusetts
Cambridge, Massachusetts
New York, New York
Chapel Hill, North Carolina
Cincinnati, Ohio
Cleveland, Ohio
Portland, Oregon
Philadelphia, Pennsylvania
Providence, Rhode Island
Houston, Texas
Madison, Wisconsin

SOUTH AMERICA

Santiago, Chile

AFRICA

Accra, Ghana

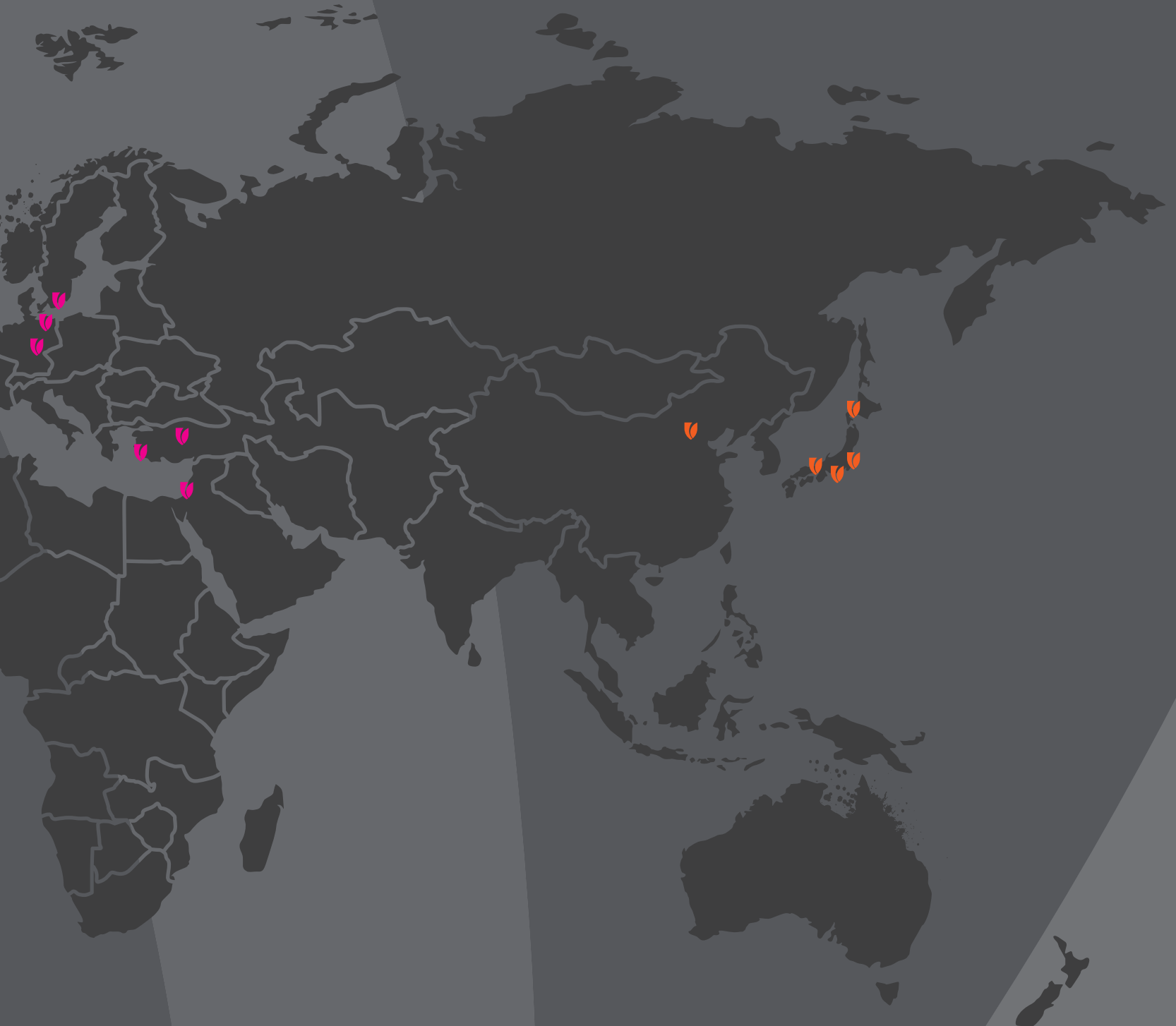
EUROPE/MIDDLE EAST

Copenhagen, Denmark
Cambridge, England
Cologne, Germany
Hamburg, Germany
Tel Aviv, Israel
Barcelona, Spain
Ankara, Turkey
Aydin, Turkey

ASIA

Beijing, China
Kanagawa, Japan
Osaka, Japan
Sapporo, Japan
Tokyo, Japan

Worldwide Impact of Sabri Ülker Center Young Investigators. One of the missions of the Sabri Ülker Center is to train a global force of investigators, dedicated to researching nutrient science and metabolism, and making tangible advancements toward eradicating the threat of metabolic disease. This is reflected by the worldwide reach of past members, as Center alumni have gone on to launch their independent scientific careers across Asia, Europe, and North and South America. These pages feature personal profiles of some of these young scientific leaders: two recent lab alumni and one current postdoctoral fellow.



The Next Generation of Scientists

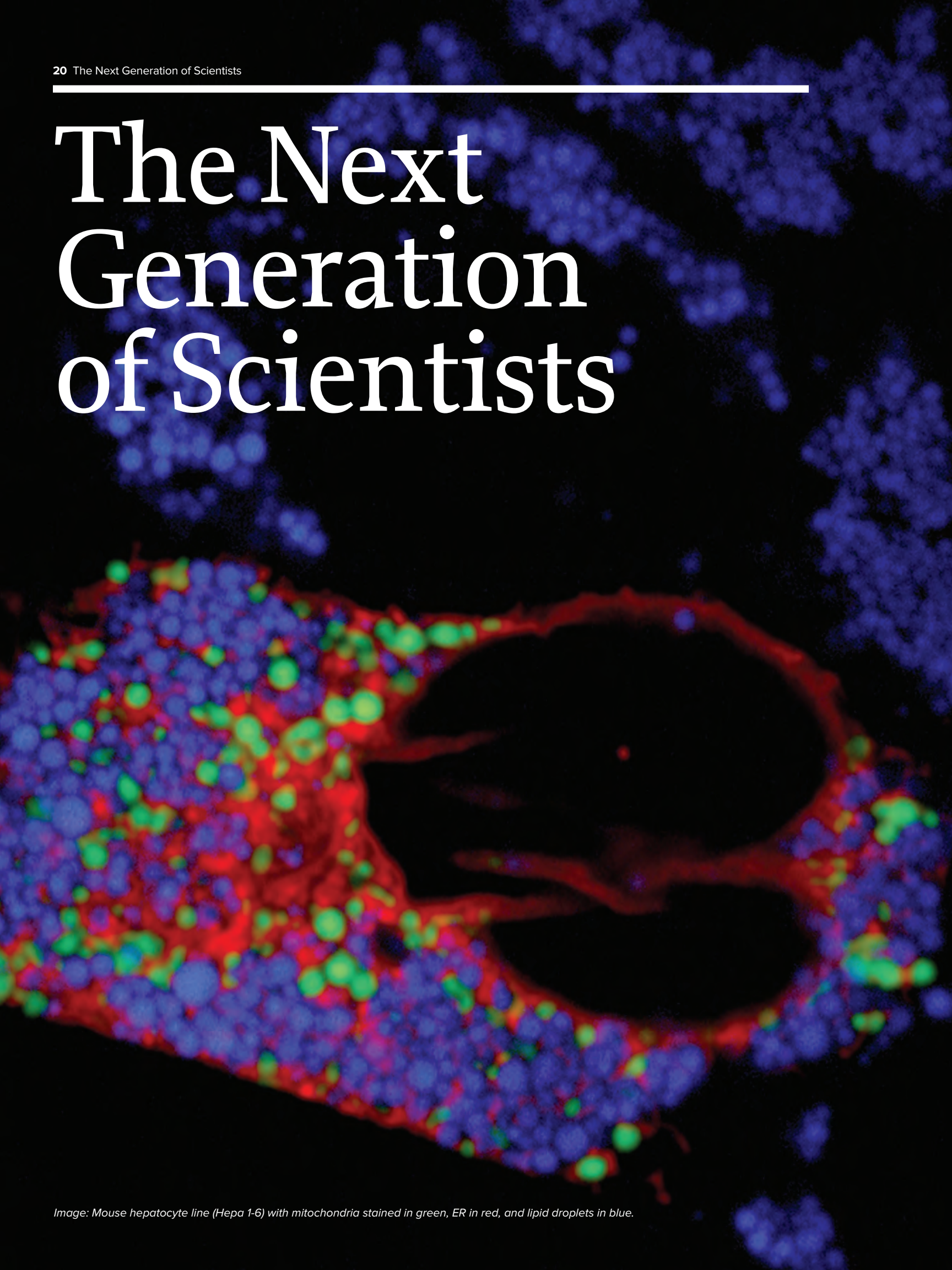


Image: Mouse hepatocyte line (Hepa 1-6) with mitochondria stained in green, ER in red, and lipid droplets in blue.



Ana Paula Arruda, PhD

Sabri Ülker Center Postdoctoral Fellow
2010-present

Q. What drew you to the Sabri Ülker Center?

I decided to apply to the Center early on: when I was just in my second year of the PhD program in Brazil, and preparing to defend my qualifying exam. In my PhD program, the qualifying exam consisted of the student presenting a seminar about a subject different from the main topic of their PhD thesis. My main topic was calcium metabolism in muscle, but I had always enjoyed reading about the field of obesity and diabetes, and when I read some articles by Dr. Hotamışlıgil, I became fascinated by the field of immunometabolism. In my mind it was very intriguing that the immune system shared so many commonalities with metabolic pathways. I also recognized from Dr. Hotamışlıgil's papers a very unique and creative thinking process. This seemed like the perfect setting for my post-doctoral training, so I decided to apply to this lab. It was just a dream in the beginning but it turned into reality.

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

In the past few years it has become clear that dysfunction of cellular organelles such as mitochondria and endoplasmic reticulum (ER) in metabolic tissues plays an important role in the pathogenesis of obesity and diabetes. I am particularly interested in studying how overnutrition impacts the architecture of these organelles and how this influences their activity. In addition, I am studying how the stress in one organelle affects the other. We recently discovered that the structure of ER and mitochondria are changed in the liver of obese mice, and that the physical association between these two organelles is more pronounced in this condition. One of the consequences of altered ER-mitochondria association is excessive transport of calcium from ER to mitochondria, which negatively influences mitochondrial metabolism. Now we are studying the physical association between ER and plasma membrane, and how this responds to nutritional changes and might influence ER function and dysfunction in obesity.

Q. What do you hope will emerge from your project?

First, I expect to have a better understanding of how overnutrition leads to alterations in the endoplasmic reticulum and mitochondrial structure, and the impact

of this for the function of these organelles and for calcium homeostasis in the cell. Ultimately, I hope to find specific molecular targets that will allow us to correct these alterations and treat metabolic disease.

Q. What is most challenging about your work?

I think about this in two ways. Broadly, I think it is extremely challenging to study metabolic disease, because of the remarkable complexity of the systems and pathways involved. There are so many intertwined molecular pathways, all of which have diverse consequences for cellular homeostasis, that when we try to study the effect of a single molecule in isolation, interpreting the results and understanding the context can be very difficult. I think that to really produce effective advances in this area, we need to develop new approaches that can take into account this complexity. For my specific project, we are trying to study structural alterations in organelle structure, and although we have very good techniques such as electron and fluorescent microscopy, the precise quantification of these alterations is very challenging. We are now developing an array of new reporters and imaging systems to overcome this limitation.

Q. What surprised you when you joined the Center?

When I joined, I found a big lab, well equipped, organized and full of very intelligent people. I was pleased by that, but in a way it was what I expected given their published work and reputation. My real surprise was to see the degree of intellectual freedom that Gökhan gives to his fellows and students and also the collaborative environment of the Center. Both of these were good surprises!

Q. Where do you see yourself in five years?

My dream is to have my own lab, leading a small group of scientists pursuing the research questions that interest me most. I also see myself teaching, which I love to do! If I establish my lab outside Brazil, my home country, I also hope that I can have some sort of collaborative program with Brazil, because it's part of my dream to contribute to the development of science in my country.



Meric Erikci Ertunc, PhD

Graduate Student 2009-2014
Postdoctoral Fellow 2014-2015

Q. Why did you decide to work in the Sabri Ülker Center?

After finishing my undergraduate studies at Bilkent University in Turkey, I became interested in metabolic disease research that has translational potential. In thinking about metabolism, it is important to see the bigger picture of biological systems – one must start from molecular events inside the cell in order to eventually understand the effects in distant organs and the broader mechanisms underlying pathology. The Sabri Ülker Center has the ideal environment to study such complex mechanisms due to Gökhan's visionary mentorship, the intellectual culture, and the diverse collection of outstanding scientists who are experts in different aspects of the metabolic system.

Q. What surprised you when you joined the Center?

I was very impressed by the weekly lab meetings. Every week, one or two people present their findings, and all members of the lab are engaged in the discussion, challenging ideas and thinking through potential problems. These discussions can take several hours and can be very demanding. It was amazing to be involved in this intellectual synergy, and to watch new ideas emerge from these meetings and discussions.

Q. Where are you now?

After completing my PhD training at the Center, I became a Postdoctoral Research Associate at the Salk Institute for Biological Studies. I am now carrying my interest in metabolism into new directions.

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

People often think of fat as a harmful nutrient that needs to be avoided. This is actually not completely true, and several labs, including the Sabri Ülker Center, have demonstrated that there exist specific lipids that have the potential to improve metabolic function and prevent harmful effects of stress and chronic inflammation in obesity and diabetes. My current project focuses on studying how these molecules exert their beneficial effects and how they are regulated

under physiological and pathophysiological conditions. A better understanding of these aspects has the potential to identify novel therapeutic targets for metabolic diseases such as diabetes and cardiovascular disease, as well as other immune-related pathologies such as multiple sclerosis.

Q. What is most challenging about your work?

I have had to learn totally new techniques rapidly, from biochemical approaches to disease models, to properly understand the structure of lipids and to study their actions. One of the new approaches I'm learning is mass spectrometry, a type of analysis that allows a researcher to get a global picture of the molecules present in a sample from an animal, such as the nutrients and their derivatives. This area and the surrounding technologies were brand new to me, and I have had to learn everything starting from how to prepare the samples to the interpretation of the results, which consists of thousands of numbers, graphs, and calculations.

Q. How do you think your time in the Center shaped you as a scientist?

I came to Sabri Ülker Center with great enthusiasm for science but limited experience related to experimental approaches and identifying critical questions. Simply put, the Center built me into an independent scientist. I learned to ask interesting scientific questions, design experiments that would answer those questions, and interpret them with a broad and objective vision. I don't hesitate to ask challenging questions and try to figure out ways to solve them, however difficult they may be. This was the collective outcome of working in a vigorous intellectual environment with outstanding colleagues and the mentorship that Gökhan himself provided.

Q. What is your best memory of your time in the Sabri Ülker Center?

My best memories are of when we had lab-wide gatherings whether it was an ice cream outing or a scientific retreat. The people in the lab are not just everyday colleagues, but a family.



Motohiro Sekiya, MD, PhD

Postdoctoral Fellow 2009-2015

Q. Why did you decide to work in the Sabri Ülker Center?

I'm a physician and was focused on lipid metabolism before joining the Center. I realized that although serum lipid levels can be easily controlled through existing medications, we lack effective treatments for diabetic patients. So I wanted to find some new clues to develop novel medicines that could treat individuals with diabetes. The Center was unique in having this perspective; integrating glucose metabolism with lipid metabolism and exploring a broad spectrum from very basic mechanisms to human applications.

Q. What surprised you when you joined the Center?

The attitude toward scientific knowledge. Gökhan always encourages us to deepen our scientific knowledge in many ways; attending seminars, reading articles etc., and trying to identify the most pressing scientific questions. I was impressed by my colleagues in their dedication to this goal and in the richness of the intellectual environment.

Q. Where are you now?

After leaving the Sabri Ülker Center, I took a position as Assistant Professor at the University of Tsukuba, in Japan.

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

While studying how lipids trigger glucose production in the Sabri Ülker Center, I discovered a novel protein complex that senses and responds to lipids in the liver. Now, I'm working on a nutrient and metabolite sensor called CtBP, trying to unravel its role in physiology and disease and the molecular mechanisms underlying its activity. In the long run, I hope that this work will help reveal novel approaches for metabolic disease treatment.

Q. What is most challenging about your work?

The pathways I worked on were very unique and therefore there was little to apply from existing knowledge to my project. I needed to develop many new reagents and techniques. Since moving back to Japan, the most challenging aspect is that I am doing both clinical practice and basic research. Finding the time to do both well is quite difficult!

Q. How do you think your time in the Center shaped you as a scientist?

I feel like I was able to increase my intellectual ability in many ways: reading literature to understand the most complex biology in the world, attending meetings, communicating with lab mates with the highest level of scientific knowledge and the guidance of my mentor to place all of this into perspective and action. I was surprised to see how much I improved in my knowledge and understanding science when I returned to Japan.

Q. What is your best memory of your time in the Center?

As I mentioned, the people in the lab are highly educated and brilliant, but as important, they are also warm and supportive and they love science. One of the things I remember most fondly was my last data presentation, when I got the chance to present the culmination of years of work and received so much support as well as critical insight and suggestions. I was very emotional and leaving the Center was difficult, although returning to my home country was very exciting.

Achievement Highlights

Image: Mouse primary hepatocyte showing nucleus in blue and lipid droplets in green.



The faculty members in our community had a successful and productive year, and their efforts were recognized by many distinctions. These include:

James R. Mitchell, PhD, Associate Professor of Genetics and Complex Diseases

Dr. Mitchell, who studies dietary restriction and its effects on lifespan extension, metabolic fitness and stress resistance, received the International Dose Response Society Outstanding New Investigator Award and the 2016 Tashjian Award, which is granted each year to a junior faculty member with a primary appointment at the Harvard T.H. Chan School of Public Health or other related departments in Harvard University. Each recipient is pursuing innovative research ideas in basic biomedical sciences relevant to endocrinology. In addition, Dr. Mitchell's commitment to teaching and mentorship was honored by his nomination for the 2015 Harvard School of Public Health Outstanding Mentor Award.

William Mair, PhD, Assistant Professor of Genetics and Complex Diseases

Dr. Mair utilizes the model system *C. elegans* to study the molecular pathways that link metabolism with aging. In 2015, he was granted the Glenn Award from the Glenn Foundation for Medical Research, an unsolicited award to support researchers investigating the biology of aging.

Brendan D. Manning, PhD, Professor of Genetics and Complex Diseases and Director of the Graduate Program in Biological Sciences

Last year, Dr. Manning was the inaugural recipient of the Outstanding Investigator Award from the National Cancer Institute, in recognition for his work unraveling how nutrients and other growth cues control metabolic processes within cells. This year, he received the Rothberg Courage Award in Research from the Tuberous Sclerosis Alliance, and was invited to be the Keynote Speaker at multiple international conferences on metabolism.

Robert V. Farese, MD, Professor of Genetics and Complex Diseases

Dr. Farese received the 2016 Avanti Lipid Award from the American Society for Biochemistry and Molecular Biology, which recognizes his outstanding contribution to the biology of lipid storage. Dr. Farese has laid the groundwork for our current understanding of lipid droplet formation and is now making important progress on the role of membrane lipids in neurodegenerative disease.

Tobias Walther, PhD, Professor of Genetics and Complex Diseases and Howard Hughes Medical Institute Investigator

Dr. Walther, who co-directs a laboratory studying lipid storage and membrane biology with Dr. Farese, was named a Distinguished Visiting Professor at Tsinghua University in Beijing, China.

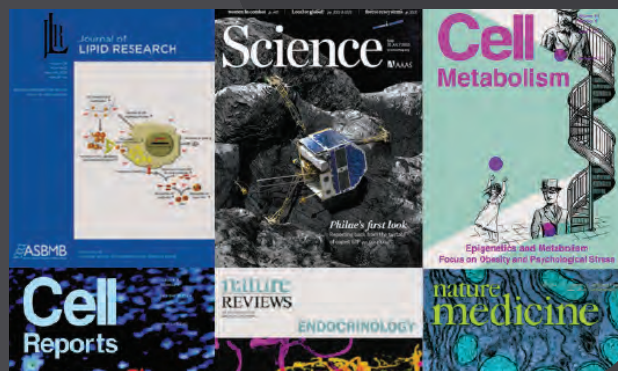
Gökhan S. Hotamışlıgil, MD, PhD, Director of the Sabri Ülker Center for Nutrient, Genetic, and Metabolic Research; Chair, Department of Genetics and Complex Diseases; James S. Simmons Professor of Genetics and Metabolism at the Harvard T.H. Chan School of Public Health

Dr. Hotamışlıgil received the Distinguished Service Award from the Society of Inflammation, honoring his seminal contribution to the establishment of inflammation as a key mechanism underlying metabolic dysfunction in obesity. He was invited to be the Keynote Speaker at multiple international conferences on metabolism and immunometabolism.

Marianne Wessling-Resnick, PhD, Professor of Nutritional Biochemistry and Genetics and Complex Diseases

Dr. Wessling-Resnick was a founding member of the department of Genetics and Complex Diseases, and is a global leader in the study of iron storage disorders. In 2016, Dr. Wessling-Resnick was appointed by the Director of the National Institutes of Health to serve as a member of the Environmental Health Services Review Committee of the National Institute of Environmental Health Sciences. The Committee reviews applications for institutional training grants and career awards to support scientists studying how the environment impacts human health.

Publications



The ongoing efforts of the Department were reflected this year by the publication of many high-quality research manuscripts and reviews. These important contributions to the scientific literature have already made an impact on the direction of our own work and that of others in our field, and are a sign that the renown of our faculty is sure to grow in the coming years. A sampling is listed below:

Seipin is Required for Converting Nascent to Mature Lipid Droplets.
Wang H, Becuwe M, Housden BE, Chittraju C, Porras AJ, Graham MM, Liu XN, Thiam AR, Savage DB, Agarwal AK, Garg A, Olarte MJ, Lin Q, Fröhlich F, Hannibal-Bach HK, Upadhyayula S, Perrimon N, Kirchhausen T, Ejsing CS, Walther TC, Farese RV Jr.
eLife, August 2016

Targeting Fat: Mechanisms of Protein Localization to Lipid Droplets.
Kory N, Farese RV Jr, Walther TC.
Trends in Cell Biology, July 2016

Lipid Droplets Go Nuclear.
Farese RV Jr, Walther TC.
Journal of Cell Biology, January 2016

Gut Microbiota, Metabolites and Host Immunity.
Rooks MG, Garrett WS.
Nature Reviews Immunology, May 2016

Tuft cells, Taste-Chemosensory Cells, Orchestrate Parasite Type 2 Immunity.
Howitt MR, Lavoie S, Michaud M, Blum AM, Tran SV, Weinstock JV, Gallini CA, Redding K, Margolskee RF, Osborne LC, Artis D, Garrett WS.
Science, March 2016

Akt-mTORC1 Signaling Regulates Acly to Integrate Metabolic Input to Control of Macrophage Activation.
Covarrubias AJ, Aksoylar HI, Yu J, Snyder NW, Worth AJ, Iyer SS, Wang J, Ben-Sahra I, Byles V, Polynne-Stapornkul T, Espinosa EC, Lamming D, Manning BD, Zhang Y, Blair IA, Horng T.
eLife, February 2016

Characterization of a Novel Adult Murine Immortalized Microglial Cell Line and its Activation by Amyloid-Beta.
McCarthy RC, Lu DY, Alkhateeb A, Gardeck AM, Lee CH, Wessling-Resnick M.
Journal of Neuroinflammation, January 2016

MicroRNA Regulation of Airway Smooth Muscle Function.
Sun M, Lu Q.
Biological Chemistry, June 2016

Patterns of Growth and Decline in Lung Function in Persistent Childhood Asthma.
McGeachie MJ, Yates KP, Zhou X, Guo F, Sternberg AL, Van Natta ML, Wise RA, Szeffler SJ, Sharma S, Kho AT, Cho MH, Croteau-Chonka DC, Castaldi PJ, Jain G, Sanyal A, Zhan Y, Lajoie BR, Dekker J, Stamatoyannopoulos J, Covar RA, Zeiger RS, Adkinson NF, Williams PV, Kelly HW, Grasemann H, Vonk JM, Koppelman GH, Postma DS, Raby BA, Houston I, Lu Q, Fuhlbrigge AL, Tantisira KG, Silverman EK, Tonascia J, Weiss ST, Strunk RC, CAMP Research Group.
New England Journal of Medicine, May 2016

A Systems Approach to Reverse Engineer Lifespan Extension by Dietary Restriction.
Hou L, Wang D, Chen D, Liu Y, Zhang Y, Cheng H, Xu C, Sun N, McDermott J, Mair WB, Han JD.
Cell Metabolism, March 2016

SREBP Regulates the Expression and Metabolic Functions of Wild-type and Oncogenic IDH1.
Ricoult SJ, Dibble CC, Asara JM, Manning BD.
Molecular Cell Biology, July 2016

CASTORing New Light on Amino Acid Sensing.
Hallett JE, Manning BD.
Cell, March 2016

mTORC1 Induces Purine Synthesis through Control of the Mitochondrial Tetrahydrofolate Cycle.
Ben-Sahra I, Hoxhaj G, Ricoult SJ, Asara JM, Manning BD.
Science, February 2016

Oncogenic PI3K and K-Ras Stimulate De Novo Lipid Synthesis through mTORC1 and SREBP.
Ricoult SJ, Yecies JL, Ben-Sahra I, Manning BD.
Oncogene, March 2016

Human C1-Inhibitor Suppresses Malaria Parasite Invasion and Cytoadhesion via Binding to Parasite Glycosylphosphatidylinositol and Host Receptors.
Mejia P, Diez-Silva M, Kamena F, Lu F, Fernandes SM, Seeberger PH, Davis AE 3rd, Mitchell JR.
Journal of Infectious Disease, January 2016

Novel Pathways of Apolipoprotein A-1 Metabolism in High-Density Lipoprotein of Different Sizes in Humans.
Mendivil CO, Furtado J, Morton AM, Wang L, Sacks FM.
Arteriosclerosis, Thrombosis, and Vascular Biology, January 2016

Distribution of Manganese and Other Biomaterials in Flatiron Mice.
Seo YA, Elkhader JA, Wessling-Resnick M.
Biomaterials, February 2016

PRR14 is a Novel Activator of the PI3K Pathway Promoting Lung Carcinogenesis.
Yang M, Lewinska M, Fan X, Zhu J, Yuan ZM.
Oncogene, April 2016

Somatic Human ZBTB7A Zinc Finger Mutations Promote Cancer Progression.
Liu XS, Liu Z, Geraduzzi C, Choi DE, Ganapathy S, Pandolfi PP, Yuan ZM.
Oncogene, June 2016

Lipid Signaling and Lipotoxicity in Metabolic Inflammation: Indications for Metabolic Disease Pathogenesis and Treatment.
Erikci Ertunc M, Hotamisligil GS.
Journal of Lipid Research, June 2016

Development of a Therapeutic Monoclonal Antibody that Targets Secreted Fatty Acid Binding Protein aP2 to Treat Type 2 Diabetes.
Burak MF, Inouye KE, White A, Lee A, Tuncman G, Calay ES, Sekiya M, Tirosh A, Eguchi K, Birrane G, Lightwood D, Howells L, Odede G, Hailu H, West S, Garlish R, Neale H, Doyle C, Moore A, Hotamisligil GS.
Science Translational Medicine, December 2015

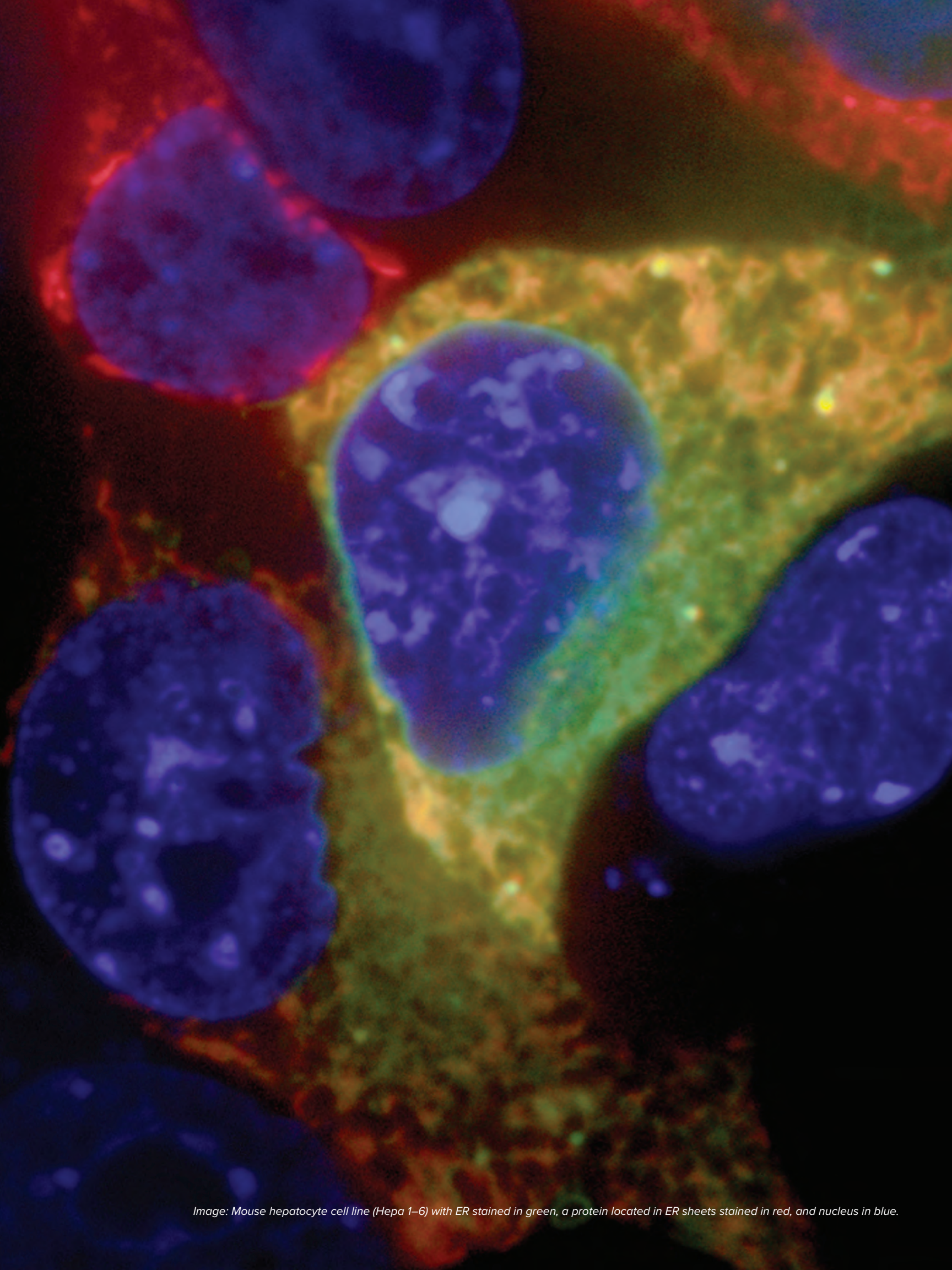


Image: Mouse hepatocyte cell line (Hepa 1–6) with ER stained in green, a protein located in ER sheets stained in red, and nucleus in blue.

Welcome Dean Michelle Williams



On July 1, 2016, Dr. Michelle Williams stepped into the role of Dean of Harvard T.H. Chan School of Public Health.

Committed to interdisciplinary approaches to promote public health, Dr. Williams recognizes the value of supporting basic and translational research, and acknowledges the tremendous burden on public welfare created by chronic metabolic diseases.

Professor Michelle A. Williams is Dean of the Faculty, Harvard T.H. Chan School of Public Health. She is an internationally renowned epidemiologist and public health scientist, an award-winning educator, and a widely recognized academic leader. Prior to becoming Dean, she was Professor and Chair of the Department of Epidemiology at the Harvard Chan School and Program Leader of Harvard's Clinical and Translational Sciences Center Population Health and Health Disparities Research Programs. Professor Williams previously had a distinguished career at the University of Washington School of Public Health. She has published over 450 scientific articles and has received numerous research and teaching awards, including the American Public Health Association's Abraham Lilienfeld Award. In 2011, President Barack Obama presented Dr. Williams with the Presidential Award for Excellence in Science, Mathematics, and Engineering Mentoring. Dean Williams' scientific work focuses on integrating genomic sciences and epidemiological research methods to identify risk factors, diagnostic markers, treatments, and prevention targets for disorders that contribute to maternal and infant mortality. She has master's and doctoral degrees in epidemiology from the Harvard Chan School and Harvard University.



HARVARD T.H. CHAN
SCHOOL OF PUBLIC HEALTH



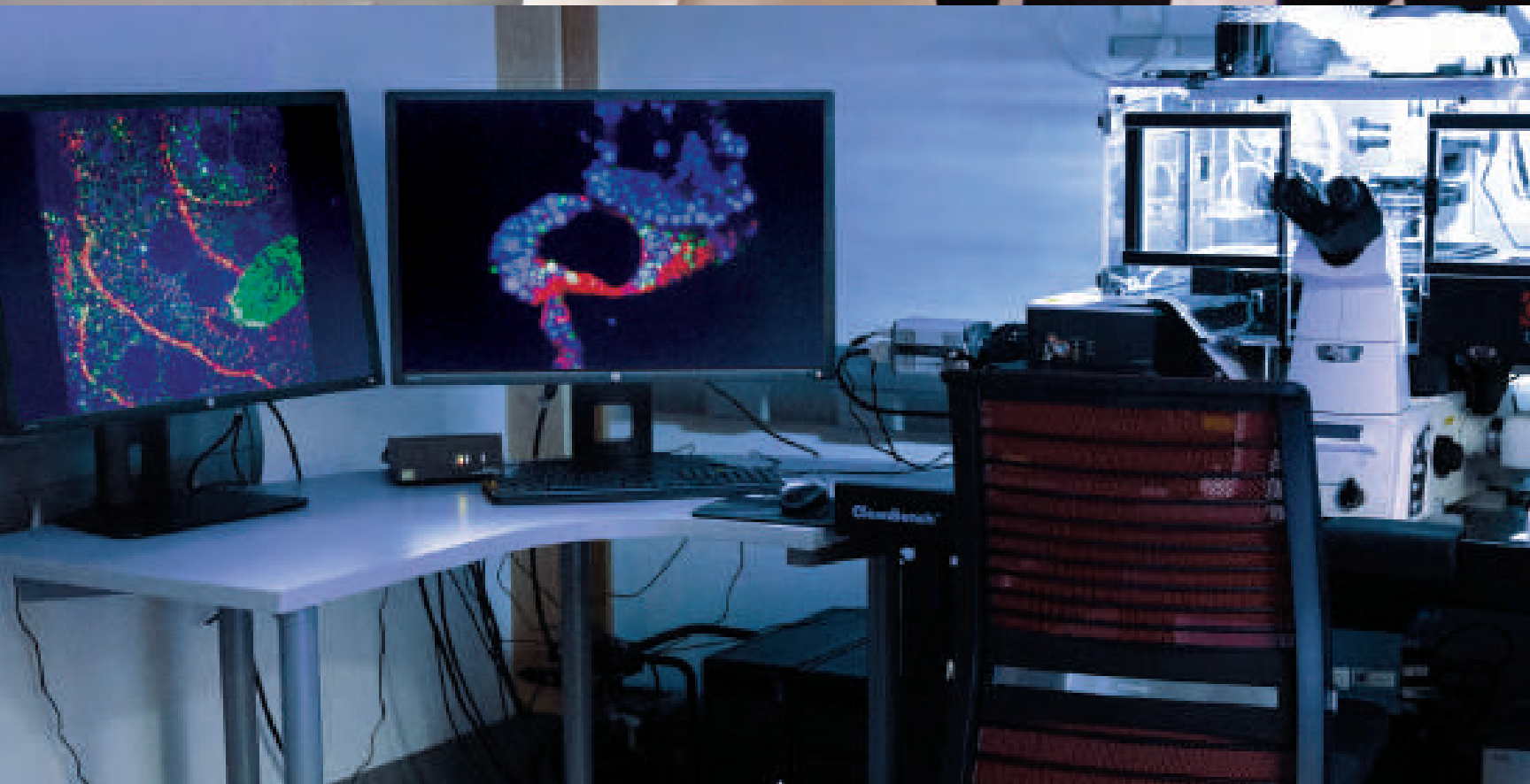
At the Harvard T.H. Chan School of Public Health, our mission is to advance global health through learning, research, discovery, and communication.

The School brings together dedicated experts from many disciplines to educate new generations of public health leaders and produce powerful ideas that improve the lives and health of people everywhere. As a community of leading scientists, educators, and students, we collaborate to take innovative ideas from the laboratory to people's lives — not only making scientific breakthroughs, but also working to change individual behaviors, public policies, and health care practices. Currently, our dedication to basic science is endangered by a struggling economy and political gridlock, which have made federal funding for research increasingly competitive and scarce.

It is a privilege to lead the School with which I have had a relationship for 30 years — first as a student, then as an alumna, faculty member, and Chair of the Department of Epidemiology. Since taking office on July 1, 2016, I have been impressed and delighted to learn about the efforts of the Sabri Ülker family, and their generous support of the Sabri Ülker Center for Nutrient, Genetic, and Metabolic Research. The work of the Center plays a critical role in our understanding of the molecular basis of obesity, diabetes, cardiovascular disease and related disorders, and the discoveries made there will lead to improved health for people around the world. Thanks to the Ülker family's unparalleled generosity, a new generation of scientists will receive world-class training, gain access to state-of-the-art equipment, and be prepared to make important discoveries about one of the most pressing threats to global health: metabolic disease. I am grateful to the Ülker family for supporting research that is critical to the central mission of the Harvard Chan School, and I am excited to be able to oversee this decade of discovery.

Sincerely,

Michelle A. Williams, ScD



I am very excited to announce that the Sabri Ülker Center Imaging Lab was launched in November of 2016. Though still in its infancy, this new facility will expand the research capacity of the Center for Nutrient, Genetic, and Metabolic Research by offering state-of-the-art microscopy and imaging capabilities.

Specifically, the Imaging Lab offers a spinning disc confocal microscope with laser scanning capability, which allows our researchers to monitor biological processes in live cells, as well as evaluate cellular sub-structure and organelle dynamics. In addition, previous work from our group demonstrated the key role of calcium in integrating inflammation and organelle function in the development of metabolic disease, and the Center is equipped with a wide-field microscope for the measurement of calcium flux in cell lines and primary cells. Finally, we have secured additional space for image analysis and eventual acquisition of a third microscope to accommodate the emerging high power superresolution technologies and apply them to metabolic analysis. I hope you will appreciate some of the beautiful images beginning to emerge from this work that are included in this report. I truly believe in the adage, "seeing is believing," and am so pleased at the way this Imaging Lab enables us to capture visual evidence of biological processes, as well as make new discoveries and progress toward a better understanding of metabolic pathology.

Looking Forward



I am exceedingly proud of our accomplishments in this second year of the Sabri Ülker Center, and as I look forward to 2017, I am confident that we will continue to make exciting scientific discoveries and progress toward our goals.

As several of our research projects are developing very well I am excited to be able to share our novel findings with the scientific community in meetings and through our publications. In multiple areas we have made paradigm-shifting observations, which are already driving our research in unanticipated directions. We are also investing in new technologies and platforms towards our long-term goals of exploring nutrients and their role in metabolism to ultimately leverage new entities for disease prevention and treatment. In addition, our newly opened Imaging Lab will undoubtedly enhance our exploratory capabilities and accelerate the pace of our discoveries, as will our pursuit of platforms for nutrient screening.

On a personal note, I am particularly proud of the impact we are making on the young generation of scientists around the world. Overseeing the development of the scientists within my group and watching our students and fellows taking their next career steps is also tremendously rewarding. Our inaugural Ülker Fellows are making great strides in their independent projects, and are rapidly developing their scientific problem solving skills. Many of our other fellows have received prestigious national and international fellowship awards for their studies. In addition, in the coming year, a few of our more senior fellows will be launching their own independent careers, bringing with them the knowledge and tools they need to establish themselves in this competitive environment. The students and fellows who have trained in our center now constitute a worldwide network of elite researchers dedicated to solving major problems in the field of metabolism, and we continually communicate and collaborate with them. I am so grateful to the Ülker family for helping us to maintain and extend that network, as we work together to find novel approaches to prevent and treat metabolic disease towards our collective dream of making a positive impact on human life. I look forward to the coming years of discovery and capacity development in the Sabri Ülker Center and expanding our reach to every corner of the world.

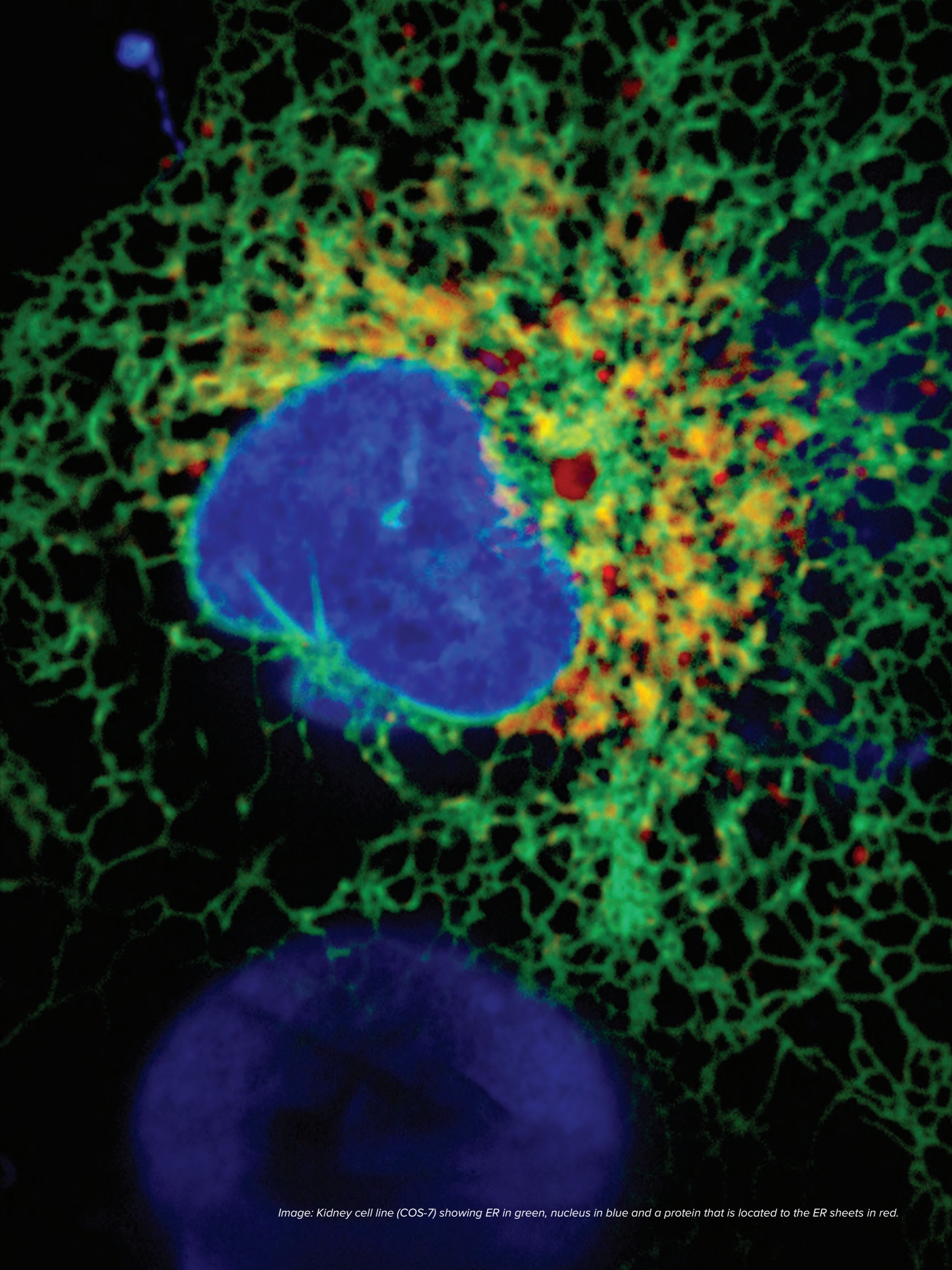


Image: Kidney cell line (COS-7) showing ER in green, nucleus in blue and a protein that is located to the ER sheets in red.



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