BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Burak, Mehmet Furkan

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Postdoctoral Research Fellow

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
Kocaeli University School of Medicine, Kocaeli	MD	07/2011	Medicine
Mount Auburn Hospital, Harvard Medical School, Cambridge, MA	Resident	07/2017	Internal Medicine
Brigham and Women's Hospital, Harvard Medical School, Boston, MA	Fellow	present	Endocrinology
Harvard Chan School of Public Health, Boston, MA	Postdoctoral Fellow	present	Metabolism, obesity and diabetes

A. Personal Statement

I am a physician scientist with strong basic science and clinical training. Currently I am an investigator-track endocrinology fellow at Brigham and Women's Hospital, Harvard Medical School and postdoctoral research fellow at Harvard Chan School of Public Health. After my postdoctoral fellowship, I will seek a faculty job to start my own research group and continue seeing patients in a multidisciplinary clinic specialized in immuno-metabolism. I hope to bring our discovery of a preclinical molecule (anti-aP2 mAb) to human practice by understanding aP2 biology and its role in obesity related immunometabolic diseases such as diabetes and asthma. This funding will help me to further investigate pathogenesis and therapeutic opportunities, to complete my research training and become an independent investigator once I complete my fellowships. It will give me the opportunity to have an impact both on my individual patients and at the population level through drug discovery and improved medical therapeutics on obesity-related diseases.

I have a strong background in basic research as well as clinical practice in areas closely related to the area of this proposal. As a 2nd year medical student, I conducted a basic science summer internship with Professor Aziz Sancar, the 2015 Nobel Laureate in Chemistry at the University of North Carolina, Chapel Hill School of Medicine. There, I worked on DNA repair and the cell cycle and was able to further develop my critical and analytical thinking skills as well as learning molecular biology, genetics and biochemistry techniques. Two years later, I was the only international student selected to participate in a very competitive Joslin Diabetes Center summer research student program at Harvard Medical School. There, I worked with Professor Mary Elizabeth Patti on obesity and lipid metabolism and further improving my technical skills and knowledge in metabolism. Within a limited time of two and half months, I was able to learn necessary molecular biology techniques and finish in vivo studies as part of a project that was later published in a high impact journal, Cell Metabolism. I followed this experience by pursuing a postdoctoral fellowship with Professor Gokhan Hotamisligil, a highly accomplished investigator in the field of metabolism, at the Harvard Chan School of Public Health beginning in August 2011. In my first two years in the lab, I was deeply involved in the very exciting discovery of a protein produced by the adipose tissue called aP2 that acts as a hormone to control glucose homeostasis. This finding shed new light on the pathogenesis of obesity-related diabetes and suggested that the aP2 hormone could be a novel therapeutic target. To this end, we produced a monoclonal antibody against aP2, and indeed observed that treatment with this antibody alleviated many of the metabolic dysfunctions in animal models of type 2 diabetes, fatty liver disease and obesity. I was thrilled to lead that drug discovery project and be the first

author of a manuscript describing those results published in Science Translational Medicine in December 2015 and highlighted in many high impact journals including Nature Drug Discovery. Participation in this study was a unique learning experience for me and I grew immensely as a researcher during my postdoctoral training. During nearly 3 years of my fellowship, I mastered most of the essential molecular biology and genetics techniques as well as physiological studies such as radioactive clamp experiments and doing microsurgery in rodents, skills which I shared when I gave a course at the University of Tel-Aviv, Israel. I became very knowledgeable in biology of lipids and fatty acid binding proteins in obesity and related immunometabolic diseases. My research experience in Dr. Hotamisligil's lab greatly increased my desire to pursue a career in academic medicine, where I envision helping patients through both clinical care and research. Academic medicine is the finest way for me to help patients, as it allows for the exploration of disease mechanisms and potential therapeutics and application of the discoveries to patient care. Due to my deep interest in seeing the translational effects of my bench work at the bedside, moved from postdoctoral laboratory studies to pursue an opportunity to train in internal medicine at Mt. Auburn Hospital of Harvard Medical School in Cambridge beginning in July 2014. As part of my residency training, I took care of many asthmatic patients and witnessed the challenges and complications of asthmatic patient life. I specifically noticed the dramatic association of obesity with asthma in many of these patients. After starting my endocrinology fellowship, I merged my innovative ideas on obesity, aP2 and asthma to develop the project outlined in this proposal. I am very confident that both my research and clinical qualifications will be well suited for this project and allow me to work independently in near future.

My mentor Gokhan Hotamisligil is one of the pioneers in the field of metabolism and he is the first person who showed the relationship between obesity, inflammation and aP2. He was the first to describe phenotypes of an aP2-deficient mice model, which is protected from obesity-induced inflammation, diabetes, atherosclerosis and asthma. He will provide lab space and funding for experiments/ and tools used in this project and guide me to merge aP2 and obesity related asthma pathobiology and will help me to become independent investigator as he has already trained more than 40 students and fellows who have moved on to develop their independent careers in very prestigious institutions both in academia and industry. While he will be involved in advising on the overall direction of the project, he always encourages fellows to pursue their own novel ideas and approaches, and will support my path toward independent research.

I took a break from full time postdoctoral research between July 2014-present to pursue an internal medicine residency and endocrinology fellowship in Harvard Medical School. Beginning July 1st, 2018, I resumed my postdoctoral research fellowship. While I was doing my residency and clinical fellowship, I remained associated with the lab as a visiting scientist and was able to complete my drug discovery paper during this period. By August 1st, 2019, I will have total 4 years full time postdoctoral research fellowship experience with some additional time spent in the same lab as a visiting scientist.

B. Positions and Honors

Positions and Employment

2011 - 2014	Postdoctoral Research Fellow, Harvard T.H. Chan School of Public Health, Boston, MA
2014 - 2017	Resident Physician, Clinical Fellow, Mount Auburn Hospital, Harvard Medical School, Cambridge, MA
2017 -	Research and Clinical Fellow, Brigham and Women's Hospital, Harvard Medical School, Boston, MA
2018 -	Postdoctoral Research Fellow, Harvard T.H. Chan School of Public Health, Boston, MA

Other Experience and Professional Memberships

2011 - 2013	Delegate of Harvard T.H. Chan School of Public Health, National Postdoc Association (NPA)
2014 -	Member, American College of Physicians (ACP)
2014 -	Member, American Medical Association (AMA)
2014 -	Member, Massachusetts Medical Society

2014 - 2016	Member, European Association for the Study of Diabetes (EASD)
2015 -	Ambassador to USA, National Institutes of Health, Turkey
2016 -	Reviewer, Journal of Gerontology: Medical Sciences
2017 -	Member, The Endocrine Society
2017 -	Member, American Diabetes Association (ADA)
2017 -	Member, American Thyroid Association (ATA)
2019 -	Reviewer, Nutrients

Honors

2009	Founder and President , Kocaeli University School of Medicine Inaugural Student Congress
2009	Full Scholarship , Joslin Diabetes Center, Harvard Medical School Summer Student Program
2009	Special Achievement Award , Honda Company Kocaeli
2011	Founder, Harvard Chan School of Public Health International Scholar Exchange Program
2011	Honorary Service Award , Kocaeli University School of Medicine 3rd Student Congress
2011 - 2013	Vice President-Publicity Chair , Harvard Chan School of Public Health Postdoctoral Association (PDA) Council
2011	Award of Excellence and Extraordinary Achievement , Kocaeli University School of Medicine
2011	Best Oral Presentation, Kocaeli University School of Medicine 3rd Student Congress
2014	Special Recognition and Service Award , Harvard Chan School PDA Faculty Advisory Board
2015	Young Scientist Travel Grant Award, European Association for the Study of Diabetes (EASD)
2015	Instructor of Metabolic Clamps Coarse , The Chaim Sheba Medical Center, Tel-Aviv University, Israel
2015	Late Breaking Abstract, American Diabetes Association (ADA)
2015	Ambassador to USA, Scientific Advisor, The Turkish Institutes for Health Sciences (TUSEB)
2016	Co-inventor, patent # WO2016176656 A3 , United States Patent and Trademark Office
2016	Best Research Project Award, MA State Winner , American College of Physicians (ACP)
2016	Ten Outstanding Young Persons (TOYP) of the World Award, Turkish Chapter Winner in Category of Medical Innovation and Scientific Development, Junior Chamber International (JCI)
2017	Young Achiever , American College of Physician (ACP)
2017	Research Excellence Award , Harvard Medical School, Discover Brigham
2018	Obesity and CVD Incubator 2018, Best Poster Award, Brigham & Women's Hospital / Harvard Medical School
2018	2018 Young Investigator 1st Place Award, The American Association of Clinical Endocrinologists (AACE)
2018	Postdoctoral Research Fellowship Award, Charles A. King - Bank of America, N.A Trust
2018	Diabetes Preceptorial Award 2018, The Endocrine Fellows Foundation (EFF)
2018	Endocrine Research Grant, Fall 2018, The Endocrine Fellows Foundation (EFF)
2019	ENDO 2019 Outstanding Abstract Award, The Endocrine Society
2019	Early Career Forum Travel Award , The Endocrine Society
2019	Diabetes Research Forum Award , The Endocrine Fellows Foundation (EFF)
2019	Best Poster Award , Harvard-Brigham 8th Annual Obesity and CVD Incubator
2019	Distinguished Obesity Research Project of 2019, The Endocrine Society (ENDO)

C. Contribution to Science

1. aP2/FABP4 has been implicated in the pathology of many immunometabolic diseases, including diabetes in humans, but aP2 has not yet been targeted for therapeutic applications. aP2 is not only an intracellular protein but also an active adipokine that contributes to hyperglycemia by promoting hepatic gluconeogenesis and interfering with peripheral insulin action. Serum aP2 levels are markedly elevated in obesity and strongly correlate with metabolic complications. These observations raise the possibility of a new strategy to treat metabolic disease by targeting serum aP2 with a monoclonal antibody (mAb) to aP2. We developed mAbs to aP2 and identified one, CA33, that lowered fasting blood glucose, improved systemic glucose metabolism, increased systemic insulin sensitivity, and reduced fat mass and liver steatosis in obese models. We examined the structure of the aP2-CA33 complex and resolved the target epitope by crystallographic studies. In hyperinsulinemic euglycemic clamp studies, we found that the antidiabetic effect of CA33 was predominantly linked to the regulation of hepatic glucose output and peripheral glucose utilization. We conclude that an aP2 mAb–mediated therapeutic constitutes a feasible approach for the treatment of diabetes and fatty liver disease. I led this project, designed-performed-interpreted most of the experiments independently and coordinated with an industrial partnership.

    a. 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. Development of a therapeutic monoclonal antibody that targets secreted fatty acid-binding protein aP2 to treat type 2 diabetes. Sci Transl Med. 2015 Dec 23;7(319):319ra205. PubMed PMID: 26702093.

2. Adipose tissue is the most effective site for energy and nutrient storage as well as for release, depending on the energy demands of the organism. Adipose tissue is also an important endocrine organ responsible for systemic metabolic regulation. aP2 occupies central role in adipose biology and cross talk between liver and fat tissue. Hepatic glucose production is dysregulated in obesity and represents a key process leading to development of diabetes. aP2 is a hormone secreted from adipocytes in response to fasting and increases hepatic glucose production. Serum aP2 levels increase in human obesity and contribute to hyperglycemia in diabetes. aP2 has thus been recognized as a link between dysmetabolism and obesity-related problems such as diabetes, fatty liver disease and atherosclerosis. I made a significant contribution to recognition of aP2 as an adipose-derived hormone. Intracellular aP2 has been known for 30 years, but the hormonal task was not noticed and therefore not studied. I provided proof of the concept of its hormonal role. The levels of this hormone are very high in obesity, diabetes, and heart disease. Therefore, blocking this hormone gave us the opportunity to create new treatment modalities for immunometabolic diseases such as diabetes and heart disease. I pursued that opportunity by leading a successful monoclonal antibody development project, taking further steps toward drug development by humanizing the antibody.

    a. Cao H, Sekiya M, Ertunc ME, Burak MF, Mayers JR, White A, Inouye K, Rickey LM, Ercal BC, Furuhashi M, Tuncman G, Hotamisligil GS. Adipocyte lipid chaperone AP2 is a secreted adipokine regulating hepatic glucose production. Cell Metab. 2013 May 7;17(5):768-78. PubMed PMID: 23663740; PubMed Central PMCID: PMC3755450.

3. Alternative mRNA splicing provides transcript diversity and may contribute to human disease. We demonstrate that expression of several genes regulating RNA processing is decreased in both liver and skeletal muscle of obese humans. We evaluated a representative splicing factor, SFRS10, downregulated in both obese human liver and muscle and in high-fat-fed mice, and determined metabolic impact of reduced expression. SFRS10-specific siRNA induces lipogenesis and lipid accumulation in hepatocytes. Moreover, Sfrs10 heterozygous mice have increased hepatic lipogenic gene expression, VLDL secretion, and plasma triglycerides. We demonstrate that LPIN1, a key regulator of lipid metabolism, is a splicing target of SFRS10; reduced SFRS10 favors the lipogenic β isoform of LPIN1. Importantly, LPIN1β-specific siRNA abolished lipogenic effects of decreased

SFRS10 expression. Together, our results indicate that reduced expression of SFRS10, as observed in tissues from obese humans, alters LPIN1 splicing, induces lipogenesis, and therefore contributes to metabolic phenotypes associated with obesity. I worked under direct supervision of Dr. Patti and Dr. Carles and finished the in vivo experiments asked by reviewers and demonstrated a new feedback mechanism in LPIN1 splicing in obesity.

   a. Pihlajamäki J, Lerin C, Kaminska D, Venesmaa S, Itkonen P, Boes T, Floss T, Schroeder J, Dearie F, Crunkhorn S, Burak F, Jimenez-Chillaron JC, Kuulasmaa T, Miettinen P, Park PJ, Nasser I, Zhao Z, Zhang Z, Xu Y, Wurst W, Ren H, Morris AJ, Stamm S, Goldfine AB, Laakso M, Patti ME. Response to Brosch et al. Cell Metab. 2012 Mar 7;15(3):267-269. PubMed PMID: 25960695; PubMed Central PMCID: PMC4425348.

4. Androgen deprivation therapy (ADT) remains the cornerstone of management of prostate cancer (PCa). Previous studies have shown that men undergoing ADT develop insulin resistance and diabetes, but the mechanisms behind ADT-induced metabolic abnormalities remain unclear.We evaluated the association between inflammatory cytokines, aP2 and ADT driven insulin resistance.

   a. Gagliano-Jucá T, Burak MF, Pencina KM, Li Z, Edwards RR, Travison TG, Basaria S. Metabolic Changes in Androgen-Deprived Nondiabetic Men With Prostate Cancer Are Not Mediated by Cytokines or aP2. J Clin Endocrinol Metab. 2018 Oct 1;103(10):3900-3908. PubMed PMID: 30032274; PubMed Central PMCID: PMC6179166.

5. Besnili B, Burak M.F, Celebi A. and Gurbuz Y: Kuppfer Cell Density and Distribution in Patients of NASH, NAFLD and Normal Controls. March 12 –14 2009. The JIAMSE Journal, April 2, Volume 19, Number 2S, ISSN: 1550-8897 Leiden-NETHERLAND.

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

259464, Charles A. King Trust Hotamisligil (PI) 10/01/18-10/01/20
The role of circulating aP2 in the pathogenesis of allergen induced and obesity related asthma and new therapeutic strategies against asthma using anti-aP2 agents
Role: Post-Doctoral Scholar

7690479, The Endocrine Fellows Foundation (EFF) Burak (PI) 12/01/18-11/01/19
The role of circulating aP2 in the pathogenesis of obesity related asthma and new therapeutic strategies against obesity related asthma using anti-aP2 agents
This is a small-pilot grant. Total amount $5,000. Mentor: Dr.Hotamisligil
Role: PI