BIOGRAPHICAL SKETCH

NAME: Feyza Engin

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

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Istanbul University, Istanbul, Turkey	B.S.	06/1998	Pharmacy
Istanbul University, Istanbul, Turkey	M.S.	06/2001	Biochemistry
Baylor College of Medicine, Houston, TX	Ph.D.	12/2007	Genetics
Harvard University, Boston, MA	Postdoc	07/2013	Diabetes & Metabolism

A. Personal Statement

Both for my doctoral and postdoctoral studies, I had the privilege of working with renowned mentors who are considered amongst the leaders in their fields. These laboratories mainly focus on translational research in the context of disorders of skeletal development and metabolic syndrome by using variety of approaches and exposure to these environments early in my career has given me a broad understanding of developmental processes, transcriptional regulations, signaling pathways, organ-organ interaction, genetics, energy and nutritional driven organelle stress, metabolism and chronic inflammation. My research interests center on the mechanisms by which organisms establish cellular homeostasis in the presence of chronic inflammation and organelle stress, with the goal of capitalizing on the underlying mechanisms to develop novel therapeutics. Thus, over the last seven years, I have focused on investigating the role of β-cell endoplasmic reticulum (ER) stress in the pathogenesis of type 1 diabetes and have gained the expertise, knowledge, discipline and leadership skills to carry out the proposed study successfully and in a timely manner. The goal of the proposed research is to investigate the ER stress and the unfolded protein response in the beta cells of type 1 diabetes mouse models and the crosstalk between the ER and the mitochondria in the context of autoimmune diabetes. This application builds on my prior work in which I demonstrated for the first time a direct link between ER stress and aberrant UPR and the type 1 diabetes pathogenesis. This work received considerable amount of attention from the scientific community and the media as evidenced by commentaries in *Nat Rev Endocrinol* and *Islets* and an article in *National Geographic* http://voices.nationalgeographic.com/2013/11/13/bear-bile-could-stall-onset-of-diabetes-study-says/. The chemical chaperone that I used in this study to prevent diabetes in mice is currently under investigation in clinical settings. In addition to my prior expertise on ER biology and the adaptive responses, I would like to expand my research to organelle-organelle interactions under stress conditions. As a result of my previous experience, I appreciate and understand the importance of the scientific communications and collaborations. Thus, I am planning to establish productive collaborations with the leading experts in the field of mitochondrial biology here at UW-Madison. In summary, I have a demonstrated record of accomplished and fruitful research projects and I believe my expertise and experience have prepared me to lead the proposed project successfully.

B. Positions and Honors

Positions

2014-current Assistant Professor, University of Wisconsin-Madison, School of Medicine and Public Health, Department of Biomolecular Chemistry,
Department of Medicine, Division of Endocrinology, Diabetes and Metabolism.
2014-2015 Visiting Scientist, Harvard School of Public Health, Department of Genetics & Complex Diseases.
2013-2014 Research Associate, Harvard School of Public Health, Department of Genetics & Complex Diseases.
2008-2013 Postdoctoral Research Fellow, Harvard School of Public Health, Department of Genetics & Complex Diseases.
2001-2007 Graduate Student, Baylor College of Medicine, Department of Molecular and Human Genetics.
1998-2001 Teaching Assistant, Istanbul University School of Pharmacy, Department of Biochemistry

Honors

2014 Research Scientist Development Award (KO1), NIDDK, National Institute of Health.
2014 Career Development Award, Juvenile Diabetes Research Foundation.
2012 Travel Award**,** Harvard School of Public Health Postdoc Association.
2007 Young Investigator Award, The American Society of Bone and Mineral Research.
2005 Second Place Platform Presenter, Annual Molecular and Human Genetics Retreat, Baylor College of Medicine.
2001 Travel Award, Istanbul University Research Fund.

C. Contribution to Science

1. **Discovering the role of Notch Signaling in bone development and related diseases.** Notch signaling was known to regulate many aspects of development and tissue renewal, and its dysregulation or loss has been associated with a wide range of human disorders, from developmental syndromes to adult-onset diseases and cancer. However, at the time that I started my graduate studies, it was unknown whether Notch signaling had a role in bone tissue development or abnormalities of this pathway could cause any diseases. My graduate research identified *for the first time* that Notch signaling had dimorphic effects in bone homeostasis. I discovered that abolishing Notch function in osteoblasts did not affect osteoblast dependent bone formation. However, these cells lacked the ability to regulate activity of osteoclasts. Thus, abnormally high rate of bone resorption led to osteoporosis in mice very reminiscent of human osteoporosis patients. In addition, I showed that Notch signaling was overactive in human osteosarcomas and demonstrated that compounds that block Notch signaling dramatically slowed the growth of human tumor xenograft models. These findings have opened up a new line of research with great therapeutic potential and laid the foundation for the future studies in the field. Of even greater significance, this discovery also provided a sound explanation for the role of Notch signaling in the early and late stages of osteoblast development which was not appreciated before.

   - **Engin, F.,** Yao, Z., Yang, T., Zhou, G., Bertin, T., Jiang, M.M., Chen, Y., Wang, L., Zheng, L., Sutton, R.E., Boyce, B.F., Lee, B. "Dimorphic effects of Notch signaling in bone homeostasis". *Nat. Med.* 2008; 14(3): 299-305. PMCID: 2671578.

   - **Engin, F.,** Bertin, T., Ma, O., Jiang, MM., Wang, L., Sutton, RE., Donehower, LA., Lee, B. "Notch signaling contributes to the pathogenesis of human osteosarcomas". *Hum Mol Genet.* 2009; 18(8): 1464-1470. PMID: 19228774. PMCID: 2733809.

   - **Engin, F.,** Lee B. "NOTCHing the bone: insights into multi-functionality". *Bone.* 2010; 46(2): 274-280. PMID: 19520195. PMCID: 2835535.

2. **Uncovering the role of endoplasmic Reticulum (ER) stress and unfolded protein response (UPR) in Type 1 diabetes pathogenesis.** Accumulating data implicate ER stress and altered UPR activity in the pathogenesis of inflammatory and autoimmune diseases, and ER stress has been implicated in β-cell failure in type 2 diabetes. However, the role of ER stress and the UPR in β-cell pathophysiology and in the initiation and propagation of the autoimmune responses in type 1 diabetes (T1D) remains incompletely defined. During my postdoctoral studies, I demonstrated that ER's adaptive capacity was markedly decreased in two different mouse models of T1D and in human patients. In addition, diabetes incidence in these mouse models was dramatically reduced by mitigating ER stress with a chemical chaperone, TUDCA, which acts via the ATF6 branch of the UPR. Reduced diabetes incidence in these mice was accompanied by improved islet architecture, preserved insulin secretion, and restored expression of UPR components. This study combined data from animal models and human patients indicated the presence of aberrant UPR during disease progression and provided the *first direct link* between the UPR and T1D pathogenesis. In addition, it supported the notion of β-cell preservation through the use of ER modulating agents as an alternative translational strategy. This novel paradigm received significant scientific attention and led to experts in the field to publish commentaries on it (Urano F. *Nat Rev Endocrinol.* 2014;10(3):129-30., Maganti A. et al., *Islets.* 2014;6(2):e28778.). In a follow up study, we also demonstrated similar defects in the β-cells of type 2 diabetes animal models as well as in human patient samples. Thus, we believe these studies will form a basis for subsequent studies in diabetes field.

- **Engin, F.,** Nguyen T., Yermalovich A., Hotamisligil, GS. "Aberrant unfolded protein response in type 2 diabetes". *Sci Rep. 2014.* Feb 11;4:4054. PMID: 24514745.

- **Engin, F.,** Yermalovich, A., Fu, W., Nguyen, T., Hummasti, S., Decio, L., Eizirik., Mathis, D., Hotamisligil, GS. "Restoration of the unfolded protein response in pancreatic beta cells protects mice against type 1 diabetes". *Sci. Transl. Med. 2013.* Dec 4;5(214):214er11. PMID: 24225943.

- **Engin, F.,** Hotamisligil, GS. "Chemical modulation of ER function in metabolic diseases". *Diabetes Obes. Metab.* 2010. 12 Suppl 2:108-15. PMID: 21029307.

- **Engin, F.** "ER Stress and Development of Type 1 Diabetes" *J Investig Med*. 2015.

- Brozzi, F., Nardelli, TR., Lopes, M., Millard, I., Barthson, J., Igoillo-Esteve, M., Grieco, FA., Villate, O., Oliveira, JM., Casimir, M., Bugliani, M., **Engin, F.,** Hotamisligil, GS., Marchetti, PM., Eizirik, DL. "Cytokines induce endoplasmic reticulum stress in human, rat and mouse beta cells via different mechanisms". *Diabetologia. 2015.*

Complete List of Published Work in PubMed: http://www.ncbi.nlm.nih.gov/pubmed/?term=feyza+engin

D. Research Support

<u>Ongoing Research Support</u>

Funding Source: National Institute of Health, NIDDK. 1K01DK102488-01
Title: Beta cell endoplasmic reticulum stress and its crosstalk with immune system in T1D pathogenesis
Dates of Support: 09/01/2014-08/31/2017
Major goals of the project: We will examine the ATF6 branch of the unfolded protein response specifically in beta cells in the context of type 1 diabetes in the NOD mice. Furthermore, we will investigate the crosstalk between the ATF6 deficient beta cells and immune cells using genetic, cellular and biochemical approaches.
Individual's role: Dr. Engin will be responsible for directing all aspects of the proposed research study, including implementation of the study protocol; personnel issues, data acquisition, management, analysis, and interpretation; budget considerations. She will also supervise the dissemination of the study results at scientific venues and to collaborators as well as direct the project.
Percent effort: 75%
Key personnel: Feyza Engin (PI)

Funding Source: Juvenile Diabetes Research Foundation. 5-CDA-2014-184-A-N
Title: Beta cell endoplasmic reticulum stress and its crosstalk with immune system in T1D pathogenesis
Dates of Support: 01/01/2015-12/31/2019
Major goals of the project: We will examine the ATF6 branch of the unfolded protein response specifically in beta cells in the context of type 1 diabetes in the NOD mice. Furthermore, we will investigate the crosstalk between the ATF6 deficient beta cells and immune cells using genetic, cellular and biochemical approaches.
Individual's role: Dr. Engin will be responsible for directing all aspects of the proposed research study, including implementation of the study protocol; personnel issues, data acquisition, management, analysis, and interpretation; budget considerations. She will also supervise the dissemination of the study results at scientific venues and to collaborators as well as direct the project.
Percent effort: 10%
Key personnel: Feyza Engin (PI)

Funding Source: UW-Madison Start up. PRJ85XK, PRJ92ZU, PRJ93UV
Title: Organelle stress, adaptive responses and diabetes
Dates of Support: 10/01/20014-10/30/2019
Major goals of the project: We are interested in understanding the molecular mechanisms of type 1 diabetes.
Individual's role: Dr. Engin is the Principle Investigator
Key personnel: Feyza Engin (PI)