BIOGRAPHICAL SKETCH

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NAME: Demircioglu, Fatma Esra

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

POSITION TITLE: Research Scientist I

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)*	Completion Date MM/YYYY	FIELD OF STUDY
Middle East Technical University, Turkey	B.S.	06/2006	Molecular Biology and Genetics
University of Goettingen, Germany	M.S.	04/2008	Molecular Biology
University of Goettingen, Germany	Ph.D.	11/2011	Molecular Biology, Biochemistry
Massachusetts Institute of Technology, USA	Postdoctoral	10/2019	Biochemistry, Structural Biology
Broad Institute, USA	Research Scientist I	Present	Biochemistry, Structural Biology

A. Personal Statement

As a staff scientist specializing in structural biology, my goal in the Zhang lab is to contribute to a number of projects aimed at characterizing and engineering molecular systems. Preparing me for this role, I have 10+ years of experience in working with challenging protein complexes, a solid background in protein crystallography, strong motivation, and collaborative and leadership skills. I am currently interested in developing novel genome editing and/or therapeutic delivery tools. For this, I plan to integrate the biodiscovery and the protein engineering approaches that are being used in the Zhang lab with a combination of structural biology techniques, X-ray crystallography, and, increasingly, cryo-EM. During my postdoctoral training, my research mainly focused on protein crystallography, but I also got experience in cryo-EM specimen preparation while characterizing a self-assembling protein in its filamentous form. Since MIT did not have an internal cryo-EM center at the time, I used the UMass Medical School Cryo-EM Core Facility for this project for both sample preparation and cryo-EM imaging. To overcome the bottleneck of poor access to streamlined computational cryo-EM resources and my limited expertise in using, I collaborated with Prof. Edward Egelman and his colleagues at the University of Virginia to determine the structure of our filamentous target. Through this work, I was able to familiarize myself with single-particle and helical reconstruction pipelines. In the long run, however, I would like to get deeper expertise in both cryo-EM imaging and structure determination, so that I can lead projects independently, and help establish a structural biology platform in the Zhang lab. My background and motivation is of highest relevance for the current application.

B. Positions and Honors

Positions and Employment

2012-2019 Postdoctoral Associate, MIT, Department of Biology, Cambridge, MA
2019- Research Scientist I, Broad Institute, Zhang Lab, Cambridge, MA

Other Experience and Professional Memberships

2008 abc6 Applications of Biocalorimetry, Heidelberg
2014 SBGrid/NE-CAT - Quo Vadis Structural Biology? Data Processing in Crystallography, Harvard Medical School
2015, 2018 ASCB (American Society for Cell Biology) postdoctoral membership
2018 MIT I-Corps TFP: Essentials program certification
2018 Participant of the "Getting Started in Cryo-EM" course as part of Independent Activities Period (IAP) at MIT

Honors

2008 GGNB (Goettingen Graduate Schools for Neurosciences and Molecular Biosciences) Excellence Fellowship Recipient
2011 Invited Speaker at the 8th Molecular Mechanisms of Exocytosis & Endocytosis meeting in Edinburgh, Scotland

C. Contribution to Science

1. During my undergraduate years, I worked in a biophysical laboratory under the supervision of Prof. Dr. Feride Severcan. We investigated whether melatonin, an antioxidant hormone, can restore radiation-induced molecular damage on the rat brain crude membrane by examining the changes in proteins and lipids using Fourier Transform Infrared (FTIR) Spectroscopy.

    a. Akkas, S.B., F.O. Kok, F.E. Demircioglu, S. Inci, F. Zorlu, F. Severcan, (2005) An FTIR investigation of the effect of radiation and the possible protective effect of melatonin on rat brain crude membrane. 2005 Biophysical Society Meeting Abstracts. Biophysical Journal, Supplement, B623, Abstract, 784-Pos.

2. During my graduate studies, I worked with SNAREs, a group of proteins involved in vesicle fusion. I initiated a project on poorly characterized members of the SNARE family, which function during ER-to-Golgi trafficking. Through intricate ITC, fluorescence anisotropy and FRET experiments, I characterized the interaction mode between the SNARE protein Sed5 and its regulating SM protein Sly1. I found that Sly1 loosens a closed, inaccessible conformation of Sed5 and facilitates SNARE complex formation. My findings revealed how the original binding mode between SM proteins and SNAREs might have evolved.

    a. Demircioglu, F.E., Burkhardt, P., and Fasshauer, D. (2014) The SM protein Sly1 accelerates assembly of the ER-Golgi SNARE complex. Proc. Natl. Acad. Sci. U.S.A. 111, 13828–13833.

3. During my postdoctoral training, I developed tools to biochemically characterize a number of nuclear envelope proteins associated with neuromuscular diseases. My research particularly focused on TorsinA, a neuronal, nuclear membrane-associated AAA+ ATPase with an unknown function. TorsinA is medically relevant, since it becomes a disease-causing molecule when its single glutamate residue at position 302 or 303 (deltaE) is deleted, leading to a prevalent neuromuscular disorder, primary dystonia. Furthermore, TorsinA, unlike its homologs, needs external activators for its ATPase activity, and TorsinAdeltaE cannot bind to these activators. I set out to understand the molecular basis of these observations using a structural biology approach. I first obtained the crystal structure of a nanobody-bound TorsinA-activator complex and characterized the activator interaction. Through structural analysis I discovered the nanobody's "connector" role between TorsinA and the activator. Implementing this knowledge also enabled me to assemble and crystallize a nanobody-bound TorsinAdeltaE-activator complex, providing a structural platform for drug

development for treatment of primary dystonia. Using cryo-electron microscopy, I next characterized TorsinA in its self-assembled filamentous form. Bioinformatics and electrostatic potential analysis of these filaments led to the hypothesis that TorsinA may engage lipids. Supporting this, I observed that TorsinA tubulates membranes in vitro. Together, these findings not only help us understand the membrane defects that occur upon TorsinA dysfunction, but they also suggest entirely new characteristics of AAA+ ATPases.

a. Sosa, B. A., Demircioglu, F. E., Chen, J. Z., Ingram, J., Ploegh, H. L., and Schwartz, T. U. (2014) How lamina-associated polypeptide 1 (LAP1) activates Torsin. Elife 3:03239

b. Demircioglu, F. E., Cruz VE & Schwartz TU (2016) Purification and Structural Analysis of SUN and KASH Domain Proteins. Meth. Enzymol. 569:63–78.

c. Demircioglu, F. E., Sosa, B.A., Ingram, J., Ploegh, H.L., and Schwartz, T.U. (2016) Structures of TorsinA and its disease-mutant complexed with an activator reveal the molecular basis for primary dystonia. Elife 5:213.

d. Schwartz, T.U., Demircioglu, F.E., Sosa, B.A. Crystal structures of human Torsin-A and methods of determining and using the same. U.S. patent 9,823,250 issued November 21, 2017.

e. Demircioglu, F.E., Zheng, W., McQuown, A.J., Maier, N.K., Watson, N., Cheeseman, I.M., Denic, V., Egelman, E.H., and Schwartz, T.U. (2019) The AAA+ ATPase TorsinA polymerizes into hollow helical tubes with 8.5 subunits per turn. Nat Commun 10:3262.