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: Aydin, Halil

eRA COMMONS USERNAME (credential, e.g., agency login): halilaydin

POSITION TITLE: Assistant Professor

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
Istanbul University, Istanbul	DVM	06/2007	Veterinary Medicine
University of Ottawa, Ottawa, Ontario	MSc	08/2011	Biochemistry and Immunology
University of Toronto, Toronto, Ontario	PhD	09/2016	Biochemistry and Cell Biology
University of California, San Francisco, San Francisco, California	Postdoctoral Fellow	12/2020	Biochemistry and Structural Biology

A. Personal Statement

How do eukaryotic cells and their organelles acquire and alter their shapes in support of their tasks? Starting with my work as a graduate student and continuing into my independent career, I am inspired by this question and interested in understanding how dynamic cellular compartments adapt their morphology, spatial distribution, and function to changing cellular conditions. The frontier problem now is to understand how nanoscale motions of macromolecular machines modulate membrane and organelle dynamics that govern cell survival, differentiation, communication, and cell death. My lab utilizes a multi-disciplinary approach that bridges detailed structural studies with a deeper knowledge of cellular function to advance our understanding of how biomolecular machines control cellular complexity and dynamics, and how they are corrupted by disease. Currently, our research interests are largely directed towards investigating the mechanisms linking membrane protein dynamics to organelle morphology and function. We aim to perform robust quantitative analysis of membrane-associated mechanisms and bridge length scales between organelles and their molecular machines. Together, this work will provide a mechanistic foundation to understand how membrane proteins communicate cellular signals to regulate organelle distribution, morphology, and function, and how perturbations of this interplay underlie the development and progression of neurodegenerative and metabolic disorders. I believe that the membrane and organelle dynamics field is at a tremendously exciting point: With a suite of advanced visualization and quantitative tools now available, the time is ripe for systematic analyses of the molecular mechanisms that regulate key cellular processes and preserve homeostasis. Such analyses are bound to be transformative for our understanding of the essential cellular functions and the roles of individual proteins. Currently, our laboratory is training 2 postdoctoral fellow, 1 professional research assistant, and 1 undergraduate researcher. Given my track record in publishing, my synergistic collaborations with other investigators, and my expertise in structural biology and biophysics, I believe I am well positioned to serve as PI of this proposal.

1. von der Malsburg, A., Sapp, G. M., Zuccaro, K. E., von Appen, A., Moss III, F. R., Kalia, R., Bennett, J. A., Abriata, L.A., Dal Peraro, M., van der Laan, M., Frost, A.[+], **Aydin, H.[+]** Structural mechanism of mitochondrial membrane remodeling by human OPA1. **Nature.** 2023 620:1101-1108 PubMed Central PMCID: 37612504.
[+]Co-corresponding authors

2. Bennett JA, Steward LR, Rudolph J, Voss AP, **Aydin H.** The structure of the human LACTB filament reveals the mechanisms of assembly and membrane binding. **PLoS Biol.** 2022 Dec;20(12):e3001899. PubMed Central PMCID: PMC9815587.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2025 -	Assistant Professor, New York University, New York, NY
2021 - 2025	Assistant Professor, University of Colorado Boulder, Boulder, CO
2016 - 2020	Postdoctoral Scholar, University of California, San Francisco, San Francisco, CA

Honors

2024	Barth Syndrome Foundation Idea Award
2024	Co-Chair – Cryo-EM Subgroup, Biophysical Society Annual Meeting in Philadelphia, PA, USA
2023	Co-Chair – Cellular Dynamics Minisymposia, ASCB | EMBO Annual Meeting Cell Bio 2023, Boston, MA, USA
2023	Boettcher Foundation Webb-Waring Biomedical Research Award
2018	Future of Science Scholarship, Keystone Symposia
2017	Human Frontiers Science Program Postdoctoral Fellowship, Human Frontiers Science Program
2017	Stuart Alan Hoffman Prize for best Ph.D. thesis, University of Toronto
2015	Travel Award, University of Toronto
2015	Poster Presentation Award 1st Place (Ph.D. Category), University of Toronto
2015	Ontario Graduate Scholarship (OGS) International, Ontario Government
2014	University of Toronto Fellowship, University of Toronto
2013	Training Award, University of Toronto
2013	School of Graduate Studies Conference Grant, University of Toronto
	Poster Presentation Award 1st Place (Ph.D. Category), University of Toronto
2012	Travel Award, University of Toronto
2012	Travel Grant, American Crystallographic Association
2011	University of Toronto Fellowship, University of Toronto
2011	Best Poster Presentation by a Graduate Student, University of Ottawa
2007	Istanbul Metropolitan Municipality Scholarship, Istanbul Municipality

C. Contribution to Science

1. ***Defining the molecular mechanisms of mitochondrial organization and connectivity.*** My research laboratory investigates the spatial and temporal organization of organelles and their molecular machines that underlie cellular processes ranging from division and migration to differentiation and communication. In mammals, the dynamic control of mitochondrial shape and connectivity depends on Optic Atrophy 1 (OPA1). OPA1 catalyzes the fusion of the mitochondrial inner membrane (IM), shapes cristae structure, and influences oxidative phosphorylation efficiency, metabolism, apoptosis, and reactive oxygen species production. By taking full advantage of advances in cryoEM and biochemical breakthroughs in our lab, we recently reported the 3D structures of OPA1 assemblies in functional states—and, most excitingly, offered direct views of membrane structure modulation by OPA1. We further elucidated, via cell-based assays and biochemical studies, how OPA1 plays critical roles in controlling the shape of mitochondrial reticulum, including cristae architecture. Our findings explained how OPA1 cooperates with lipids to regulate mitochondrial morphology and how loss of function leads to disease. Recently, we also reported unexpected functions for human MiD49 and MiD51 proteins, which regulate the activity of mitochondrial fission machinery and induce mitochondrial division. Overall, our research provides molecular insights into the fundamental principles of mitochondrial membrane organization and function.

    1. Liu, A., Kage, F., Albulkareem, A. F., Aguirre-Huamani, M. P., Sapp, G.M., **Aydin, H.**, Higgs, H.N. Fatty acyl-coenzyme A activates mitochondrial division through oligomerization of MiD49 and MiD51. **Nature Cell Biology**. 2024 26, 731-744 PubMed Central PMCID:

38594588.

2. von der Malsburg, A., Sapp, G. M., Zuccaro, K. E., von Appen, A., Moss III, F. R., Kalia, R., Bennett, J. A., Abriata, L.A., Dal Peraro, M., van der Laan, M., Frost, A.[+], **Aydin, H.[+]** Structural mechanism of mitochondrial membrane remodeling by human OPA1. **Nature**. 2023 620:1101-1108 PubMed Central PMCID: 37612504.

[+]Co-corresponding authors

3. *Bennett JA, *Steward LR, Rudolph J, Voss AP, **Aydin H.** The structure of the human LACTBfilament reveals the mechanisms of assembly and membrane binding. **PLoS Biol.** 2022 Dec;20(12):e3001899. PubMed Central PMCID: PMC9815587.

*These authors contributed equally.

2. ***Investigating the molecular cues and steps driving mitochondrial Coenzyme Q biosynthesis.*** Quinones are central to energy-transducing systems in organisms across all kingdoms of life. Coenzyme Q (CoQ, or ubiquinone) is an essential component of the mitochondrial electron transport chain and a key cellular antioxidant. In eukaryotes, inadequate production of CoQ underlies a wide range of clinically diverse human disorders whose pathophysiology is not well defined. I have elucidated the molecular basis of a dynamic, multicomponent mitochondrial protein complex to map the CoQ biosynthesis, metabolism, and transport pathways. Using a multidisciplinary approach, I have determined the molecular mechanisms of enzyme activation, substrate channeling, and membrane remodeling. Our results provide a mechanism for how proteins cooperate at a lipid membrane to selectively extract and process an extremely hydrophobic substrate for CoQ biosynthesis. These data provide novel insights into the molecular architecture of complex Q components and a foundation for gaining mechanistic insights into the molecular functions that facilitate CoQ biosynthesis.

   1. *Manicki M, ***Aydin H**, Abriata LA, Overmyer KA, Guerra RM, Coon JJ, Dal Peraro M, Frost A, Pagliarini DJ. Structure and functionality of a multimeric human COQ7:COQ9 complex. **Mol Cell**. 2021 Nov 17;82(22):4307-4323.e10. PubMed Central PMCID: PMC10058641.

   *These authors contributed equally.

3. ***Establishing the biochemical basis of mammalian fertilization.*** Cell fusion is a process that is crucial at many crossroads in cell biology. In sexually reproducing species, the fusion of sperm and egg plasma membranes results in the creation of a new genetically distinct diploid organism termed zygote. The mechanism of sperm-egg fusion requires the involvement of sperm Izumo1 and egg Juno proteins. Izumo1 and Juno are the only known proteins that are essential for sperm and egg fusion. Mice models lacking Juno or Izumo1 are healthy but infertile. As a graduate student at the University of Toronto, I determined the crystal structures of human Izumo1 and Juno alone, and as a complex, and characterized the molecular details of this essential protein complex with biochemistry and biophysical methods. These are the first atomic-resolution structures of any protein complex between sperm and egg at the point of conception for any organism. Izumo1 and Juno complex displays an interface stabilized through extensive interactions and a major conformational change within Izumo1 upon Juno binding. I used a hybrid approach that combined mutagenesis, deuterium exchange mass spectrometry (DXMS), and other biophysical techniques to validate the molecular interactions between Izumo1 and Juno, and revealed the structural determinants required for binding. My results now provide the foundation to further characterize the interactions of sperm and egg and allow us to understand the fundamental principles of mammalian fertilization.

   1. **Aydin H**, Sultana A, Li S, Thavalingam A, Lee JE. Molecular architecture of the human sperm IZUMO1 and egg JUNO fertilization complex. **Nature**. 2016 534:562-565. PubMed Central PMCID: PMC5319863.

4. ***Elucidating the mechanistic bases of viral and host cell membrane fusion.*** As a graduate student, I have taken an integrated, multidisciplinary approach to unravel the molecular mechanisms of virus-cell fusion. Membrane fusion is a key step in the obligate intracellular life cycle of all enveloped viruses. Viral-host cell fusion is catalyzed by one or more virion-associated surface glycoproteins that are embedded in the viral lipid bilayer. I determined the crystal structures of viral fusion proteins from model

organisms and performed functional assays to elucidate the role of key residues involved in critical interactions. Our analyses revealed how enveloped viruses utilize similar mechanisms for membrane fusion. Structures of viral fusion proteins unveiled that electrostatic interactions are critical for protein stability in viruses that fuse at neutral pH, whereas salt bridges do not play a stabilizing role in fusion proteins that proceed through low pH. Instead, hydrophobic residues stabilize the fusion core, and histidine/arginine residues in the membrane-distal end stabilize a helix dipole moment. My results describe key features of viral fusion machinery and improve our overall understanding of viral entry.

1. **Aydin H**, Al-Khooly D, Lee JE. Influence of hydrophobic and electrostatic residues on SARS-coronavirus S2 protein stability: insights into mechanisms of general viral fusion and inhibitor design. **Protein Sci**. 2014 May;23(5):603-17. PubMed Central PMCID: PMC4005712.
2. **Aydin H**, Cook JD, Lee JE. Crystal structures of beta- and gammaretrovirus fusion proteins reveala role for electrostatic stapling in viral entry. **J Virol**. 2014 Jan;88(1):143-53. PubMed Central PMCID: PMC3911763.
3. **Aydin H**, Smrke BM, Lee JE. Structural characterization of a fusion glycoprotein from a retrovirusthat undergoes a hybrid 2-step entry mechanism. **FASEB J**. 2013 Dec;27(12):5059-71. PubMed Central PMCID: PMC7164122.
4. ***Aydin H**, *Azimi FC, *Cook JD, Lee JE. A convenient and general expression platform for theproduction of secreted proteins from human cells. **J Vis Exp**. 2012 Jul 31; PubMed Central PMCID: PMC3476395.

   *These authors contributed equally.

5. ***Characterizing the interplay between viruses and host immune defenses.*** The mammalian innate immune system has evolved multiple cellular restriction factors that impair the rapid replication of viruses. Human APOBEC3 (A3) proteins are host-encoded intrinsic restriction factors that inhibit the replication of many retroviral pathogens. A3 proteins substantially bolster the intrinsic immune system by providing a powerful block to the transmission of retroviral pathogens; however, most retroviruses, such as human immunodeficiency virus 1 (HIV-1), can subvert this replicative restriction in their natural host. I have helped develop a high-throughput screening method called hyperHRM to screen genomic DNA for mutated proviral sequences. HRM is a powerful method for the detection of mutated proviral DNA sequences potentially associated with a disease or retroviral drug resistance. In addition, I contributed to the functional characterization of retroviruses that employ posttranslational modification to antagonize and modulate the activity of host genome-encoded retroviral restriction factors. These results elucidate the structure-function relationships between A3 proteins and HIV-1 macromolecules and allow us to understand how retroviruses can manipulate their host.

   1. Rosales Gerpe MC, Renner TM, Bélanger K, Lam C, **Aydin H**, Langlois MA. N-linked glycosylationprotects gammaretroviruses against deamination by APOBEC3 proteins. **J Virol**. 2015 Feb;89(4):2342-57. PubMed Central PMCID: PMC4338886.
   2. ***Aydin H**, *Taylor MW, Lee JE. Structure-guided analysis of the human APOBEC3-HIV restrictome. **Structure**. 2014 May 6;22(5):668-84. PubMed PMID: 24657093.

      *These authors contributed equally.

   3. Bélanger K, Savoie M, **Aydin H**, Renner TM, Montazeri Z, Langlois MA. Deamination intensity profiling of human APOBEC3 protein activity along the near full-length genomes of HIV-1 and MoMLV by HyperHRM analysis. **Virology**. 2014 Jan 5;448:168-75. PubMed PMID: 24314647.

Complete List of Published Work in My Bibliography:

https://www.ncbi.nlm.nih.gov/myncbi/1xgEwwaTqUVQR/bibliography/public/