BIOGRAPHICAL SKETCH

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NAME: Nelli Mnatsakanyan

eRA COMMONS USER NAME (credential, e.g., agency login): MNATSAKANYAN79430

POSITION TITLE: Associate 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)*	Completion Date MM/YYYY	FIELD OF STUDY
Yerevan State University, Yerevan, Armenia	B.S., M.S.	06/1999	Biophysics
Yerevan State University, Yerevan, Armenia	Ph.D.	12/2003	Biophysics
Texas Tech University, Lubbock, TX	Postdoctoral	06/2011	Biophysics/Biochemistry
Texas Tech University Health Sciences Center, Lubbock, TX	Postdoctoral	08/2014	Biophysics/Cell Physiology
Yale University, School of Medicine, New Haven, CT	Postdoctoral	07/2019	Biophysics/Neuroscience/ Structural Biology

A. Personal Statement

The main focus of my laboratory is to investigate the structure, molecular composition, and regulation of mitochondrial permeability transition pore (mPTP) and its role in neurodegenerative disease and aging. We apply a multidisciplinary research approach to fully characterize the ATP synthase leak channel and other components of mPTP. We routinely perform mitochondrial metabolic studies, and super-resolution imaging to study organellar and molecular interactions; patch-clamp and planar lipid bilayer recordings to investigate biophysical properties of ion channels; high-resolution structural biology techniques, such as cryo-electron microscopy, and cryo-electron tomography to capture the gating and regulatory mechanisms of ion channels at atomic level. We have recently determined the cryo-electron microscopy model of liposome-reconstituted ATP synthase and showed that monomeric ATP synthase forms the large-conductance channel of mPTP. We have also shown that the membrane-embedded c-ring is the main channel-forming component of ATP synthase. We identified an important cluster of amino acid residues within the ATP synthase c-ring that controls the leak channel conductance and generated a mouse containing this neuroprotective mutation by the CRISPR/Cas9 genome editing. We are currently testing if introducing this neuroprotective mutation in the transgenic mouse model of Alzheimer's disease (AD) will protect the mice from the onset of AD-like features. For the proposed project, we will study the cryo-EM atomic model of ATP synthase in its open channel conformation to characterize molecular determinants of voltage-dependent gating of ATP synthase leak channel.

Ongoing projects that I would like to highlight include:

RF1 AG072484-01
Mnatsakanyan (PI)
05/06/21-04/31/2026
Title: "Structural and functional characterization of ATP synthase c-subunit leak channel and its role in Alzheimer's disease pathogenesis".

K01 AG054734
Mnatsakanyan (PI)

07/15/2017 – 03/31/2023
Title: “Molecular components of the mitochondrial permeability transition pore and its role in neurodegenerative diseases”.

Citations:

1. **N. Mnatsakanyan***, M. Llaguno, Y. Yang, Y. Yan, J. Weber., F. Sigworth, E. Jonas*. A mitochondrial megachannel resides in monomeric F_1F_O ATP synthase. **Nature Communications.** 2019. PMID: 31862883 PMCID: PMC6925261 ***Corresponding Authors.**
2. **N. Mnatsakanyan*,** E. Jonas. The new role of F_1F_o ATP synthase in mitochondria-mediated neurodegeneration and neuroprotection. Experimental Neurology. 2020. V. 332. 113400. PMCID: PMC7877222 ***Corresponding Author.**
3. **N. Mnatsakanyan,** H. Park, J. Wu, X. He, M. Llaguno, M. Latta, P. Miranda, B. Murtishi, M. Graham, J. Weber, R. Levy, E. Pavlov, E. Jonas. Mitochondrial ATP synthase c-subunit leak channel triggers cell death upon loss of its F1 subcomplex. **Cell Death and Differentiation.** 2022. PMID: 35322203 PMCID: PMC9433415 ***Corresponding Authors.**

B. Positions, Scientific Appointments, and Honors

01/2022-Present	Associate Professor, Department of Cellular and Molecular Physiology, Penn State University College of Medicine
01/2022-Present	Assistant professor Adjunct, Department of Internal Medicine, Yale University School of Medicine
07/2019-01/2022	Assistant Professor, Department of Internal Medicine, Yale University School of Medicine
09/2014-06/2019	Associate Research Scientist, Department of Internal Medicine, Yale University School of Medicine
07/2011-01/2014	Senior Research Associate, Department of Cell Physiology and Molecular Biophysics, Center for Membrane Protein Research, Texas Tech University Health Sciences Center
01/2006-07/2011	Postdoctoral Research Associate, Department of Chemistry and Biochemistry, Texas Tech University
01/2004	Research Scientist, Department of Biophysics, Yerevan State University

Honors

2018	Young Bioenergeticist Award, Biophysical Society
2017	K01 Research Scientist Development Award, National Institutes of Aging

C. Contributions to Science

1. <u>Chemo-mechanical coupling mechanism of ATP synthase</u>: ATP synthase is an exceptional molecular machine, which uses the rotation of its own subunits to convert chemical energy into mechanical energy during ATP synthesis and hydrolysis. During my post-doctoral studies at Texas Tech University, I was challenged to understand how ATP binding and hydrolysis at the catalytic centers of the beta subunits drive the rotation of the ATP synthase central stalk subunits. I successfully showed that the conserved motif of the negatively charged residues at the C-terminal domain of the beta subunit, the so-called DELSEED-loop, has an important role in coupling of catalysis and subunit rotation of ATP synthase. By using mutagenesis and fluorescence resonance energy transfer experiments, I have shown that the beta DELSEED-loop works as a push rod to force the rotation of central stalk subunits during ATP binding and hydrolysis. I have also shown that the beta DELSEED-loop has a critical length required for coupling the catalytic reaction of ATP synthase with subunit rotation. In another study, we have shown that the conserved negative charges of the DELSEED-loop are not directly involved in the catalytic function of ATP synthase, but instead, they play a crucial regulatory function by interacting with the positively charged residues of the epsilon subunit, which works as an intrinsic inhibitor of ATP synthase. Next, I was keen to understand the functional role of the ATP synthase rotor subunits, gamma and epsilon, which play a central role in energy conversion. Using a site-directed mutagenesis approach, we have shown that the N-terminal helix alone is able to fulfill the function of the full-length gamma subunit, by driving the effective synthesis and hydrolysis of ATP.

a. **N. Mnatsakanyan**, A. Krishnakumar, T. Suzuki and J. Weber. The role of the Beta DELSEED-loop in ATP synthase. **Journal of Biological Chemistry.** 2009. V.284 (17), p. 11336-45. PMCID:PMC2670139

b. **N. Mnatsakanyan,** J. Hook, L. Quisenberry, J. Weber. ATP synthase with its gamma subunit reduced to the N-terminal helix can still catalyze ATP synthesis. **Journal of Biological Chemistry.** 2009. V.284 (39), p. 26519-25. PMCID:PMC2785340

c. **N. Mnatsakanyan,** SK. Kemboi, Salas J and Weber J. The beta subunit loop that couples catalysis and rotation in ATP synthase has a critical length. **Journal of Biological Chemistry.** 2011. V.286 (34), p. 29788-96. PMCID:PMC3191020

d. **N. Mnatsakanyan,** L. Yunxiang and J. Weber. Identification of two segments of the γ subunit responsible for the differences in affinities of the catalytic binding sites of ATP synthase. **Journal of Biological Chemistry.** 2019**.** PMID 30510135, PMCID:PMC6349107

2. <u>Structure-function relationship of pentameric ligand-gated ion channels.</u> Pentameric ligand-gated ion channels or cys-loop receptors have been studied extensively, however, very little information was available about the structure and function of their intracellular domain, which is the most divergent domain in all cys-loop receptors and, therefore, can be used as a target for more specific, receptor sub-type-based drug design. I have designed diverse eukaryotic-prokaryotic chimeras of ligand-gated ion channels by adding the intracellular domain from different eukaryotic neurotransmitter receptors (nicotinic acetylcholine, glycine, GABAρ1) into the *Gloeobacter violaceus* ligand-gated ion channel (GLIC). These chimeras served as valuable tools for functional and structural studies of the intracellular domain, which will pave the way for structure-based subtype-selective drugs to treat different neurological and neurodegenerative diseases. While investigating pentameric ligand-gated ion channels I also resolved the accurate structural information about the vertical alignment between the second and third transmembrane segments of muscle nicotinic acetylcholine receptors. This was important for solving an existing discrepancy between the cryo-EM model of the acetylcholine receptor and the x-ray structures of other ligand-gated ion channels, GLIC and GluCl.

a. **N. Mnatsakanyan** and M. Jansen. The correct register between the second and third transmembrane segments of muscle nicotinic acetylcholine receptors. **Journal of Neurochemistry.** 2013. V. 125(6), p. 843-54.

b. **N. Mnatsakanyan,** SN Nishtala, Pandhare A, Fiori MC, Goyal R, Pauwels JE, Navetta AF, Ahrorov A, Jansen M. Functional Chimeras of GLIC Obtained by Adding the Intracellular Domain of Anion- and Cation-Conducting Cys-Loop Receptors. **Biochemistry.** 2015 Apr 28;54(16):2670-82. doi: 10.1021/acs.biochem.5b00203. Epub 2015 Apr 17. PMCID:PMC4414916

c. SN Nishtala, **N. Mnatsakanyan**, C Leung, M. Jansen. Direct interaction of the chaperone resistance to inhibitors of cholinesterase (RIC-3) with the serotonin receptor type 3A (5-HT3A) intracellular domain demonstrated with heterologously expressed purified proteins. **Journal of Neurochemistry.** 2016. p. 528-538. PMCID:PMC4860158

3. <u>Structural and pharmacological characterization of mitochondrial permeability transition pore (mPTP).</u> The mPTP plays crucial physiological and pathological roles, but its molecular identity, the mechanism and regulation of channel conductance remain controversial. We have recently discovered that mitochondrial F_1F_O ATP synthase with its membrane-embedded c-subunit constitutes the pore of mitochondrial permeability transition. By combining the cryo-EM and patch-clamp electrophysiology techniques we demonstrated that the minimal unit for forming a channel is the ATP synthase monomer. We have also found that the F_1 subcomplex is the gate of the ATP synthase c-subunit leak channel and dissociation of ATP synthase F_1 from F_O increases the probability of channel opening and triggers cell death.

a. **N. Mnatsakanyan***, M. Llaguno, Y. Yang, Y. Yan, J. Weber., F. Sigworth, E. Jonas*. A mitochondrial megachannel resides in monomeric F_1F_O ATP synthase. **Nature Communications.** 2019. PMID 31862883 PMCID: PMC6925261 ***Corresponding Authors.**

b. **N. Mnatsakanyan*,** E. Jonas*. ATP synthase c-subunit ring as the channel of mitochondrial permeability transition: Regulator of metabolism in development and degeneration. **Journal of Molecular and Cellular Cardiology.** 2020. V. 144, p. 109-118. PMCID: PMC7877492 ***Corresponding Authors.**

c. P. Licznerski; H. Park; H. Rolyan; R. Chen; **N. Mnatsakanyan**; P. Miranda; M. Graham; J. Wu; L. Brandao; N. Cruz-Reyes; N. Mehta; S. Sohail; J. Salcedo; E. Song; C. Effman; S. Effman; G. Xu; A. Braker; V. Gribkoff; R. Levy; E. Jonas, ATP synthase c-subunit leak causes aberrant cellular metabolism in Fragile X syndrome. **Cell.** 2020 Sep 3;182(5):1170-1185.e9. doi: 10.1016/j.cell.2020.07.008. Epub 2020 Aug 13 PMCID: PMC7484101

d. **N. Mnatsakanyan*,** H. Park, J. Wu, X. He, M. Llaguno, M. Latta, P. Miranda, B. Murtishi, M. Graham, J. Weber, R. Levy, E. Pavlov, E. Jonas*****. Mitochondrial ATP synthase c-subunit leak channel triggers cell

death upon loss of its F_1 subcomplex. **Cell Death and Differentiation.** 2022. PMID: 35322203 PMCID: PMC9433415 ***Corresponding Authors.**

Complete List of Published Work in MyBibliography:
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