BIOGRAPHICAL SKETCH

NAME: Nelli Mnatsakanyan

eRA COMMONS USER NAME: MNATSAKANYAN79430

POSITION TITLE: Associate Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	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	01/2006-06/2011	Biophysics/Biochemistry
Texas Tech University Health Sciences Center, Lubbock, TX	Postdoctoral	07/2011-08/2014	Biophysics/Cell Physiology
Yale University, School of Medicine, New Haven, CT	Postdoctoral	09/2014-7/2019	Biophysics/Neuroscience/ Structural Biology

A. Personal Statement

The main focus of my laboratory is to investigate the molecular composition, structure, and regulation of mitochondrial permeability transition pore (mPTP) and its role in neurodegenerative disease. We apply a multidisciplinary research approach, patch-clamp recordings of mitochondria and proteoliposomes, planar lipid bilayer recordings, high-resolution structural biology techniques, cryo-electron microscopy, and cryo-electron tomography to fully characterize the ATP synthase leak channel and other components of mPTP. We have recently determined the cryo-electron microscopy model of liposome-reconstituted ATP synthase and showed that monomeric ATP synthase forms a large conductance channel with biophysical characteristics of mPTP. We have identified an important cluster of amino acid residues in the ATP synthase c-ring that controls channel conductance and currently generating a mouse that contains this mutation by the CRISPR/Cas9 genome editing.

Ongoing projects that I would like to highlight include:

R01 AG072484-01 converted into 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

Positions, Scientific Appointments

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. I was challenged to understand how ATP binding and hydrolysis in the catalytic sites of the beta subunit can drive the rotation of the gamma subunit. I successfully showed that the conserved motif at the C-terminal domain of the beta subunit, the 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 we showed that the Beta DELSEED-loop works as a push rod to force the gamma subunit to rotate during ATP binding and hydrolysis and that the Beta DELSEED-loop has a critical length required for the coupling of catalysis and rotation. We also showed that the conserved negative charges of the DELSEED-loop are not directly involved in the catalytic mechanism, instead, the reason for the conservation of these charges among different species appears to involve regulation of enzymatic activity, via the interaction with the positively charged residues at the C terminus of the epsilon subunit, which works as an intrinsic inhibitor of ATP synthase. Next, I studied the functional role of the ATP synthase rotor subunits, gamma and epsilon, which play a central role in energy conversion. Using a truncation approach, we showed that the N-terminal helix alone is able to fulfill the function of the full-length gamma subunit, providing effective ATP synthesis and hydrolysis.

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. **Structure-function relationship of pentameric ligand-gated ion channels.**

Pentameric ligand-gated ion channels have been studied extensively, however very little information is available on the structure and function of the intracellular domain, which is the most divergent domain in all cys-loop receptors and can be used as a target for more specific, sub-type based drug design. I have designed diverse eukaryotic-prokaryotic chimeras of ligand-gated ion channels by adding the intracellular domain from different 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. **Structural and pharmacological characterization of mitochondrial permeability transition pore (mPTP).**

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 constitute 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 studied the pharmacological regulation of ATP synthase megachannel, which is crucial for designing drugs to treat mPTP-related disorders.

a. **N Mnatsakanyan**, Beutner G, Porter GA, Alavian KN, Jonas EA. Physiological roles of the mitochondrial permeability transition pore. **J Bioenerg Biomembr.** 2016. 10.1007/s 10863-016-9652-1. PMCID:PMC4981558
b. **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.**
c. **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.**

d. 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

Complete List of Published Work in MyBibliography:

https://pubmed.ncbi.nlm.nih.gov/?term=Mnatsakanyan+N