BIOGRAPHICAL SKETCH

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NAME: Sobolevsky, Alexander

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

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)	END DATE MM/YYYY	FIELD OF STUDY
Moscow Inst. of Physics and Technology, Moscow	MS	06/1996	Bioengineering
Moscow Inst. of Physics and Technology, Moscow	PHD	11/1999	Biophysics

A. Personal Statement

My lab studies structure and function of ion channels, including ionotropic glutamate receptors (iGluRs) and transient receptor potential (TRP) channels, using a combination of biochemical and biophysical methods and cryo-electron microscopy (cryo-EM) in particular. I have an expertise in solving structures of integral membrane proteins by both X-ray crystallography and cryo-EM and an extensive experience in using methods of characterizing ion channels function, including patch-clamp, double-electrode voltage-clamp recordings and Fura-2-based ratiometric fluorescent measurements of intracellular calcium. I also have an expertise in analyzing different types of ion channel inhibition using a combination of electrophysiology, protein engineering and kinetic modeling. With such expertise and experiences, I studied the mechanisms of ionotropic glutamate receptor (iGluR) inhibition by ion channel blockers, including the only FDA-approved NMDA receptor channel blocker Memantine, currently used for treatment of Alzheimer's disease. I solved the first full length crystal structure of ionotropic glutamate receptor. My lab solved numerous structures of full-length iGluRs, including the first agonist-bound, open and desensitized state structures and proposed the first complete structural model of iGluR gating. Using X-ray crystallography, my lab determined the structural mechanism of iGluR inhibition by noncompetitive inhibitors, including Perampanel that is currently used for treatment of epilepsy. My lab also solved the first TRP channel crystal structure (the structure of TRPV6). Using cryo-EM, my lab determined structures of human TRPV6 in different conformations and proposed the mechanism of TRPV6 activation. Similarly, my lab solved the first TRPV3 structure and structures of TRPV3 in different conformations and proposed the mechanism of ligand-induced TRPV3 activation. Recently, we solved structures of TRPV3 in temperature-dependent closed, intermediate and open states, which for the first time uncovered the structural bases of TRP channel activation by temperature. As a result of my previous experiences, I am aware of the importance of frequent communication among project members and of constructing a realistic research plan, timeline, and budget. My current research plans build logically on my prior work.

1. McGoldrick LL, Singh AK, Saotome K, Yelshanskaya MV, Twomey EC, Grassucci RA, Sobolevsky AI. Opening of the human epithelial calcium channel TRPV6. **Nature**. 2018 Jan 11;553(7687):233-237. PubMed PMID: 29258289; PubMed Central PMCID: PMC5854407.
2. Twomey EC, Yelshanskaya MV, Grassucci RA, Frank J, Sobolevsky AI. Channel opening and gating mechanism in AMPA-subtype glutamate receptors. **Nature**. 2017 Sep 7;549(7670):60-65. PubMed PMID: 28737760; PubMed Central PMCID: PMC5743206.
3. Saotome K, Singh AK, Yelshanskaya MV, Sobolevsky AI. Crystal structure of the epithelial calcium channel TRPV6. **Nature**. 2016 Jun 23;534(7608):506-11. PubMed PMID: 27296226; PubMed Central PMCID: PMC4919205.
4. Yelshanskaya MV, Li M, Sobolevsky AI. Structure of an agonist-bound ionotropic glutamate receptor. **Science**. 2014 Aug 29;345(6200):1070-4. PubMed PMID: 25103407; PubMed Central PMCID: PMC4383034.

B. Positions and Honors

Positions and Employment

1993 - 1996	Pre-diploma Research Fellow, Moscow Institute of Physics and Technology, Moscow
1996 - 1999	Pre-doctoral Research Fellow, Moscow Institute of Physics and Technology, Moscow
2000 - 2004	Post-doctoral Research Fellow, Stony Brook University, Stony Brook, NY
2004 - 2005	Post-doctoral Research Fellow, Columbia University, New York, NY
2005 - 2010	Post-doctoral Research Fellow, Vollum Institute, Oregon Health and Science University, Portland, OR
2010 - 2017	Assistant Professor, Columbia University, New York, NY
2017 -	Associate Professor, Columbia University, New York, NY

Other Experience and Professional Memberships

2013 -	Member, American Heart Association
2017 -	Member, Biophysical Society
2017 -	Member, American Chemical Society
2018 -	Member, Society for Neuroscience

Honors

1998	International Soros Science Education Program Grant, Soros Foundation
1998	Travel Grant for participation in the 29th Annual Meeting of the Society for Neuroscience, International Brain Research Organization
1999	International Soros Science Education Program Grant, Soros Foundation
2000	Travel Grant for participation in the 31st Annual Meeting of the Society for Neuroscience, International Brain Research Organization
2002	Postdoctoral Travel Award for participation in the 32nd Annual Meeting of the Society for Neuroscience, Burroughs Wellcome Fund
2011	Klingenstein Fellowship Award in the Neurosciences, Esther A. & Joseph Klingenstein Fund
2012	Schaefer Research Scholar Award, Dr. Ludwig Schaefer Fund
2013	Pew Scholar Award, Pew Charitable Trusts
2015	Irma T. Hirschl Career Scientist Award, Irma T. Hirschl Trust
2017	Amgen Young Investigator Award, Amgen

C. Contribution to Science

1. N-methyl-D-aspartate (NMDA) receptors are a subtype of ionotropic glutamate receptors that is critical to neuronal development and synaptic plasticity, associated with memory formation and learning and implicated in acute and chronic neuronal death, associated with brain trauma and neurological disorders. Ion channel blockers of NMDA receptors therefore have an enormous drug potential. We have been among the first research groups to study the mechanism of ion channel block of NMDA receptors by various derivatives of aminoadamantane, one of which, Memantine (NAMENDA), have become the first and so far the only drug acting at NMDA receptors that has been approved by FDA for treatment of moderate to severe Alzheimer's disease. We developed a set of new kinetic criteria to analyze the mechanism of blocker interaction with ion channel gating machinery. Using this set, we were the first to discover that Mg2+ interacts with NMDA receptors via the trapping block mechanism. The discovery of the trapping block of NMDA receptor channels by Mg2+ led to reevaluation of the role of Mg2+ and NMDA receptors in neurotransmission across excitatory synapses in the brain.

    a. Sobolevsky AI, Yelshansky MV. The trapping block of NMDA receptor channels in acutely isolated rat hippocampal neurones. **J Physiol.** 2000 Aug 1;526 Pt 3:493-506. PubMed PMID: 10922002; PubMed Central PMCID: PMC2270033.

    b. Sobolevsky AI, Koshelev SG, Khodorov BI. Probing of NMDA channels with fast blockers. **J Neurosci.** 1999 Dec 15;19(24):10611-26. PubMed PMID: 10594045.

c. Sobolevsky AI, Koshelev SG, Khodorov BI. Interaction of memantine and amantadine with agonist-unbound NMDA-receptor channels in acutely isolated rat hippocampal neurons. **J Physiol.** 1998 Oct 1;512 (Pt 1):47-60. PubMed PMID: 9729616; PubMed Central PMCID: PMC2231181.

d. Sobolevsky A, Koshelev S. Two blocking sites of amino-adamantane derivatives in open N-methyl-D-aspartate channels. **Biophys J.** 1998 Mar;74(3):1305-19. PubMed PMID: 9512028; PubMed Central PMCID: PMC1299478.

2. Before the structures of the full length iGluR become available, one could only guess what are the structural organization of the iGluR channel and the mechanisms of pore opening and closure. To gain insights into the structure of the NMDA receptor ion channel pore and the structural rearrangements during gating, we used the substituted cysteine accessibility method (SCAM). The NMDA receptor is an obligate heterotetramer composed of two or more different subunits. We individually mutated residues in the transmembrane portion of the two major subtypes of NMDA receptor subunits, NR1 and NR2. We identified the boundaries and the pore-facing surfaces of the transmembrane domains, their relative contribution to the ion channel pore and gating and the amino acid residues in the pore involved into receptor activation and desensitization as well as binding of the channel blockers. We were among the first to discover the asymmetrical contribution of the NR1 and NR2 subunits to channel pore structure and gating and the central role of the M3 segment in NMDA receptor gating.

a. Sobolevsky AI, Prodromou ML, Yelshansky MV, Wollmuth LP. Subunit-specific contribution of pore-forming domains to NMDA receptor channel structure and gating. **J Gen Physiol.** 2007 Jun;129(6):509-25. PubMed PMID: 17504910; PubMed Central PMCID: PMC2151626.

b. Wollmuth LP, Sobolevsky AI. Structure and gating of the glutamate receptor ion channel. **Trends Neurosci.** 2004 Jun;27(6):321-8. PubMed PMID: 15165736.

c. Sobolevsky AI, Rooney L, Wollmuth LP. Staggering of subunits in NMDAR channels. **Biophys J.** 2002 Dec;83(6):3304-14. PubMed PMID: 12496098; PubMed Central PMCID: PMC1302406.

d. Sobolevsky AI, Beck C, Wollmuth LP. Molecular rearrangements of the extracellular vestibule in NMDAR channels during gating. **Neuron**. 2002 Jan 3;33(1):75-85. PubMed PMID: 11779481.

3. We used SCAM and patch-clamp recordings to study structure and function of homotetrameric AMPA subtype iGluRs. We identified pore-forming elements and residues involved in AMPA receptor gating. We discovered mutations outside the ligand binding domain (LBD) – in the linkers connecting the LBD to the ion channel – that resulted in either enhancement or nearly complete oblation of AMPA receptor desensitization. We found that AMPA receptors are unique compared to other tetrameric ion channels and that despite the subunit assembly is homomeric, contribution of individual subunits to the ion channels pore is different leading to the overall two- rather than four-fold rotation symmetry of the ion channel in the active state.

a. Sobolevsky AI, Yelshansky MV, Wollmuth LP. State-dependent changes in the electrostatic potential in the pore of a GluR channel. **Biophys J.** 2005 Jan;88(1):235-42. PubMed PMID: 15516523; PubMed Central PMCID: PMC1305001.

b. Yelshansky MV, Sobolevsky AI, Jatzke C, Wollmuth LP. Block of AMPA receptor desensitization by a point mutation outside the ligand-binding domain. **J Neurosci.** 2004 May 19;24(20):4728-36. PubMed PMID: 15152033.

c. Sobolevsky AI, Yelshansky MV, Wollmuth LP. The outer pore of the glutamate receptor channel has 2-fold rotational symmetry. **Neuron**. 2004 Feb 5;41(3):367-78. PubMed PMID: 14766176.

d. Sobolevsky AI, Yelshansky MV, Wollmuth LP. Different gating mechanisms in glutamate receptor and K+ channels. **J Neurosci.** 2003 Aug 20;23(20):7559-68. PubMed PMID: 12930794.

4. The transient receptor potential (TRP) channels are a superfamily of cation permeable ion channels that are widely known for their role as transducers of sensory modalities, including temperature, taste, olfaction, vision, hearing and touch. TRP channels are also crucial for a diverse range of physiological processes, such as neurite outgrowth, hormone secretion and control of vascular tone. Accordingly, mutations or malfunction of TRP channels are associated with numerous human diseases, including cardiovascular, renal, nociceptive and metabolic disorders. We solved the first crystal structure of TRP channel, Ca^{2+}-selective channel TRPV6 that plays vital roles in calcium homeostasis as a Ca^{2+} uptake channel in epithelial tissues and is implicated

in development and progression of numerous forms of cancer. We also determined the structural bases of TRPV6 allosteric regulation and calcium-induced calmodulin-mediated inactivation. We solved the first structure of TRPV3 and determined structural bases of TRPV3 activation by a ligand. We also solved structures of TRPV3 in temperature-dependent closed, intermediate and open states, which for the first time uncovered structural bases of TRP channel activation by temperature. Our results provide a structural foundation to understand the regulation of TRP channels and their role in physiology and pathophysiology and provide information necessary for drug design.

a. Singh A. K., McGoldrick L. L., Demirkhanyan L., Leslie M., Zakharian E. and *Sobolevsky A. I.* Structural bases of temperature sensation by the TRP channel TRPV3. **Nat Struct Mol Biol**. 2019 Nov;26: 994-998. PubMed PMID: 31636415; PubMed Central PMCID: PMC6858569.

b. Singh AK, McGoldrick LL, Sobolevsky AI. Structure and gating mechanism of the transient receptor potential channel TRPV3. **Nat Struct Mol Biol**. 2018 Sep;25(9):805-813. PubMed PMID: 30127359; PubMed Central PMCID: PMC6128766.

c. McGoldrick LL, Singh AK, Saotome K, Yelshanskaya MV, Twomey EC, Grassucci RA, Sobolevsky AI. Opening of the human epithelial calcium channel TRPV6. **Nature**. 2018 Jan 11;553(7687):233-237. PubMed PMID: 29258289; PubMed Central PMCID: PMC5854407.

d. Saotome K, Singh AK, Yelshanskaya MV, Sobolevsky AI. Crystal structure of the epithelial calcium channel TRPV6. **Nature**. 2016 Jun 23;534(7608):506-11. PubMed PMID: 27296226; PubMed Central PMCID: PMC4919205.

5. High resolution structural information about ionotropic glutamate receptors opens new horizons to understanding their gating mechanism and regulation at the molecular level as well as makes iGluRs a novel pharmacological platform for characterizing new compounds with diverse activities for use as therapies in neurological diseases. My lab has solved the first crystal structure of the full length AMPA receptor in complex with agonist, crystallographically discovered novel binding sites of antiepileptic drugs, obtained the first cryo-EM structures of AMPA receptor complexes with the auxiliary subunits stargazin and GSG1L, and solved the first structures of AMPA receptor in the open and desensitized states.

a. Twomey EC, Yelshanskaya MV, Grassucci RA, Frank J, Sobolevsky AI. Channel opening and gating mechanism in AMPA-subtype glutamate receptors. **Nature**. 2017 Sep 7;549(7670):60-65. PubMed PMID: 28737760; PubMed Central PMCID: PMC5743206.

b. Yelshanskaya MV, Singh AK, Sampson JM, Narangoda C, Kurnikova M, Sobolevsky AI. Structural Bases of Noncompetitive Inhibition of AMPA-Subtype Ionotropic Glutamate Receptors by Antiepileptic Drugs. **Neuron**. 2016 Sep 21;91(6):1305-1315. PubMed PMID: 27618672; PubMed Central PMCID: PMC5033713.

c. Twomey EC, Yelshanskaya MV, Grassucci RA, Frank J, Sobolevsky AI. Elucidation of AMPA receptor-stargazin complexes by cryo-electron microscopy. **Science**. 2016 Jul 1;353(6294):83-6. PubMed PMID: 27365450; PubMed Central PMCID: PMC5125255.

d. Yelshanskaya MV, Li M, Sobolevsky AI. Structure of an agonist-bound ionotropic glutamate receptor. **Science**. 2014 Aug 29;345(6200):1070-4. PubMed PMID: 25103407; PubMed Central PMCID: PMC4383034.

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

R01 NS083660, NIH/NINDS
Sobolevsky, Alexander (PI)
09/30/13-06/30/23
Structure and Function of AMPA subtype ionotropic glutamate receptors
The major goal of this project is to study mechanisms of desensitization and ion channel block in ionotropic glutamate receptors.

R01CA206573, NIH/NCI

Sobolevsky, Alexander (PI)
01/12/17-12/31/21
Structure and Function of Transient Receptor Potential channels
The major goal of this project is to study molecular mechanisms of TRP channel gating and regulation by calcium and various small molecules.

R01NS107253, NIH/NINDS
Sobolevsky, Alexander (PI)
08/01/18-05/31/23
Single-particle cryo-EM characterization of AMPA receptor functional states
The major goal of this project is to study structure and function of AMPA-subtype ionotropic glutamate receptors using advances in single-particle cryo-electron microscopy.

1818213, NSF/MCB-BSF
Sobolevsky, Alexander (co-PI)
08/01/18-07/31/22
Collaborative Research: Towards development of the structural determinants of the Glutamate receptor gating regulation by auxiliary membrane anchored proteins
The major goal of this project is to characterize structural determinants of the interaction of AMPARs with the cystine-knot AMPAR modulating proteins (CKAMPs), and their interplay with the transmembrane AMPAR regulatory proteins (TARPs).

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Yelshanskaya, Maria V.	Research Assistant
eRA COMMONS USER NAME (credential, e.g., agency login) MVYELSH	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Moscow Institute of Physics and Technology	B.S.	06/97	Bioengineering
Moscow Institute of Physics and Technology	Ph.D.	11/01	Biophysics
State University of New York at Stony Brook	Postdoctoral	08/04	Physiology and Neuroscience

A. Personal Statement

My work has focused on understating the complex regulation of the ionotropic glutamate receptors (iGluRs) ion channel gating. I started to address this problem while being undergraduate student in Moscow Institute of Physic and Technology in the B.I. Khorov lab. During my PhD study at the Moscow Institute of Physics and Technology, I carried out electrophysiological studies of NMDA subtype iGluRs in hippocampal neurons acutely isolated from the rat brain and studied interaction of NMDA receptor ion channels with blockers and modulators such as arachidonic acid. After I finished my PhD study, I joined the laboratory of Dr. Wollmuth at the Stony Brook University for my postdoctoral training, where I studied recombinant iGluRs using mutagenesis and outside-out patch-clamp recordings. In 2010, after maternity leave, I joined the laboratory of Dr. Sobolevsky to work on the structure and function of ionotropic glutamate receptors using a combination of biophysical and biochemical approaches including X-ray crystallography. Dr. Sobolevsky's experience in crystallizing the first full length structure of iGluR as well as my enthusiasm and extensive expertise in iGluR structure and function are the best assets to successful completion of this project. Specifically, I plan to determine structures of iGluR in different conformational states and with different ligands and to study their function using mutagenesis and electrophysiology. My future research interests lie in investigating the molecular mechanisms and regulation of ion channel conduction using a combination of biochemical and biophysical approaches. My versatile training provides me with strong biophysical, biochemical, molecular and structural biology background indispensable to successfully achieve my research goals.

Technical skills

Electrophysiology
Patch-clamp recordings in whole cell and outside-out configurations (neurons, HEK cell lines), fast solution-exchange techniques (piezo and magnetic devices), multi-channel perfusion systems.

Molecular biology
PCR, DNA restriction analysis, subcloning of DNA fragments, DNA sequencing, site-directed mutagenisis, chimera construction, RNA synthesis, RNA and DNA purification, agarose gel electrophoresis, spectrophotometry.

Cell culture and Protein expression: Worked with a wide range of mammalian cell lines, both adherent and in suspension. Generated multiple stable cell lines by expressing proteins using adenovirus and transient expression systems in mammalian cells. Expressed proteins using baculovirus in insect cells. Acute isolation of neurons from brain (rats), defolliculation and RNA injection of *Xenopus laevis* oocytes.

Biochemistry and crystallography
Membrane protein purification and crystallization, affinity and size-exclusion chromatography, SDS PAGE and western blotting, crystallography robotics (Mosquito, Rock Imagers), experience working at the APS and NSLS beamlines.

Data analysis and computation
Kinetic modelling (receptor activation, desensitisation and inhibition; ion channel block); mathematical calculations and statistics (Igor Pro, Origin, Excel); image processing and graphics (Photoshop, Canvas, Nikon software); DNA construct design and analysis (DNA strider, Vector NTI, Prism).

B. Positions and Honors

Positions and Employment

1997-1998 – *Research Technician.*
Dept. Neurophysiology, Bogomoletz Institute of Physiology, Kiev, Ukraine.

1998-2001 – *Pre-doctoral Research Fellow.*
Institute of General Pathology & Pathophysiology and Moscow Institute of Physics and Technology, Moscow, Russia.
The title of the doctoral thesis: "Study of the effects of arachidonic acid on biophysical and chemoreceptive properties of NMDA receptor channels". Supervisor – Prof. Boris I. Khodorov.

2001-2004 – *Post-doctoral Research Fellow.*
Department of Neurobiology and Behavior, State University of New York at Stony Brook, Stony Brook, NY, USA. Studies of structure, function and molecular biology of glutamate receptors.
Supervisor – Lonnie P. Wollmuth.

2004-2010 – Maternity leave.

2010-present – Research Associate, Department of Biochemistry and Molecular Biophysics, Columbia University, New York, NY. Structure and function of iGluRs. Supervisor – Alexander I. Sobolevsky.

Honors

1999 - Travel grant from Russian Foundation for Basic Research for participation in the 29th Annual Meeting of the Society for Neuroscience (Miami, Florida, October 1999).
2000 - Women in Neuroscience/Eli Lilly Student Travel Award for participation in the 30th Annual Meeting of the Society for Neuroscience (New Orleans, Lousiana, November 2000).
2000 - Young Scientist Award, 2-d Pathology Congress, Moscow, Russia.
2000-2001 - International Soros Science Education Program Grant (# A2001-358), Moscow, Russia
2001 - Young Scientist Award from the Russian Foundation for Basic Research.
2001 - International Brain Research Organization Travel Grant for participation in the 31st Annual Meeting of the Society for Neuroscience (San Diego, California, November 2001).
2001-2002 - NSF-NATO Fellowship (#10108434 1 22060).

Teaching

1996-1997 – Teaching chemistry, "Phystekh-college", Dolgoprudny, Russia.
1993-2001 – Teaching physics and mathematics, Correspondence courses, MIPT, Dolgoprudny, Russia.

2011-2020 – Supervising rotation students, undergraduates, graduate students and postdocs on their projects.

C. Selected Peer-reviewed Publications

1. Sobolevsky A. I., **Yelshansky M. V**., and Khodorov B. I. (2000) Eosine-induced blockade of N-Methyl-D-Aspartate Channels in Acutely Isolated Rat Hippocampal Neurones. *Molecular Pharmacology,* **57**: 334-341.
2. Sobolevsky A. I. and **Yelshansky M. V.** (2000) The trapping block of NMDA-receptor channels in acutely isolated rat hippocampal neurones. *J. Physiol.* **526:** 493-506.
3. **Elshanskaia M. V.,** Sobolevskii A. I., Val'dman E. A. and Khodorov B. I. (2000) Interaction of a new adamantane derivative (A-7), a potential antiparkinsonian drug, with NMDA receptor channels. *Exp. Clinical Pharmacol. (in Russian)* **64:** 18-21.
4. Vergun O., Sobolevsky A. I., **Yelshansky M. V.,** Keelan J., Khodorov B. I. and Duchen M. R. (2001) Exploration of the role of reactive oxygen species in glutamate neurotoxicity in rat hippocampal neurones in culture. *J. Physiol.* **531:** 147-163.
5. **Yelshansky M. V.,** Sobolevsky A. I. and Khodorov B. I. (2002) Study of the Effect of Arachidonic Acid on NMDA Channels in Acutely Isolated Rat Hippocampal Neurons. *Biolog. Membranes (in Russian)* **19:** 93-108.
6. Sobolevsky A. I., **Yelshansky M. V.** and Wollmuth L. P. (2003) Different Gating Mechanisms in Glutamate Receptor and K^+ Channels. *J. Neurosci.* **23:** 7559-7568.
7. Sobolevsky A. I., **Yelshansky M. V.** and Wollmuth L. P. (2004) The Outer Pore of the Glutamate Receptor Channel has Two-fold Rotational Symmetry. *Neuron* **41:** 367-378 (Cover; Preview by Y. Stern-Bach. AMPA Receptor Activation: Not a Square Dance. *Neuron* **41:** 309-311).
8. **Yelshansky M. V.**, Sobolevsky A. I., Jatzke C. and Wollmuth L. P. (2004) Block of AMPA Receptor Desensitization by a Point Mutation outside the Ligand-Binding Domain. *J. Neurosci.* **24:** 4728-4736.
9. Sobolevsky A. I., **Yelshansky M. V.** and Wollmuth L. P. (2005) State-dependent changes in the electrostatic potential in the pore of a GluR channel. *Biophys. J*. Jan 88(1):235-42.
10. Sobolevsky A. I., Prodromou M. L., **Yelshansky M. V.** and Wollmuth L. P. (2007) Subunit-specific Contribution of Pore-Forming Domains to NMDA Receptor Channel Structure and Gating. *J. Gen. Physiol.* 129: 509-525.
11. **Yelshanskaya M. V**., Li M. and *Sobolevsky A. I.* (2014) Structure of an agonist-bound ionotropic glutamate receptor. ***Science*** 345: 1070-1074.
12. **Yelshanskaya M. V**., Saotome K., Singh A. K. and *Sobolevsky A. I*. (2016) Probing Intersubunit Interfaces in AMPA-subtype Ionotropic Glutamate Receptors. ***Scientific Reports*** 6: 19082.
13. Saotome K., Singh A. K., **Yelshanskaya M. V**. and *Sobolevsky A. I*. (2016) Crystal structure of the epithelial calcium channel TRPV6. ***Nature*** 534: 506–511.
14. Twomey E. C., **Yelshanskaya M. V**., Grassucci R. A., Frank J. and *Sobolevsky A. I.* (2016) Elucidation of AMPA receptor-stargazin complexes by cryo-electron microscopy. ***Science*** 353: 83-86.
15. **Yelshanskaya M. V.,** Singh A. K., Sampson J. M., Narangoda C., Kurnikova M. and *Sobolevsky A. I*. (2016) Structural Bases of Noncompetitive Inhibition of AMPA-Subtype Ionotropic Glutamate Receptors by Antiepileptic Drugs. ***Neuron*** 91: 1305-1315 (**Preview** by Regan M. C. and Furukawa H. Deeper Insights into the allosteric modulation of ionotropic glutamate receptors. ***Neuron*** 91: 1187-1189).
16. **Yelshanskaya M. V.**, Mesbahi-Vasey S., Kurnikova M. and *Sobolevsky A. I*. (2017) Role of the Ion Channel Extracellular Collar in AMPA Receptor Gating. ***Scientific Reports*** 7: 1050.
17. Twomey E. C., **Yelshanskaya M. V**., Grassucci R. A., Frank J. and *Sobolevsky A. I.* (2017) Structural Bases of Desensitization in AMPA Receptor-Auxiliary Subunit Complexes. ***Neuron*** 94: 569-580.
18. Twomey E. C., **Yelshanskaya M. V.**, Grassucci R. A., Frank J. and *Sobolevsky A. I.* (2017) Channel opening and gating mechanism in AMPA-subtype glutamate receptors. ***Nature*** 549: 60-65.
19. McGoldrick L. L., Singh A. K., Saotome K., **Yelshanskaya M. V**., Twomey E. C., Grassucci R. A. and *Sobolevsky A. I.* (2018) Opening of the Human Epithelial Calcium Channel TRPV6. ***Nature*** 553: 233-237.
20. Twomey E. C., **Yelshanskaya M. V**., Vassilevski A. A. and *Sobolevsky A. I.* (2018) Mechanisms of Channel Block in Calcium-Permeable AMPA Receptors. ***Neuron*** 99: 956-968 (**Cover**).
21. Twomey E. C., **Yelshanskaya M. V**. and *Sobolevsky A. I.* (2019) Transmembrane AMPA receptor regulatory protein complexes. Submitted to ***Journal of General Physiology*** 151 (12): 1347–1356.
22. **Yelshanskaya MV**, Nadezhdin KD, Kurnikova MG, Sobolevsky AI. (2020) Structure and function of the calcium-selective TRP channel TRPV6. ***Journal of Physiology***: (00) 1-25.

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: Gangwar, Shanti Pal

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

POSITION TITLE: Post-Doctoral Research Scientist

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)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
Kumaun University, India	MSc	July 2005	June 2007	Biotechnology
Jawaharlal Nehru University, India	PhD	July 2007	Feb 2014	Biophysics/Structural Biology
University of Texas Medical Branch (UTMB), USA	Postdoc	Sep 2014	Jan 2019	Biophysics/Structural Biology/Neuroscience
Columbia University, USA	Postdoc	March 2019	Current	Biophysics/Structural Biology/Neuroscience

A. Personal Statement

My long-term goal is to understand the structural and functional perspective of ion channels involved in neuronal communication and several neurological disorders including Alzheimer's disease, amyotrophic lateral sclerosis, epilepsy, and ischemia. My academic and research training has provided me skills in biophysics, X-ray crystallography, molecular biology, biochemistry, and Cryo-EM. As a graduate student, I learned X-ray crystallography studying transcript factors from human and *Mycobacterium tuberculosis*. As a postdoc under the guidance of Dr. Gabrielle Rudenko at UTMB, I was introduced to the scope and importance of neurodevelopmental/neuropsychiatric disorders and I started studying on synaptic proteins. Subsequently, my research findings on the structural and mechanistic details of synapse adhesion molecules (Neuroligin-MDGA1) have suggested strategies to design structure-guided peptides/small molecules modulating protein-protein interactions as therapeutics for neurodevelopmental disorders. Now I am advancing my research further by studying the neuronal ion channels under the supervision of Dr. Alexander Sobolevsky at Columbia University. The proposed research on the structural studies of the ionotropic glutamate receptors and its outcomes would expand our understanding of the gating mechanism as well as modulation by small molecules/inhibitor to develop therapeutics. The proposed research outlines a set of career developmental activities such as grant writing, public speaking, management in the lab, mentoring students, and altogether enhancing my abilities in becoming a successful independent

investigator. Given the competitive nature of the proposed research area, it will be an excellent opportunity for me to work on the structure-function relationship of ion channels.

- **Gangwar, SP.,** Green, M., and Sobolevsky, A.I. (2019) Structure of the Glutamate-Like Receptor GLR3.2 ligand-binding domain**.** *BioRxiv.* 2019, (Dec 24): 1-22

B. Honors and Awards

- Awarded Best Poster Prize in a poster presentation at *23rd Annual Sealy Center for Structural Biology Symposium*, 28th April 2018, University of Texas Medical Branch, Texas USA.

- Awarded Best Poster Prize in a poster presentation at a 4th International Symposium on "*Recent trends in Macromolecular Structure and Function"*, Jan 21-23, 2010, University of Madras, Chennai, India.

- Awarded Junior Research Fellowship and Senior Research Fellowship from Council of Scientific and Industrial Research (CSIR) and University Grants Commission (UGC) India and Qualified Graduate Aptitude Test in Engineering (GATE) 2006 by Department of Higher Education, MHRD, Government of India.

C. <u>Positions and Employment</u>

2014 - 2019 Postdoctoral Researcher, University of Texas Medical Branch, Galveston, TX
2019 - Postdoctoral Researcher, Columbia University, New York, NY

D. Contributions to Science

Graduate Career

My graduate research contributions focused on the transcription factors from human and *Mycobacterium tuberculosis*. The outcomes of the research were of significate importance that provided insights that full-length Erg is a highly nonglobular protein, which is subjected to DNA binding autoinhibition mechanism. The DNA binding domain (ETS domain) of human Erg is a winged helix-turn-helix and binds to DNA using its particular helix. Modulation of this DNA-Protein interaction by small molecules/peptides may open up new therapeutic avenues in the field of prostate cancer.

The *Mycobacterium tuberculosis* transcriptional regulator EspR contains an N-terminal helix–turn–helix DNA binding domain and a C-terminal dimerization domain. Structural study and comparison of EspR in different crystal forms indicated that the N-terminal helix–turn–helix domain of EspR acquires a rigid structure in different crystal forms. However, significant structural differences were observed in the C-terminal domain of EspR. The interaction, stabilization energy and buried surface area analysis of EspR in the different crystal forms have provided information about the physiological dimer interface of EspR.

Sharma, R., **Gangwar, SP.,** Saxena, A.K. (2018) Comparative structure analysis of the ETSi domain of ERG3 and its complex with the E74 promoter DNA sequence. *Acta Crystallogr. Section F Biol. Crystallogr*.F74. 656-663.

Gangwar, S. P., Meena, S. R. and Saxena, A. K. (2014). Comparison of four different crystal forms of Mycobacterium tuberculosis ESX-1 secreted protein regulator, EspR. *Acta Crystallogr. Section F Biol. Crystallogr*.F70.

Gangwar, S. P., Dey, S., and Saxena, A. K. (2012). Structural modeling and DNA binding auto-inhibition analysis of Ergp55, a critical transcription factor in prostate cancer. *PLoS ONE* 7(6), e39850.

Postdoctoral Career

During my postdoc at UTMB, Texas, I have studied the structural perspective of the synapse-related, organizers/adhesion, proteins critical in brain development using X-ray crystallography, and other biophysical methods. The outcomes of this research focus on how a synapse organizer, MDGA1, interacts with Neuroligin and regulates the interaction with Neurexin and Neuroligin. On the basis of this structural information, we designed small peptides modulating the Neuroligin and MDGA1 interaction and tested their efficacy by related biophysical methods. The next goal of this project is to increase the binding affinity of these peptides by optimizing the peptide sequence making them protease-resistant and then test *in vivo* / in animal models to explore the therapeutic potential to recalibrate excitation-inhibition imbalances at the synapse.

Gangwar, SP., Zhong, X., Seshadrinathan, S., Chen, H., Machius, M., and Rudenko, G. (2017). Molecular Mechanism of MDGA1: Regulation of Neuroligin 2: Neurexin Trans-synaptic Bridges**.** *Neuron.* 2017 Jun 21;94(6):1132-1141.e4.

Kim, M.J., Biag, J., Fass, D.M., Lewis, M.C., Zhang, Q., Fleishman, M., **Gangwar, S.P.**, Machius, M., Fromer, M., Purcell, S.M., Premont, R.T., McCarroll, S.A., Rudenko, G., Scolnick, E.M., Haggarty, S.J. Functional analysis of rare variants found in schizophrenia implicates a critical role for GIT1-PAK3 signaling in neuroplasticity. *Molecular Psychiatry*.2017, 22(3):417-429.

D. **Additional Information: Research Support and/or Scholastic Performance**

Scholastic Performance

OMB No. 0925-0001 and 0925-0002 (Rev. 03/2020 Approved Through 02/28/2023)

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: Klykov, Oleg

eRA COMMONS USER NAME (credential, e.g., agency login): oklykov (login for for NCCAT)

POSITION TITLE: Postdoctoral Researcher

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*)*	START DATE MM/YYYY	END DATE MM/YYYY	FIELD OF STUDY
Lomonosov Moscow State University	diploma	09/2007	06/2012	Organic Chemistry
Utrecht University	PHD	10/2015	10/2019	Analytical Chemistry
Columbia University Medical Center	POSTDOC	01/2020	present	Structural Biology

A. Personal Statement

My long-term research and career interest are to fully understand how the neuronal networks communicating within human brain. In additional to potential discovery of several drug targets, I aim to delve into the mechanisms of how our brain is developing and functioning by several multidisciplinary approaches. My academic training and diverse research experience have provided me with an excellent background in analytical, organic and biochemistry. As an undergraduate, I have received training in laboratories of analytical chemistry, organic catalysis, organic synthesis, analysis of bioorganic samples, supramolecular biomaterials, inorganic materials development and two different physical chemistry laboratories. I was able to get a basic training and learn how to use and maintain instrumentation used in each of the laboratories. With this experience I have joined the lab of Protein Analysis led by Dr. Michael Weller in Federal Institute for Materials Research and Testing (Berlin, Germany). While being in this lab, I have continued my instrumental training and my main goal was to maintain the Chromatography and Mass Spectrometry analytical instruments. After several years in this laboratory I have decided to pursue career in academia and I have to the group of internationally recognized leader in mass spectrometry and proteomics Dr. Albert J.R. Heck in Utrecht University (Utrecht, The Netherlands) for my predoctoral studies. My research there was focused on development and application of Mass Spectrometry based structural characterization of various biological samples. I took a part in developing a novel protocol for crosslinking mass spectrometry analysis of complex biological samples such as whole cell lysates and biopolymers. Additionally, I have gained expertise in molecular modelling and docking. I was the first author on the several methodological peer-reviewed papers and on paper describing structural investigations of human blood clot in its native environment. During my predoctoral studies, I have received three travel awards (ASMS, EMBO and one from Dutch

Society for Mass Spectrometry). After completing PhD training, I have joined the lab of Dr. Alexander Sobolevsky at the Columbia University Medical Center. This lab is mostly focused on structural characterization of ion channels. My main project here is to decipher the structures of ionotropic glutamate receptors (iGluRs) named AMPA and Kainate receptors (AMPARs and KARs respectively). Both receptor types and specifically AMPARs are the necessary components of the synaptic cleft and are involved in communication between neurons. The proposed research will provide me with training in protein design, expression, and comprehensive protein analysis by Electron Microscopy and electrophysiological methods. My choice of the host lab, sponsor, and training will provide me with necessary skills to establish my own research line, expand my instrumental toolbox and give me a solid basis in my future studies of the human brain. During my first postdoctoral period Columbia University has been shut down for 1.5 months due to the COVID-19. No wet lab work can be performed during this period which significantly reduces my scientific productivity as well as integration into the new research group.

1. Klykov O, van der Zwaan C., Heck A.J.R., Meijer A.B., Scheltema R.A. (2020) Missing regions within the molecular architecture of human fibrin clots structurally resolved by XL-MS and integrative structural modeling. PNAS 117(4):1976-1987
2. Klykov O., Steigenberger B., Pektas S., Fasci D., Heck A.J.R., Scheltema R.A. (2018) Efficient and robust proteome-wide approaches for proteome-wide crosslinking mass spectrometry. Nat. Protoc. 13: 2694-2990.

B. Positions and Honors

Positions and Employment

2012 - 2015	BAM Federal Institute For Materials Research and Testing, Berlin, Germany. Protein Analysis Division
2020 -	Postdoctoral Researcher, Columbia University Medical Center

Other Experience and Professional Memberships

2012-2015	DGMS, German Society for Mass Spectrometry
2015 -	NVMS, Dutch Society for Mass Spectrometry

Honors

2008	Undergraduate Annual Thesis Competition on Analytical Chemistry at the Lomonosov University, Winner
2018	American Society for Mass Spectrometry (ASMS), Sanibel Conference Travel Grant
2019	Netherlands Society for Mass Spectrometry (NVMS) Conference, Fund Award
2019	EMBO Practical Course: Integrative and cellular structural Biology, Travel Award

C. Contribution to Science

1. **Early Career:** My early career contributions were focused on method developments and application of analytical techniques for analysis of biological samples. More specifically, I worked at the physical chemistry lab at the university of North Dakota where I was operating the Graphite Atomic Absorption Furnace Spectrometer and performed the analysis of the acquired data. Next, I was also analyzing a part of mass spectrometric

outputs within a laboratory of Organic Analysis at the Lomonosov Moscow State University. I was also a part of the Protein Analysis group within a Federal research Institute in Germany where I was mostly maintaining the chromatography equipment and eventually me and my supervisor developed a quantitative chromatography-based technique to detect one of the products of decomposition of commonly used biochemical reagent.

a. Raeva A.A., Klykov O.V., Kozliak E.I., Pierce D.T., Seames W.S. (2011) In Situ Evaluation of Inorganic Matrix Effects on the Partitioning of Three Trace Elements (As, Sb, Se) at the Outset of Coal Combustion. Energy & Fuels 25: 4290-4298
b. Samgina T.Y., Gorshkov V.A., Artemenko K.A., Vorontsov E.A., Klykov O.V., Ogourtsov S.V., Zubarev, R.A., Lebedev A.T. (2012) LC–MS/MS with 2D mass mapping of skin secretions' peptides as a reliable tool for interspecies identification inside Rana esculenta complex. Peptides 34: 296-302.
c. Klykov O., Weller M.G. (2015) Quantification of N-hydroxysuccinimide and N-hydroxysulfosuccinimide by hydrophilic interaction chromatography (HILIC) Anal. Methods 7:6443-6448.

2. **Graduate Career:** My graduate research contributions focused on development and application of crosslinking mass spectrometry methods. As a result of my work this method become widely accepted and applicable to whole cell and extremely complex biological samples as in comparison to the protein complexes of limited complexity. I have developed and optimized the whole pipeline including sample preparation, data acquisition protocol and data analysis platform. I have applied this protocol to get an insight into structures of gene editing protein complex and mechanism of neuronal dense-core vesicle transport. This protocol has been evaluated in the multi-lab collaborative project and this evaluation. Results of these investigations were published in peer-reviewed scientific journals.

a. Klykov O, van der Zwaan C., Heck A.J.R., Meijer A.B., Scheltema R.A. (2020) Missing regions within the molecular architecture of human fibrin clots structurally resolved by XL-MS and integrative structural modeling. PNAS 117(4):1976-1987
b. Klykov O., Steigenberger B., Pektas S., Fasci D., Heck A.J.R., Scheltema R.A. (2018) Efficient and robust proteome-wide approaches for proteome-wide crosslinking mass spectrometry. Nat. Protoc. 13: 2694-2990.
c. de Graaf S.C., Klykov O., van den Toorn H., Scheltema R.A. (2018) Cross-ID: Analysis and Visualization of Complex XL–MS-Driven Protein Interaction Networks. J. Proteome Res. 18: 642-651.
d. Fagerlund R.D., Wilkinson M.E., Klykov O, Barendregt A., Pearce G.F., Kieper S.N., Maxwell H.W.R., Capolupo A., Heck A.J.R., Krause K.L., Bostina M., Scheltema R.A., Staals R.H.J., Fineran P.C. (2017) Spacer capture and integration by a type IF Cas1–Cas2-3 CRISPR adaptation complex. PNAS 114:E5122-E5128.
e. Iacobucci C., Piotrowski C., Aebersold R., Amaral B.C., Andrews P., Bernfur K., Borchers C., Brodie N.I., Bruce J.E., Cao Y., Chaignepain S, Chavez J.D., Claverol S., Cox J., Davis T., Degliesposti G., Dong M.Q., Edinger N., Emanuelsson C., Gay M., Goetze M., Gomes-Neto F., Gozzo F.C., Gutierrez C., Haupt C., Heck A.J.R., Herzog F., Huang L., Hoopmann M.R., Kalisman N., Klykov O., Kukacka Z., Liu F., MacCoss

M.J., Mechtler K., Mesika R., Moritz R.L., Nagaraj N., Nesati V., Neves-Ferreira A.G.C., Ninnis R., Novák P., O'Reilly F.J., Pelzing M., Petrotchenko E., Piersimoni L., Plasencia M., Pukala T., Rand K.D., Rappsilber J., Reichmann D., Sailer C., Sarnowski C.P., Scheltema R.A., Schmidt C., Schriemer D.C., Shi Y., Skehel J.M., Slavin M., Sobott F., Solis-Mezarino V., Stephanowitz H., Stengel F., Stieger C.E., Trabjerg E., Trnka M., Vilaseca M., Viner R., Xiang Y., Yilmaz S., Zelter A., Ziemianowicz D., Leitner A., Sinz A. (2019) First Community-Wide, Comparative Cross-Linking Mass Spectrometry Study. Anal. Chem. 91: 6953-6961.

f. Stucchi R., Plucinska G., Hummel J.J.A., Zahavi E.E., San Juan I.G., Klykov O., Scheltema R.A., Altelaar A.F.M., Hoogenraad C.C. (2018) Regulation of KIF1A-driven dense core vesicle transport: Ca2+/CaM controls DCV binding and Liprin-a/TANC2 recruits DCVs to postsynaptic sites. Cell Rep. 24: 685-700

3. **Postdoctoral Career:** As a postdoctoral fellow, I have recently joined the lab of Dr. Alexander Sobolevsky at the Department of Biochemistry and Molecular Biophysics at the Columbia University Medical Center. My main focus here is to get a close-to-native structures of ionotropic glutamate receptors (iGluRs) and specifically AMPA and Kainate receptors (AMPARs and KARs respectively) by means of Cryo-EM. iGluRs are responsible for the majority of excitatory neurotransmission in the brain and complete understanding of mechanism of their action will shed a light on nervous system development and function. Currently I have spent about 3.5 months in this lab including 1 month under university shutdown due to the COVID-19. Nonetheless, in close collaboration with my colleagues, we were able to design the relevant construct, express and purify GluA2 protein complex in its desensitized state. So far, the resolution of obtained structure is significantly higher than any of previously reported ones and brings us one step closer to understand the gating mechanism of AMPARs. In case of KARs, we have successfully designed the construct, expressed and purified the GluK2-WT protein complex and currently we are waiting for EM facilities to reopen and acquire EM data.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1ZEenY0ebbnAq/bibliography/public/

D. Additional Information: Research Support and/or Scholastic Performance

Scholastic Performance

YEAR	COURSE TITLE	GRADE

I have attended all the courses in Russia and Europe and therefore I do not indicate them here.

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: Marriah Green

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

POSITION TITLE: Graduate Student Research Assistant

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)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
University of California San Diego 9500 Gilman Dr La Jolla, CA 92093	BS	09/2014	01/2017	Biochemistry/ Chemistry
MiraCosta College 1 Barnard Drive Oceanside, CA 92056	Associate in Arts (A.A)	08/2011	06/2014	A.A. in Biological Sciences A.A. in Liberal Arts Emphasis in Mathematics and Sciences
Palomar College 1140 West Mission Road San Marcos, CA 92069	NA	06/2010	01/2011	NA
Columbia University, Graduate School of Arts and Sciences 535 W 116th St #109 New York, NY 10027	MA MP PhD	08/2017 08/2017 08/2017	02/2019 Present Present	Nutritional and Metabolic Biology

A. Personal Statement

My long-term research and career interest are to use an interdisciplinary approach centered on structural biology to provide novel insights into ion-channels and neuronal-like networks illustrating novel cell signaling in plant models. I plan to pursue these goals in my graduate education and ultimately as a professor and principal investigator in charge of my own lab. Passionate for participating in scientific discovery, I have always been tenaciously driven towards a scientific career. As an academic researcher, I will provide research opportunities to underrepresented students, encourage campus diversity by participating in admissions, and influence the next generation of budding scientists from diverse backgrounds to achieve their academic and scientific career goals. As a principle investigator at an academic institution, I would also cultivate an environment that is accepting of all learning styles and encourage students with learning disabilities that they are not disabled from pursuing their dreams. Due to one of my learning disabilities (I have been clinically diagnosed with dyslexia), weaknesses in my grammar arise and to address this issue I participated in this years Funding and

Grantsmanship for Research and Career Development Activities Course. In addition to this course, I will continue to improve my writing by working with my mentor and expanding my knowledge of electron microscopy as I attended the 2020 EM Course at the New York Structural Biology Center and the Single Particle Analysis Short Course to enhance my scientific training.

Although I had to work multiple jobs to put myself through college, I still managed to gain some laboratory experience. This exposure allowed me the opportunity to explore different fields, learning which areas of research I preferred and solidifying my desire to become a scientific academic researcher. As an undergraduate, I studied biochemistry in the chemistry department at University of California, San Diego (UCSD). Initially I worked as a research assistant in the Farquhar Lab at UCSD's Medical School Department of Cellular and Molecular Medicine; in the Farquhar Lab, I practiced basic cell biology and biochemical techniques. Next, I was awarded a summer scholars fellowship for the Cornell University Food Science Summer Scholar Program. Through this program I conducted novel research and presented my findings in micronutrient metabolism and physiology with Dr. Elad Tako at the United States Department of Agriculture (USDA) Agricultural Research Service Trace Minerals and Nutrition Unit. I continued to gain laboratory research experience in the Sharpless Lab while being a full-time undergraduate student at UCSD by participating in a synthetic chemistry lab at the Scripps Research Institute, Department of Chemistry. As Nobel Laureate K. Barry Sharpless's research intern, I earned chemistry internship course credit and then was hired as a summer intern to continue my research in exploring advances on drug delivery and design.

As a PhD candidate at the Columbia University Medical Center, I continue my passion for scientific research in the structural biology lab of Dr. Alexander Sobolevsky. I have learned new techniques in X-ray crystallography and cryogenic electron microscopy (Cryo-EM). The proposed research focuses on Glutamate Receptor-Like (GLR) ion channel biology. Calcium signaling is an example of fundamental signaling for all eukaryotic cells and abnormalities in signaling are involved in numerous pathologies from cancer to neurodegenerative diseases. Thus, studying GLRs as calcium permeable ion channels will increase our understanding of this complex biological process. GLR proteins are found in numerous species of plants, crops, moss and a model plant organism, Arabidopsis thaliana. GLRs are important for a myriad of plant physiological roles, such as hardiness against environmental stressors. Understanding how these vital proteins function and relate to iGluRs is important for insight into glutamate receptors, iGluRs expressed in non-neuronal cells, as well as the evolution of calcium signaling. Investigating the GLR structure and function will require the application of techniques in biochemistry, biophysics, electrophysiology, and structural biology, including X-ray crystallography as well as cryo-EM. Dr. Sobolevsky uses all of these techniques to conduct cutting-edge research of ion channels and thus I am well positioned to accomplish my projected goals; the proposed research plan will provide me with the training that I will need to operate my own lab within an academic setting.

B. Positions and Honors

Positions

2012-2014 Learning Center Tutor, MiraCosta College, Highest Level of Tutor for Chemistry, Microbiology, Biology, Calculus, Organic Chemistry, and Algebra
2013-2014 Chemistry Teaching Assistant
2014 MiraCosta Science Fair
2015 Undergraduate Research Assistant, University of California, San Diego, Lab of Dr. Farquhar
2015 Cornell University Food Science Summer Scholar Program
2016 Research Intern, The Scripps Research Institute, Lab of Dr. Sharpless
2017- PhD Candidate, Columbia University
2019- Woman in Science at Columbia (WISC) Board Member, Position: Marketing Chair
2019 Group Leader, Girls Science Day Volunteer, Columbia University

Other Experiences

2013 Carlsbad Unified School District High School Junior Varsity Head Coach
2014-2015 American Chemical Society Student Affiliates (ACSSA) Member
2015 International Society for Pharmaceutical Engineering (ISPE)
2014-2016 Biochemistry Club University of California, San Diego
2015 Institute of Food Technologists (IFT) Conference

2017 The 20th Annual Institute of Human Nutrition Retreat and Wu Lectureship
2017- NMB Liaison Committee Member
2018 The 21th Annual Institute of Human Nutrition Retreat and Wu Lectureship
2018 Ionotropic Glutamate Receptor (iGluR) Retreat
2019 The 22th Annual Institute of Human Nutrition Retreat and Wu Lectureship
2019 Presented Thesis Research at Nutrition Departmental Seminar
2019 Girls Science Day Group Leader, Columbia University
2019 Mentor to Undergraduate Research Volunteer
2019 Women in Science at Columbia (WISC) Participant
2019-2020 Knitting Instructor at Columbia University Irving Medical Center (CUIMC) Student Wellness Center
2019-2020 Women in Science at Columbia (WISC) Marketing Chair

Honors and Awards
2011-2013 Honors Scholar Program, MiraCosta College
2011-2014 Permanent Honor Roll, Member of Phi Theta Kappa Honors Society, and President's List, MiraCosta College
3012-2013 MiraCosta Muriel Kaplan Scholarship
2013-2014 MiraCosta College Linda Koelkebech Memorial Merit Scholarship
2014 Highest Honors Certificate of Achievement in IGETC, MiraCosta College
2014-2015 Provost Honors, University of California, San Diego
2016 American Chemical Society Certification Award, University of California, San Diego
2017 Columbia Minority Supplement, Provost Diversity Fellowship
2017-2018 Graduate Training in Nutrition (Project number: 5T32DK007647-29)

C. Contributions to Science

Undergraduate Education

My diverse prior research experience includes different types of lab work, ranging from synthetic chemistry to biomedical research to nutrition. My most fulfilling research experience was in 2015, when I studied micronutrient metabolism and physiology at the United States Department of Agriculture - Agricultural Research Service (USDA-ARS) Trace Minerals and Nutrition Unit. I was selected to participate in the Food Science Summer Scholar Program at Cornell University, where I conducted research with Dr. Elad Tako at the USDA-ARS. I found the area of research fascinating and I loved that I was helping work toward discoveries that could help people suffering from anemia in developing countries. Taken together, the results from my research suggest that the prebiotics affected probiotic increase, iron bioavailability, and BBM functionality. I enjoyed participating in the investigations that have led to a greater understanding of these various prebiotics' effects on intestinal health. At the end of the Food Science Summer Scholar Program, I presented my project and findings at the final Food Science Department seminar open to the whole department. I submitted my abstract for this project was it printed in the seminar's booklet, also open to all in the Food Science Department.

I participated in drug delivery and design research at Nobel Laureate Dr. K. Barry Sharpless's lab at The Scripps Research Institute (TSRI) in the Department of Chemistry. My contributions to the project identified covalent drug candidates using a new aryl fluorosulfate small molecular library. I took advantage of multivalent, but easily stageable electrophilic molecular core, onto which an aryl fluorosulfate, an alkyne "pull-down", and a variable part were installed sequentially, making a multifunctional molecule. Through synthetic chemistry, I helped build a small molecular library specifically with aryl fluorosulfate incorporated; as well, I created dendrimers for improving drug delivery, specifically increasing antitumor activity and chemotherapeutics' ability to pass the blood brain barrier. Future work on the project will include researching different biological assays that can screen these compounds to identify a drug candidate.

Graduate Education

I am conducting my thesis research in the lab of Dr. Alexander Sobolevsky at the Columbia University Medical Center. Currently, I am using both structural and functional techniques to characterize the structure and function of the elusive Glutamate Receptor-Like (GLR) ion channels. Initially I am focusing on a single domain of GLR1, the ligand binding domain (LBD), which binds activating ligands and initiates gating in neuronal iGluRs. I was able to subclone GLR1 LBD into a plasmid for large-scale expression in bacterial cells and purify sufficient amounts of protein for crystallographic studies. Thus far, we succeeded in obtaining crystals of the GLR1 LBD in the presence of various ligands and solved the first high-resolution structure using X-ray crystallography. We have also started structural characterization of the full-length protein using cryo-EM and successfully solved the first 3D structure, albeit at low resolution. We aim to improve resolution of this preliminary reconstruction and to solve the full-length GLR structure at high resolution. No full length GLR structure has yet been reported, so our project will greatly contribute to revealing novel structural and functional information about this elusive protein. A GLR structure would lead to valuable insight to help understand how GLRs play a role in the cellular uptake of Calcium, improving our understanding of plant neuronal like networks. This project's research findings will impact the enhancement agricultural methods for nutritiously hardy yields, enrich support to explain why neuroactive compounds from plants work on mammalian receptors, and offer functional insight of non-neuronal iGluRs.

D. Additional Information: Research Support and/or Scholastic Performance

The grading scale for all the undergraduate institutions: 4.0 GPA scale (meaning A+ is equal points as an A).

YEAR	COURSE TITLE	GRADE
2008	Introduction to Sociology (SOC 100)	A
2010	College Algebra (Math 110)	B
2010	German I (GERM 101)	A
2010	German II (GERM 102)	A
2010	Oral Communication (SPCH 100)	A
2010	MGMT of Speech Activities (SPCH 145)	A
2010	Practical Public Speaking (SPCH 160)	A
2011	General Biology (BIOL 100)	A
2011	Computer Applications (CSIT 110)	A
2011	Sensory Analysis of Wines (HORT 145)	A
2011	Principles of Economics (Micro) (ECON 102)	A
2011	German III (GERM 201)	A
2012	Preparatory Chemistry (CHEM108)	B
2012	Western Civ Since 1648 (Hon) (HIST 104H)	A
2012	Calculus & Analytical Geometry I (MATH 150)	B
2012	General Chemistry (CHEM 110)	A
2012	Fundamentals of Microbiology (BIO 230)	B
2013	Critical thinking, Composition & Literature (ENGL 201)	A
2013	General Chemistry (CHEM 111)	A
2013	Calculus & Analytical Geometry II (MATH 155)	A
2013	Statistics for Behavioral Sci (SOC 104)	A
2013	Evolution, Biodiversity, Organismal (BIO 202)	A
2013	Organic Chemistry I (CHEM 210)	A
2013	Intro Physics I (PHYS 111)	A
2014	Biochemistry, Cell, Gene, Molecular (BIO 204)	A
2014	Organic Chemistry II (CHEM 211)	A
2014	Principles of Physics II (PHYS 152)	A
2014	General Psychology (PHYC 101)	A
2014	Genetics (BICD 100)	B

YEAR	COURSE TITLE	GRADE
2014	Biochemical Structure & Function (CHEM 114A)	A-
2014	Intermediate German I (LTGM 2A)	A
2015	Biochem Energetics & Metabolism (CHEM 114B)	A
2015	Intermediate German II (LTGM 2B)	A
2015	Calculus & Analyt Geom/Sci&Engnr (MATH 20C)	A+
2015	Biosynthesis of Macromolecules (CHEM 114C)	C
2015	Intermediate German III (LTGM 2C)	A
2015	Intro/Differential Equations (MATH 20D)	A-
2015	Protein Biochemistry Lab (CHEM 108)	B+
2015	Inorganic Chemistry I (CHEM 120A)	B
2015	Physics-Flu, Wav, Thrmdyn, Optics (PHYS 2C)	B-
2016	Recombinant DNA Laboratory (CHEM 109)	A-
2016	Physical Chem: Quantum Mech (CHEM 126)	B
2016	Drug Synthesis and Design (CHEM 168)	B+
2016	Analytical Chemistry Lab (CHEM 100A)	B
2016	Physical Chem: Thermodynamics (CHEM 127)	A-
2016	Chemistry Internship (CHEM 197)	P
2016	Language, Culture & Education (SOCI 117)	P
2017	Physical Chemistry Laboratory (CHEM 105A)	C
2017	Pharmacology and Toxicology (CHEM 118)	C+
2017	Physics-Mechanics (PHYS 2A)	C
2017	Biochem/Molecular/Cell Bi (BCHM 6300 G)	B
2017	Doctoral Research in Nutrition (NUTR 9011 G)	P
2017	Doctoral Seminar in Nutrition (NUTR 9205 G)	P
2017	Mechanisms in Hum Disease (PATH 6003 G)	A-
2018	Resp Cond of Res/Rel Plcy (CMBS 4010 G)	P
2018	Biochem,Cell/Molecular Bi (CMBS 6301 G)	B+
2018	Molecular/Cell Bio of Nutr (NUTR 4020 G)	A-
2018	Doctoral Research in Nutr (NUTR 9011 G)	P
2018	Doctoral Seminar in Nutri (NUTR 9205 G)	P
2018	Mechanisms in Hum Disease (Path 6004 G)	A-
2018	Intro-Biostatistical Meth (BIST 6104 P)	B
2018	Doctoral Seminar in Nutri (NUTR 9205 G)	P
2018	Reviews in Nutrition (NUTR 9300 G)	P
2019	Doctoral Seminar in Nutri (NUTR 9205 G)	P
2019	Reviews in Nutrition (NUTR 9205 G)	P
2020	Funding and Grantsmanship (MEDIM9780)	TBD
2020	Cryo-Electron Microscopy (BCHMGR6400)	TBD
2020	Single Particle Analysis Short Course	NA