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## BIOGRAPHICAL SKETCH

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NAME Yelshanskaya, Maria V.	POSITION TITLE Research Assistant		
eRA COMMONS USER NAME (credential, e.g., agency login) MVEYELSH			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	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 mutagenesis, 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**

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|-----------|---|
| 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, Louisiana, 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.

2011-2019 – 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<sup>+</sup> 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*.

**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: 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. 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 structures of TRPV3 in different conformations and proposed the mechanism of ligand-induced TRPV3 activation. 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.

- 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](#).
- 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](#).
- 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](#).
- 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 Mg<sup>2+</sup> interacts with NMDA receptors via the trapping block mechanism. The discovery of the trapping block of NMDA receptor channels by Mg<sup>2+</sup> led to reevaluation of the role of Mg<sup>2+</sup> 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 ablation 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<sup>+</sup> 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<sub>2</sub>+



selective channel TRPV6 that plays vital roles in calcium homeostasis as a Ca<sup>2+</sup> 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 also solved the first structure of TRPV3 and determined structural bases of TRPV3 activation. Our results provide a structural foundation to understand the regulation of epithelial Ca<sup>2+</sup> uptake and its role in pathophysiology and provide information necessary for drug design.

- a. 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](#).
  - b. Singh AK, Saotome K, McGoldrick LL, Sobolevsky AI. Structural bases of TRP channel TRPV6 allosteric modulation by 2-APB. **Nat Commun**. 2018 Jun 25;9(1):2465. PubMed PMID: [29941865](#); PubMed Central PMCID: [PMC6018633](#).
  - 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.

Irma T. Hirschl Career Scientist Award, the Irma T. Hirschl Trust

Alexander Sobolevsky (PI)

07/01/15-06/30/20

Molecular mechanisms of ionotropic glutamate receptor gating, assembly and regulation

The major goal of this project is to study structural mechanisms of ionotropic glutamate receptor gating, assembly and regulation by auxiliary subunits.

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.