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
Stony Brook University, NY	Post-Doc	08/2004	Neurobiology
Columbia University, NY/Vollum Institute, OHSU, OR	Post-Doc	08/2010	Structural Biology

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 channel function, including patch-clamp, double-electrode voltage-clamp and single-channel recordings as well as 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. We also solved the first structure of a plant glutamate receptor-like channel (GLR). My lab solved the first crystal structure of a TRP channel (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. We then solved structures of TRPV3 in temperature-dependent closed, intermediate, and open states, which for the first time uncovered the structural basis of TRP channel activation by temperature. We also solved the first structure of a TRP channel from alga and the first structures of two (human and squirrel) out of three (plus rat) orthologs of TRPV1 for which structures are available. We solved structures of TRPM7 in different conformations and proposed mechanisms of ligand-induced and spontaneous opening as well as inhibition of this channel. For many TRP channels, we solved structures in complex with different agonists or antagonists and proposed the mechanisms of activation and inhibition, respectively. 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.

Ongoing and recently completed projects that I would like to highlight include:

R01 CA206573
Sobolevsky (PI)
01/12/2017-12/31/2027
Structure and Function of Transient Receptor Potential channels

R01 AR078814
Sobolevsky (PI)
02/01/2022-1/31/2027
Structural and functional principles of activation and regulation of the transient receptor potential channel TRPV3

R01 NS083660
Sobolevsky (PI) / Kurnikova (co-PI)
09/30/2013-06/30/2023
Structure and Function of AMPA subtype ionotropic glutamate receptors

R01 NS107253
Sobolevsky (PI)
08/01/2018-03/31/2028
Single-particle cryo-EM characterization of AMPA receptor functional states

NSF 1818086
Sobolevsky/Kurnikova/Stern-Bach (MPI)
08/01/2018-07/31/2022
Collaborative Research: Towards development of the structural determinants of the Glutamate receptor gating regulation by auxiliary membrane anchored proteins

Citations:

1. Yelshanskaya MV, Patel D. S., Kottke C. M., Kurnikova M. G. and *Sobolevsky A. I.* (2022) Opening of glutamate receptor channel to subconductance levels. ***Nature*** 605: 172-178. PubMed Central PMCID: PMC9068512.
2. McGoldrick LL, Singh AK, Saotome K, Yelshanskaya MV, Twomey EC, Grassucci RA, Sobolevsky AI. (2018) Opening of the human epithelial calcium channel TRPV6. ***Nature*** 553: 233-237. PubMed Central PMCID: PMC5854407.
3. Twomey EC, Yelshanskaya MV, Grassucci RA, Frank J, Sobolevsky AI. (2017) Channel opening and gating mechanism in AMPA-subtype glutamate receptors. ***Nature*** 549: 60-65. PubMed Central PMCID: PMC5743206.
4. Saotome K, Singh AK, Yelshanskaya MV, Sobolevsky AI. (2016) Crystal structure of the epithelial calcium channel TRPV6. ***Nature*** 534: 506-11. PubMed Central PMCID: PMC4919205.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

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

Honors

2023	Keynote speaker at Three-Dimensional Electron Microscopy GRS, Newry, ME
2017	Amgen Young Investigator Award, Amgen
2015	Irma T. Hirschl Career Scientist Award, Irma T. Hirschl Trust
2015	Future of Biophysics Symposium Speaker, Biophysical Society 59th Annual Meeting, Baltimore
2013	Pew Scholar Award, Pew Charitable Trusts
2012	Schaefer Research Scholar Award, Dr. Ludwig Schaefer Fund
2011	Klingenstein Fellowship Award in the Neurosciences, Esther A. & Joseph Klingenstein Fund

2002	Postdoctoral Travel Award for participation in the 32nd Annual Meeting of the Society for Neuroscience, Burroughs Wellcome Fund
2000	Travel Grant for participation in the 31st Annual Meeting of the Society for Neuroscience, International Brain Research Organization
1999	International Soros Science Education Program Grant, Soros Foundation
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

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^{2+} interacts with NMDA receptors via the trapping block mechanism. The discovery of the trapping block of NMDA receptor channels by Mg^{2+} led to reevaluation of the role of Mg^{2+} 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 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 Central PMCID: PMC6784965.
    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 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 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 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 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 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 Central PMCID: PMC6729461.
   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 Central PMCID: PMC6740752.

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 basis of TRPV6 allosteric regulation and calcium-induced calmodulin-mediated inactivation. We also solved the first structures of TRPV3 and determined structural basis of TRPV3 activation by both ligands and temperature. Our results provide structural foundations to understand the role of TRP channels in physiology and disease, and provide information necessary for drug design.

   a. Nadezhdin KD, Neuberger A, Trofimov YA, Krylov N, Sinica V, Kupko N, Vlachova V, Zakharian E, Efremov RG and *Sobolevsky AI.* Structural mechanism of heat-induced opening of a temperature-sensitive TRP channel. **Nat Struct Mol Biol**. 2021 Jul 8;28(7):564-572. PubMed Central PMCID: PMC8283911.
   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 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 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 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,

gamma5 and GSG1L, and solved the first structures of AMPA receptor in the open and desensitized states, and in complex with ion channel blockers.

a. Yelshanskaya MV, Patel D. S., Kottke C. M., Kurnikova M. G. and *Sobolevsky A. I.* (2022) Opening of glutamate receptor channel to subconductance levels. **Nature** 605: 172-178. PubMed Central PMCID: PMC9068512.
b. 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 Central PMCID: PMC5743206.
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 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 Central PMCID: PMC4383034.

Complete List of Published Work in PubMed:
https://www.ncbi.nlm.nih.gov/myncbi/alexander.sobolevsky.1/bibliography/public/