

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Lee, Seok-Yong	POSITION TITLE Associate Professor		
eRA COMMONS USER NAME (credential, e.g., agency login) SYLEE1			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Yonsei University, Seoul, Korea	B.S.	05/1998	Biochemistry
University of California at Berkeley, Berkeley, California	Ph.D.	05/2003	Biophysics
Rockefeller University, New York City, New York	Postdoctoral fellow	07/2009	Structural Biology and Biophysics

A. Personal Statement

I have more than 15 years of experience in the field of structural biology and biophysics of membrane transport proteins. During my independent career at Duke University School of Medicine, my laboratory has carried out structural and mechanistic studies of ion channels and transporters that are important in many different physiological processes. My group has solved the structures of many ion channels, transporters, and enzymes using either cryo-electron microscopy (cryo-EM) or X-ray crystallography. Notably, in the past several years, my laboratory has focused on cryo-EM structural studies of Ca^{2+} -permeable ion channels, and as a result has published a number of important ion channel structures including Transient receptor potential (TRP) channels (TRPV2, TRPV3, TRPML3, TRPM2, and TRPM8) and Mitochondrial Calcium Uniporter (MCU). In summary, I have demonstrated expertise and productivity in the area of structural and functional studies of integral membrane proteins and are well prepared to carry out the proposed research program.

- Ying Yin, Son C. Lee, Allen H. Hsu, Mario J. Borgnia, Huanghe Yang, Seok-Yong Lee*, Structural basis of cooling agent and lipid sensing by the cold activated TRPM8 channel. **Science**, 2019. First Release 07 Feb doi: 10.1126/science.aav9334 PMID:PMC6478609
- Lejla Zubcevic[‡], William Borschel[‡], Allen L. Hsu, Mario J. Borgnia, Seok-Yong Lee*, Regulatory switch at the cytoplasmic interface controls TRPV channel gating, **eLife**, 2019, May 9;8. pii:e47746. Doi:10.7554/eLife.47746 PMID:31070581
- Ying Yin[‡], Mengyu Wu[‡], Lejla Zubcevic, William F. Borschel, Gabriel C. Lander*, Seok-Yong Lee*, Structure of the cold- and menthol-sensing ion channel TRPM8. **Science**, 2017. First Release 07 Dec doi: 10.1126/science.aan4325. PMID: PMC5810135
- Lejla Zubcevic, Mark A Herzik Jr, Ben C Chung, Zhirui Liu, Gabriel C Lander*, Seok-Yong Lee*, Cryo-electron microscopy structure of the TRPV2 ion channel. **Nat Struct Mol Biol**, 2016 Epub Jan 18. doi: 10.1038/nsmb.3159. PMID: PMC4876856

B. Positions and Honors.

Positions and Employment

2003.7 – 2009.7 Postdoctoral fellow, The Rockefeller University, New York, NY.
2009.9 – 2016.6 Assistant Professor of Biochemistry, Duke University School of Medicine, Durham, NC.
2016.7 – Associate Professor of Biochemistry, Duke University School of Medicine, Durham, NC.

Honors

1998-2003	Predoctoral Fellow, Korean Foundation for Advanced Study
2004-2007	Postdoctoral Fellow, Jane Coffin Childs Memorial Fund
2009	Whitehead Scholar, Duke University Medical Center
2010-2013	McKnight Scholar Award, The McKnight Endowment Fund for Neuroscience
2010-2013	Klingenstein Fellowship Award in the Neurosciences, The Klingenstein Fund
2010-2013	Mallinckrodt Scholar, Edward Mallinckrodt, Jr, Foundation
2011-2013	Basil O'Connor Starter Scholar Research Award, March of Dimes Foundation
2011-2013	Alfred P. Sloan Research Fellow, Alfred P. Sloan Foundation
2011-2016	NIH Director's New Innovator Award
2012	NIGMS award, 56 th Biophysical Society Annual Meeting
2014	NIH EUREKA award, Neuroscience and Disorders of the Nervous System
2016	NIH Research Program Award, Neuroscience and Disorders of the Nervous System
2018	The SER-CAT Outstanding Science Award
2018	Hanseong Science Award, Hanseong Sonjaehan Foundation, Korea
2018	Outstanding Postdoc Mentor Award at Duke University

C. Contribution to Science

1. Structure, function, and pharmacology of calcium-permeable ion channels

Transient receptor potential (TRP) channels are polymodal sensors involved in sensory transduction such as pain and itch. By sensing changes in temperature, ligands (e.g. irritants), and lipids, TRP channels regulate Ca^{2+} flow into neuronal (and non-neuronal) cells. Despite the crucial importance of TRP channels in human physiology and diseases, our understanding of these channels is still far from satisfactory, mainly because of a lack of structural information and atomic-level understanding of the channel operation. To these ends, we have carried out structural studies of TRPV channels. We have determined the first near-atomic structures of the TRPV2, TRPV3, TRPML3, and TRPM8 ion channel using cryo-electron microscopy (cryoEM). These structures together with our functional studies led us to propose the mechanism of ligand-, temperature-, and lipid-dependent gating transitions in TRPV channels.

- e) Marscha Hirschi[‡], Mark A. Herzik Jr.[‡], Jinhong Wie, Yang Suo, William F. Borschel, Dejian Ren, Gabriel C. Lander*, and Seok-Yong Lee*, Cryo-EM structure of the lysosomal Ca^{2+} permeable channel TRPML3. **Nature**, 2017. published online 11 Oct doi:10.1038/nature24055. PMCID: PMC5762132
- f) Jiho Yoo[‡], Mengyu Wu[‡], Ying Yin, Mark A. Herzik Jr, Gabriel C. Lander*, Seok-Yong Lee*, Cryo-EM structure of a Mitochondrial Calcium Uniporter. **Science**, 2018. First Release 28 June doi: 10.1126/science.aar4056 PMCID: PMC6155975
- g) Lejla Zubcevic, Allen L. Hsu, Mario J. Borgnia, Seok-Yong Lee*, Symmetry transitions during gating of the TRPV2 ion channel in lipid membranes, **eLife**, 2019, May 15;8. pii: e45779. doi:10.7554/eLife.45779 PMCID: PMC6544438
- h) Ying Yin, Son C. Lee, Allen H. Hsu, Mario J. Borgnia, Huanghe Yang, Seok-Yong Lee*, Structural basis of cooling agent and lipid sensing by the cold activated TRPM8 channel. **Science**, 2019. First Release 07 Feb doi: 10.1126/science.aav9334. PMCID:PMC6478609

* Corresponding author

2. Structure, function, and chemical biology of nucleoside transporters

Nucleoside transport is associated with many important physiological processes such as nucleic acid synthesis and the termination of adenosine signaling. Because nucleosides are hydrophilic molecules, they require specific membrane transporter proteins known as nucleoside transporters (NTs) to carry nucleosides across cell membranes. Remarkably, NTs are important for the transport of many nucleoside-derived anticancer and antiviral drugs into cells, evidenced by multiple clinical studies. Therefore, understanding the mechanism of transport by NTs is critical to understanding not only nucleoside-related physiological processes but also

nucleoside drug pharmacology. The biggest hurdle to revealing this mechanism was the lack of atomic structures that show the design principles behind these NTs. We solved the crystal structure of a CNT from *Vibrio cholerae*, the first structure of a member of the CNT family. We have also determined crystal structures of vcCNT in complex with nucleoside-derived anticancer and antiviral drugs and studied their interactions using functional assays using ITC, fluorescence-based equilibrium binding, and a radioactive flux assay to understand the principles of substrate recognition by CNTs. With the knowledge gained from the structural studies, we modified an existing anticancer drug to be better transported by and selective for a single human CNT subtype. This work provides proof of principle for utilizing transporter structural and functional information for the design of compounds that enter cells more efficiently and selectively.

- a) Zachary Johnson, Cheom-Gil Cheong, and Seok-Yong Lee*, Crystal structure of a concentrative nucleoside transporter from *Vibrio cholerae* at 2.4 Å. **Nature**, 2012, Mar 11;483(7390):489-93. PMCID: PMC3310960
- b) Zachary Johnson, Jun-Ho Lee, Kiyeon Lee, Minhee Lee, Do-Yeon Kwon, and Jiyong Hong, and Seok-Yong Lee*, Structural Basis of Nucleoside and Nucleoside Drug Selectivity by Concentrative Nucleoside Transporters. **eLife**, 2014, Jul 31:e03604. PMCID: PMC4139061
- c) Marscha Hirschi, Zachary Johnson and Seok-Yong Lee*, Visualizing multistep elevator-like transitions of a nucleoside transporter. **Nature**, 2017. May 4;545(7652):66-70. Epub 2017 Apr 17 doi:10.1038/nature22057 PMCID: PMC5567992
- d) Nicholas Wright and Seok-Yong Lee*, Structures of human ENT1 in complex with adenosine reuptake inhibitors, **Nat. Struct. & Mol. Bio.**, 2019. Jul;26(7):599-606. PMID: 31235912

* Corresponding author

3. Structural biology of lipid transport in bacterial cell wall synthesis

My recent research has focused on a class of membrane proteins responsible for lipid transport in bacterial cell wall synthesis. Lipid transport in bacterial cell wall synthesis involves Lipid I production and Lipid II flipping, which are carried out by *MraY* and *MurJ*, respectively. Both Lipid I production and Lipid II flipping are essential steps in bacterial cell wall synthesis. *MraY* (phospho-MurNAc-pentapeptide translocase) is considered a very promising target for the development of new antibiotics, as *MraY* is the target of five different classes of natural product antibiotics and a bacteriolytic protein from bacteriophage phiX174. However, despite many years of efforts, development of antibiotics against *MraY* has been stagnant largely because of the lack of a structural and mechanistic understanding of *MraY* function and inhibition. Significant progress in the field depends upon the structure determination and subsequent mechanistic understanding of *MraY*. We have solved the structure of *MraY_{AA}*, the first structure of a member of the *MraY* family. We also solved the structure of *MraY* bound to its inhibitor, muraymycin at 2.95 Å, which revealed significant conformational rearrangements near the active site upon inhibitor binding. Our crystallographic and functional studies revealed the structural basis of *MraY* catalysis and inhibition. The molecular identity of the Lipid II flippase has recently been revealed and thus the structural basis of Lipid II flipping by *MurJ* has been unclear. We solved the first structure of *MurJ* and performed mutagenesis studies. Our structural and functional analyses have provided the structural basis of Lipid II recognition by *MurJ* and showed that alternate access mechanism is utilized for Lipid II flipping, which is an important conceptual advance, as lipid flipping was previously considered alternate-access independent.

- a) Ben C. Chung, Jinshi Zhao, Robert A. Gillepsie, Do-Yeon Kwon, Ziqiang Guan, Jiyong Hong, Pei Zhou, and Seok-Yong Lee*, Crystal structure of *MraY*, an Essential Membrane Enzyme for Bacterial Cell Wall Synthesis. **Science**, 2013 Aug 30; 341(6149):1012-6. PMCID: PMC3906829
- b) Ben C. Chung, Ellene H. Mashalidis, Tetsuya Tanino, Mijung Kim, Akira Matsuda, Jiyong Hong, Satoshi Ichikawa, Seok-Yong Lee*, Structural insights into inhibition of lipid I production in bacterial cell wall synthesis. **Nature**, (2016). DOI:10.1038/nature17636. PMCID: PMC4882255.

- c) Alvin C. Y. Kuk, Ellene H. Mashalidis, Seok-Yong Lee^{*}, Crystal structure of the MOP flippase MurJ in an inward-facing conformation. *Nat. Struc. & Mol. Biol.*, (2016). DOI:10.1038/nsmb.3346. PMCID: PMC5382020
- d) Jiho Yoo[†], Ellene H. Mashalidis[†], Alvin C. Y. Kuk[†], Kazuki Yamamoto, Benjamin Kaeser, Satoshi Ichikawa, Seok-Yong Lee^{*}, GlcNAc-1-P-transferase-tunicamycin complex structure reveals basis for inhibition of N-glycosylation. *Nat. Struc. & Mol. Biol.*, 2018. Published online 19 Feb doi: 10.1038/s41594-018-0031-y. PMCID: PMC5840018

Complete List of Published Work in MyBibliography:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/seok-yong.lee.1/bibliography/43450645/public/?sort=date&direction=descending>

D. Research Support

Completed

NIH Director's New Innovator Award (Lee)	09/30/11-06/30/16
Pharmacological and biophysical studies of the voltage-gated sodium channel Na _v 1.7	
Role: PI	

NIH R01 GM100984-01A1 (Lee)	05/01/13-02/28/17
Structure and function of concentrative nucleoside transporters	
Role: PI	

Current

NIH R35 NS09724-01 (Lee)	09/01/16-08/31/24
Structure, Function, and pharmacology of neuronal membrane transport proteins	
Role: PI	

NIH R01 GM120594-01 (Lee)	01/01/17-11/30/20
Structure and Mechanistic Characterization of MraY Catalysis and Inhibition	
Role: PI	