BIOGRAPHICAL SKETCH

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NAME: Lee, Seok-Yong

eRA COMMONS USER NAME (credential, e.g., agency login): SYLEE1

POSITION TITLE: 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)*	Completion Date MM/YYYY	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 nearly 18 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 structures of many ion channels, transporters, and enzymes using cryo-electronmicroscopy (cryo-EM) and performed structure-guided functional studies to elucidate the mechanisms of their function. They include concentrative nucleoside transporter (CNT) and equilibrative nucleoside transporter (ENT), transient receptor potential (TRP) channels (TRPM8, TRPV2, TRPV3, TRPML3, TRPM2, and TRPA1), mitochondrial calcium uniporter (MCU), bacterial cell wall synthesis membrane enzyme MraY, eukaryotic N-glycosylation membrane enzyme GPT/DPAGT1, and Lipid II flippase MurJ. Besides my research focus, I would like to stress that student and postdoc training has been an important component to my career goal. 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.

a) Yang Suo, Zilong Wang, Lejla Zubcevic, Allen L. Hsu, Qianru He, Mario J. Borgnia, Ru-Rong Ji, Seok-Yong Lee*. “Structural Insights into Electrophile Irritant Sensing by the Human TRPA1 Channel.” ***Neuron,*** 2019 Dec 19. Available online. doi:10.106/j.neuron.2019.11.023 PMCID:PMC7205012

b) 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

c) 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. PMCID: PMC6705415

d) 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

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 – 2020.6 Associate Professor of Biochemistry, Duke University School of Medicine, Durham, NC.
2020.7- 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, 56th 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

B. Contributions 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 near-atomic structures of the TRPV2, TRPV3, TRPML3, TRPM2, TRPM8, and TRPA1 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 TRP channels.

a) 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 PMCID:PMC5810135

b) 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

c) 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

d) 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 Transporter*s*. ***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:

https://www.ncbi.nlm.nih.gov/sites/myncbi/seok-yong.lee.1/bibliography/43450645/public/

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

Ongoing Research Support

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

NIH R01 GM137421 (Lee) 04/01/20-01/31/24
Molecular Basis of Adenosine Transport and Reuptake Inhibition in Human
Role: PI

NIH R01 EY031698 (Lee) 09/30/20-04/30/24
TRPM8 in eye health and disease
Role: PI

BASF Corporation sponsored research (Lee) 04/01/20-03/31/22
Structural studies of insect TRP channels
Role: PI