BIOGRAPHICAL SKETCH

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NAME: Lee, Seok-Yong

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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 20 years of experience in the field of membrane protein structural biology and biophysics. During my independent career at Duke University School of Medicine, my laboratory has carried out structural and mechanistic studies of membrane transport proteins that are important in many different physiological processes using cryo-electronmicroscopy (cryo-EM), X-ray crystallography, electrophysiology, and various biophysical methods. My lab has contributed significantly to our molecular-level understanding of 1) the sensations of heat, capsaicin (spiciness), menthol (coolness), and wasabi (pungent compounds) in humans, 2) antiviral/anticancer drug and adenosine uptake in humans and 3) lipid transport critical for the bacterial cell wall synthesis. These studies have not only significantly advanced our fundamental understanding of these mechanisms, but also contribute information for the future development of analgesic, antiviral, anticancer and antibiotic agents. In summary, I have demonstrated expertise and productivity in the area of structural, functional, and pharmacological studies of sensory receptor proteins and am well prepared to carry out the proposed research program.

Citations:

a) Nicholas Wright, Justin Fedor, Han Zhang, Pyeonghwa Jeong, Yang Suo, Jiho Yoo, Jiyong Hong, Wonpil Im, **Seok-Yong Lee***. *Nature,* 2022. “Methotrextate recognition by the human reduced folate carrier SLC19A1”. Online ahead of print. PMID: 36071163

b) Zhenning Ren‡, Abhishek Chhetri‡, Ziqiang Guan, Yang Suo, Kenichi Yokoyama*, **Seok-Yong Lee***. “Structural basis for inhibition and regulation of a chitin synthase from *Candida albicans”*. *Nat. Struct. & Mol. Biol*., 2022. Jul;29(7):653-664. PMID:35788183

c) Dohoon Kwon, Feng Zhang, Yang Suo, Jonathan Bouvette, Mario J. Borgnia, **Seok-Yong Lee***. “Heat-dependent opening of TRPV1 in the presence of capsaicin.” *Nat. Struct. & Mol. Biol*., 2021. 28:554-563. PMCID: PMC8335751

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. 363:aav9334. PMCID: PMC6478609

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2020.7 – Present 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.
2009.9 – 2016.6 Assistant Professor of Biochemistry, Duke University School of Medicine, Durham, NC.
2003.7 – 2009.7 Postdoctoral fellow, The Rockefeller University, New York, NY.

Honors

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

C. 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. We have contributed to understanding the mechanisms for sensation of cooling and noxious chemicals by the transient receptor potential (TRP) calcium-permeable channels (TRPM8, TRPV2, TRPV3, TRPA1, TRPML3, and TRPM2) and their regulation by PIP_2. Notably, we have uncovered the molecular basis of heat sensing by the heat and capsaicin sensor TRPV1, the molecular basis of cooling agent sensing by the cold/menthol receptor TRPM8, the mechanism of irritant sensing by the wasabi receptor TRPA1, the mechanism of ligand-dependent gating of TRPV2 and TRPV3. Our work has allowed us to propose fundamental design principles of TRP channels, including the unusual π-helix, reduced symmetry in channel gating and the role of the distal C-terminal domain in TRPV channel regulation.

a) 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. PMCID: PMC4876856
b) 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. 550:411-414. PMCID: PMC5762132
c) 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. 363:aav9334. PMCID: PMC6478609
d) Dohoon Kwon, Feng Zhang, Justing G. Fedor, Yang Suo, Seok-Yong Lee*. "Vanilloid-dependent conformational trajectory of TRPV1 opening revealed through cryoEM ensembles". ***Nat. Commun***. 2022. May 24;13(1):2874. PMICID:PMC9130279

***** 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 have elucidated the mechanisms of nucleoside and nucleoside-derived drug uptake by CNT and ENT, two types of nucleoside transporters in humans, and the mechanism of human ENT1 inhibition by adenosine reuptake inhibitor (AdoRI) drugs. From these studies, we have advanced our understanding of the "elevator" transport model, provided a proof-of-concept to engineer drugs with enhanced selectivity, and provided a platform to develop novel AdoRIs.

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. 483:489-493. PMCID: PMC3310960
b) Marscha Hirschi, Zachary Johnson and **Seok-Yong Lee***, Visualizing multistep elevator-like transitions of a nucleoside transporter. *Nature*, 2017. 545:66-70. PMCID: PMC5567992
c) Nicholas Wright and **Seok-Yong Lee***, Structures of human ENT1 in complex with adenosine reuptake inhibitors, *Nat. Struct. & Mol. Biol*., 2019. 26:599-606. PMCID: PMC6705415
d) Nicholas Wright, Justin Fedor, Han Zhang, Pyeonghwa Jeong, Yang Suo, Jiho Yoo, Jiyong Hong, Wonpil Im, **Seok-Yong Lee***. *Nature,* 2022. "Methotrextate recognition by the human reduced folate carrier SLC19A1". Online ahead of print. PMID: 36071163

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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. Significant progress in the field depends upon the structure determination and subsequent mechanistic understanding of MraY and MurJ. We have solved the structure of $MraY_{AA}$, the first structure of a member of the MraY family. We also solved the structures of MraY bound to five different types of peptidyl nucleoside inhibitors, thereby providing the chemical logic of MraY inhibition by naturally occurring nucleoside inhibitors. We have uncovered not only the mechanisms of LLO translocation and flipping by MraY and MurJ in bacterial cell wall synthesis, but also the inhibition of MraY by antibiotics. Our work guides novel approaches to selectively target bacterial cell wall synthesis for antibiotic development. We have recently expanded our program to fungal cell wall synthesis.

a) 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. 533:557-560. PMCID: PMC4882255
b) 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. 24:171-176. PMCID: PMC5382020
c) Alvin C. Y. Kuk, Aili Hao, Ziqiang Guan, **Seok-Yong Lee**[*], Visualizing conformation transitions of the Lipid II flippase MurJ. *Nat. Commun.* 2019. 10:1736. PMCID: PMC6465408
d) Zhenning Ren[‡], Abhishek Chhetri[‡], Ziqiang Guan, Yang Suo, Kenichi Yokoyama*, **Seok-Yong Lee***. "Structural basis for inhibition and regulation of a chitin synthase from *Candida albicans*. *Nat. Struct. & Mol. Biol*., 2022. Epub advanced online. 10.1038/s41594-022-00791-x

***** Corresponding author

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/seok-yong.lee.1/bibliography/43450645/public/