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 over 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) drug and metabolite 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 and mechanistic studies of integral membrane proteins and am well prepared to carry out the proposed research program.

Citations:

a) Ying Yin, Feng Zhang, Shasha Feng, Kevin John Butay, Mario J. Borgnia, Wonpil Im, **Seok-Yong Lee***, Activation mechanism of the mouse cold-sensing TRPM8 channel by cooling agonists and PIP_2. *Science*, 2022. 378, add1268. PMCID: PMC9795508

b) Nicholas Wright, Justin Fedor, Han Zhang, Pyeonghwa Jeong, Yang Suo, Jiho Yoo, Jiyong Hong, Wonpil Im, **Seok-Yong Lee***. "Methotrextate recognition by the human reduced folate carrier SLC19A1". *Nature,* 2022. Sep;609(7929):1056-1062. PMCID: PMC9822521

c) Yang Suo, Nicholas Wright, Hugo Guterres, Justin Fedor, Kevin John Butay, Mario J. Borgnia, Wonpil Im, **Seok-Yong Lee***. Molecular basis of polyspecific drug and xenobiotic recognition by OCT1 and OCT2. *Nat. Struct. Mol. Biol.*, 2023 Jul;30(7):1001-1011. PMID:37291422

d) Nicholas Wright, Feng Zhang, Yang Suo, Linyang Kong, Ying Yin, Kedar Sharma, Mario Borgnia, Wonpil Im, **Seok-Yong Lee***. Antiviral drug recognition and elevator-type transporter motions of CNT3. *Nat. Chem. Biol.* 2024 In press, doi:10.1038/s41589-024-01559-8

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2023.7 – Present George Barth Geller Distinguished Professor of Molecular Biology, Duke University

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

2023	Distinguished Professorship, Duke University
2023	Biophysical Society New and Notable Symposium Lecturer
2022	Duke Science and Technology (DST) scholar
2018	Outstanding Postdoc Mentor Award at Duke University
2018	Hanseong Science Award, Hanseong Sonjaehan Foundation, Korea
2018	The SER-CAT Outstanding Science Award
2018	Biophysical Society New and Notable Symposium Lecturer
2016	NIH Research Program Award, Neuroscience and Disorders of the Nervous System
2016	Biophysical Society New and Notable Symposium Lecturer
2014	NIH EUREKA award, Neuroscience and Disorders of the Nervous System
2012	Biophysical Society New and Notable Symposium Lecturer
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) 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
c) 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
d) Ying Yin, Feng Zhang, Shasha Feng, Kevin John Butay, Mario J. Borgnia, Wonpil Im, **Seok-Yong Lee***, Activation mechanism of the mouse cold-sensing TRPM8 channel by cooling agonists and PIP_2. *Science*, 2022. 378, add1268. PMCID: PMC9795508

***** Corresponding author

2. Structure, function, and chemical biology of drug/metabolite transporters

We are interested in a detailed mechanistic understanding of the cellular uptake of drugs and metabolites/nutrients by solute carriers (SLCs), as well as the often-inevitable drug-drug and drug-nutrient interactions that occur. Specifically, we are interested in nucleoside and nucleoside-derived drug transport mediated by Concentrative and Equilibrative Nucleoside Transport proteins (CNTs/ENTs), folate and anti-folate drug transport by the Reduced Folate Carrier (RFC), and organic cation transport by organic cation transporters (OCTs). These transporters are vital to a wide variety of physiological processes including metabolism, cellular signaling, and drug uptake and excretion.

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 transport model, provided a proof-of-concept to engineer drugs with enhanced selectivity, and provided a platform to develop novel AdoRIs. Our study of RFC and OCTs paves the way for a comprehensive understanding of drug recognition and selectivity by hRFC and OCTs.

a) Marscha Hirschi, Zachary Johnson and **Seok-Yong Lee***, Visualizing multistep elevator-like transitions of a nucleoside transporter. *Nature*, 2017. 545:66-70. PMCID: PMC5567992
b) 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
c) Yang Suo, Nicholas Wright, Hugo Guterres, Justin Fedor, Kevin John Butay, Mario J. Borgnia, Wonpil Im, **Seok-Yong Lee***. Molecular basis of polyspecific drug and xenobiotic recognition by OCT1 and OCT2. *Nat. Struct. Mol. Biol.*, 2023 Jul;30(7):1001-1011. PMID:37291422
d) Nicholas Wright, Feng Zhang, Yang Suo, Linyang Kong, Ying Yin, Kedar Sharma, Mario Borgnia, Wonpil Im, **Seok-Yong Lee***. Antiviral drug recognition and elevator-type transporter motions of CNT3. *Nat. Chem. Biol.* 2024 In press, doi:10.1038/s41589-024-01559-8

***** 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. 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. Jul;29(7):653-664. PMCID: PMC9359617

***** Corresponding author

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

BIOGRAPHICAL SKETCH

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NAME: HAO, AILI

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

POSITION TITLE: Research Scholar

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
University of Wisconsin - Madison, Madison, WI	BS	05/2016	Microbiology
Duke University, DURHAM, NC	PHD	07/2023	Biochemistry
Duke University, DURHAM, NC	Other training	present	Research Scholar

A. Personal Statement

During my graduate and post-graduate training, I have specialized in membrane protein structural biology with an emphasis on bacterial cell wall biogenesis pathway. My work focuses on elucidating the structural and functional mechanisms of multiple membrane proteins involved in bacterial cell wall synthesis and remodeling. My training has provided me with extensive experience in membrane protein purification, grid preparation and structural determination.

1. Yamamoto K, Sato T, Hao A, Asao K, Kaguchi R, Kusaka S, Ruddarraju RR, Kazamori D, Seo K, Takahashi S, Horiuchi M, Yokota SI, Lee SY, Ichikawa S. Development of a natural product optimization strategy for inhibitors against MraY, a promising antibacterial target. Nat Commun. 2024 Jun 14;15(1):5085. PubMed Central PMCID: PMC11178787.
2. Hao A, Suo Y, Lee SY. Structural insights into the FtsEX-EnvC complex regulation on septal peptidoglycan hydrolysis in Vibrio cholerae. Structure. 2024 Feb 1;32(2):188-199.e5. PubMed PMID: 38070498.
3. Kuk ACY, Hao A, Guan Z, Lee SY. Visualizing conformation transitions of the Lipid II flippase MurJ. Nat Commun. 2019 Apr 15;10(1):1736. PubMed Central PMCID: PMC6465408.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2023 - Research Scholar, Duke University, DURHAM, NC

C. Contribution to Science

1. Antibiotic resistance poses a significant global health challenge, necessitating the development of novel antibiotics. Phospho-MurNAc-pentapeptide translocase (MraY), an essential enzyme in peptidoglycan biosynthesis, is a promising target for new antibiotics. Our work explores the mechanism of MraY interacting with inhibitory natural products by obtaining high resolution structures of MraY in complex with these products, leading to the identification of potent analogues against drug-resistant bacteria and providing insights into designing new MraY inhibitors with improved chemical tractability and antibacterial efficacy.

    a. Yamamoto K, Sato T, Hao A, Asao K, Kaguchi R, Kusaka S, Ruddarraju RR, Kazamori D, Seo K, Takahashi S, Horiuchi M, Yokota SI, Lee SY, Ichikawa S. Development of a natural product optimization strategy for inhibitors against MraY, a promising antibacterial target. Nat Commun.

2024 Jun 14;15(1):5085. PubMed Central PMCID: PMC11178787.

b. Kwak SH, Lim WY, Hao A, Mashalidis EH, Kwon DY, Jeong P, Kim MJ, Lee SY, Hong J. Synthesis and evaluation of cyclopentane-based muraymycin analogs targeting MraY. Eur J Med Chem. 2021 Apr 5;215:113272. PubMed Central PMCID: PMC8009818.

2. During bacterial cell division, hydrolysis of septal peptidoglycan (sPG) is crucial for cell separation. This sPG hydrolysis is performed by the enzyme amidases whose activity is regulated by the integral membrane protein complex FtsEX-EnvC. FtsEX is an ATP-binding cassette transporter, and EnvC is a long coiled-coil protein that interacts with and activates the amidases. The molecular mechanism by which the FtsEX- EnvC complex activates amidases remains largely unclear. We present the cryo-electron microscopy struc- ture of the FtsEX-EnvC complex from the pathogenic bacteria V. cholerae (FtsEX-EnvCVC). FtsEX-EnvCVC in the presence of ADP adopts a distinct conformation where EnvC is ‘‘horizontally extended’’ rather than ‘‘vertically extended’’. Subsequent structural studies suggest that EnvC can swing between these conformations in space in a nucleotide-dependent manner. Our structural analysis and functional studies suggest that FtsEX-EnvCVC employs spatial control of EnvC for amidase activation, providing mechanistic insights into the FtsEX-EnvC regulation on septal peptidoglycan hydrolysis.

a. Hao A, Suo Y, Lee SY. Structural insights into the FtsEX-EnvC complex regulation on septal peptidoglycan hydrolysis in Vibrio cholerae. Structure. 2024 Feb 1;32(2):188-199.e5. PubMed PMID: 38070498.