

**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-electron microscopy (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:

- 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<sub>2</sub>. *Science*, 2022. 378, add1268. PMCID: PMC9795508
- Nicholas Wright, Justin Fedor, Han Zhang, Pyeonghwa Jeong, Yang Suo, Jiho Yoo, Jiyong Hong, Wonpil Im, **Seok-Yong Lee\***. "Methotrexate recognition by the human reduced folate carrier SLC19A1". *Nature*, 2022. Sep;609(7929):1056-1062. PMCID: PMC9822521
- 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
- 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, 56<sup>th</sup> 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<sup>2+</sup> 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<sub>2</sub>. 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  $\pi$ -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. PMCID: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<sub>2</sub>. *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. Borgia, 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 Borgia, 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<sub>AA</sub>, 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. Struct. & 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<sup>‡</sup>, Abhishek Chhetri<sup>‡</sup>, 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: Suo, Yang

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

POSITION TITLE: Postdoctoral Associate

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
Shanghai Jiao Tong University	BS	06/2014	Bioengineering
Duke University, Durham, North Carolina	PHD	03/2021	Biochemistry
Duke University, Durham, North Carolina	Postdoctoral Fellow	present	

**A. Personal Statement**

I am currently a postdoctoral associate at Dr. Seok-Yong Lee's laboratory at Duke University. I have several years of training and expertise in membrane protein biochemistry, biophysics and structural biology methods on cryo-electron microscopy. During my doctoral and postdoctoral training, under the guidance of Dr. Seok-Yong Lee, I dedicated in the structural biology studies of several critical ion channels such as TRPA1, TRPV1 and TRPML3 channels, as well as drug transporters of the SLC22 family. I have demonstrated expertise in the area of structural and functional studies of membrane channels and transporters and am well prepared to carry out the proposed research.

**B. Positions, Scientific Appointments and Honors****Positions and Scientific Appointments**

2021 - Postdoctoral Associate, Duke University, Durham, NC

**C. Contribution to Science**

- Structural and functional studies on irritant-sensing TRPA1 ion channels.** Transient Receptor Potential Ankyrin 1 (TRPA1) ion channels are integral components of the sensory nervous system, known for their role in detecting environmental irritants and contributing to nociception and inflammation. TRPA1 channels respond to a diverse array of chemical stimuli, including environmental irritants, endogenous inflammatory mediators, and noxious cold. Understanding the structural and functional mechanisms underlying TRPA1 activation and regulation is crucial, as these channels are implicated in various pain and inflammatory disorders. We reported cryo-EM structures of human TRPA1 channels under ligand or agonist-bound states, and proposed models for electrophile irritant sensing mechanism of TRPA1, paving the way for the development of targeted therapeutic interventions aimed at modulating channel activity in pathological conditions.
  - Suo Y, Lee SY. Sample preparation of the human TRPA1 ion channel for cryo-EM studies. *Methods Enzymol.* 2021;653:75-87. PubMed Central PMCID: PMC10316410.
  - Suo Y, Wang Z, Zubcevic L, Hsu AL, He Q, Borgnia MJ, Ji RR, Lee SY. Structural Insights into Electrophile Irritant Sensing by the Human TRPA1 Channel. *Neuron.* 2020 Mar 4;105(5):882-894.e5. PubMed Central PMCID: PMC7205012.
- Structural and functional studies on SLC22 drug transporters.** The Solute Carrier 22 (SLC22) family of drug transporters plays a pivotal role in the pharmacokinetics of numerous drugs by mediating their cellular uptake and disposition. This family includes key transporters such as organic cation transporters (OCTs) and organic anion transporters (OATs), which are essential for the hepatic and renal clearance of a broad spectrum of drugs, respectively. Despite their clinical significance, the structural and functional

characteristics of SLC22 transporters remain incompletely understood. Utilizing cryo-EM, we have solved several structures of OCT1 and 2 in ligand-free and substrate or inhibitor bound states. Our findings set the stage for a more comprehensive structure-based understanding of OCT-mediated drug-drug interactions, which will prove critical in the preclinical evaluation of emerging therapeutics.

- a. Suo Y, Wright NJ, Guterres H, Fedor JG, Butay KJ, Borgnia MJ, Im W, Lee SY. Molecular basis of polyspecific drug and xenobiotic recognition by OCT1 and OCT2. *Nat Struct Mol Biol.* 2023 Jul;30(7):1001-1011. PubMed Central PMCID: PMC10895701.