BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

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

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Kwon, Do Hoon

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

POSITION TITLE: Research 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
Korea University, Seoul	BS	02/2013	Biotechnology
Korea University, Seoul	PHD	02/2019	Biochemistry
Duke University School of Medicine, Durham, NC	Postdoctoral Fellow	present	

A. Personal Statement

I have more than 10 years of experience in the field of structural biology and biophysics of various types of proteins. During my PhD course at Korea University and postdoctoral period, I carried out structural and mechanistic studies of autophagy-related proteins and ion channels that are important in many diverse physiological processes. I have solved the structures of many autophagy-related proteins and ion channels using either cryo-electron microscopy (cryo-EM) or X-ray crystallography. Notably, in the past several years, I have focused on cryo-EM structural studies of Ca2+-permeable ion channels and, as a result, have published several important ion channel structures, including Transient receptor potential (TRP) channels (TRPV1 and TRPV4). In summary, I have demonstrated expertise and productivity in the field of structural and functional studies of integral membrane proteins and am well prepared to carry out the proposed research program.

1. Kwon D, Zhang F, McCray B, Feng S, Kumar M, Sullivan J, Im W, Sumner C, Lee S. TRPV4-Rho GTPase complex structures reveal mechanisms of gating and disease. Nature Communications. 2023 June 23; 14(1):-. Available from: https://www.nature.com/articles/s41467-023-39345-0 DOI: 10.1038/s41467-023-39345-0
2. Kwon D, Zhang F, Fedor J, Suo Y, Lee S. Vanilloid-dependent TRPV1 opening trajectory from cryoEM ensemble analysis. Nature Communications. 2022 May 24; 13(1):-. Available from: https://www.nature.com/articles/s41467-022-30602-2 DOI: 10.1038/s41467-022-30602-2
3. Kwon D, Zhang F, Suo Y, Bouvette J, Borgnia M, Lee S. Heat-dependent opening of TRPV1 in the presence of capsaicin. Nature Structural & Molecular Biology. 2021 July 08; 28(7):554-563. Available from: https://www.nature.com/articles/s41594-021-00616-3 DOI: 10.1038/s41594-021-00616-3
4. Kwon D, Park O, Kim L, Jung Y, Park Y, Jeong H, Hyun J, Kim Y, Song H. Insights into degradation mechanism of N-end rule substrates by p62/SQSTM1 autophagy adapter. Nature Communications. 2018 August 17; 9(1):-. Available from: https://www.nature.com/articles/s41467-018-05825-x DOI: 10.1038/s41467-018-05825-x

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2024 - Research Associate, Duke University School of Medicine, Durham, NC
2019 - 2024 Postdoctoral Associate, Duke University School of Medicine, Durham, NC

Honors

2019 - 2020 Basic Science Postdoctoral Fellowship, National Research Foundation of Korea (NRF)
2013 - 2015 Graduate Research Scholarship, National Research Foundation of Korea (NRF)
2007 - 2012 National Science & Technology Scholarship, Korea Student Aid Foundation (KOSAF)

2022 Outstanding Postdoc Award, Duke University School of Medicine
2021 KSMCB Travel Grant Awards, Korean Society for Molecular and Cellular Biology
2018 KU Achievement Awards, Korea University Graduate School
2012 Research Award, Korean Society for Biochemistry and Molecular Biology

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 temperature changes, ligands (e.g., irritants), and lipids, TRP channels regulate Ca2+ 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 this end, we have carried out structural studies of TRPV channels. We have determined the near-atomic structures of the TRPV1 and TRPV4 ion channels using cryo-electron microscopy (cryo-EM). Together with our functional studies, these structures led us to propose the mechanism of ligand-, temperature-, and lipid-dependent gating transitions in TRP channels.

    a. Kwon D, Zhang F, McCray B, Feng S, Kumar M, Sullivan J, Im W, Sumner C, Lee S. TRPV4-Rho GTPase complex structures reveal mechanisms of gating and disease. Nature Communications. 2023 June 23; 14(1):-. Available from: https://www.nature.com/articles/s41467-023-39345-0 DOI: 10.1038/s41467-023-39345-0
    b. Kwon D, Zhang F, Fedor J, Suo Y, Lee S. Vanilloid-dependent TRPV1 opening trajectory from cryoEM ensemble analysis. Nature Communications. 2022 May 24; 13(1):-. Available from: https://www.nature.com/articles/s41467-022-30602-2 DOI: 10.1038/s41467-022-30602-2
    c. Kwon D, Zhang F, Suo Y, Bouvette J, Borgnia M, Lee S. Heat-dependent opening of TRPV1 in the presence of capsaicin. Nature Structural & Molecular Biology. 2021 July 08; 28(7):554-563. Available from: https://www.nature.com/articles/s41594-021-00616-3 DOI: 10.1038/s41594-021-00616-3

2. 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 temperature changes, ligands (e.g., irritants), and lipids, TRP channels regulate Ca2+ 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 this end, we have carried out structural studies of TRPV channels. We have determined the near-atomic structures of the TRPV1 and TRPV4 ion channels using cryo-electron microscopy (cryo-EM). Together with our functional studies, these structures led us to propose the mechanism of ligand-, temperature-, and lipid-dependent gating transitions in TRP channels.

    a. Kwon D, Zhang F, McCray B, Feng S, Kumar M, Sullivan J, Im W, Sumner C, Lee S. TRPV4-Rho GTPase complex structures reveal mechanisms of gating and disease. Nature Communications. 2023 June 23; 14(1):-. Available from: https://www.nature.com/articles/s41467-023-39345-0 DOI: 10.1038/s41467-023-39345-0
    b. Kwon D, Zhang F, Fedor J, Suo Y, Lee S. Vanilloid-dependent TRPV1 opening trajectory from cryoEM ensemble analysis. Nature Communications. 2022 May 24; 13(1):-. Available from: https://www.nature.com/articles/s41467-022-30602-2 DOI: 10.1038/s41467-022-30602-2
    c. Kwon D, Zhang F, Suo Y, Bouvette J, Borgnia M, Lee S. Heat-dependent opening of TRPV1 in the presence of capsaicin. Nature Structural & Molecular Biology. 2021 July 08; 28(7):554-563. Available from: https://www.nature.com/articles/s41594-021-00616-3 DOI: 10.1038/s41594-021-00616-3

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Lee, Hyuk-Joon

eRA COMMONS USER NAME (credential, e.g., agency login): HYUKJLEE1

POSITION TITLE: Postdoctoral Fellow

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
Korea University, Seoul	BS	02/2018	Biochemistry
Korea University, Seoul	PHD	08/2023	Biochemistry
Duke University, Durham, North Carolina	Postdoctoral Fellow	present	Structural Biology and Biophysics

A. Personal Statement

I am interested in studying membrane proteins, especially detailed gating mechanism of channels. I've been working on Gap Junction Channel (GJC) during my Ph.D. course. I have made remarkable discoveries in Gap Junction field by determining over 20 structures having different conformations. For these results, I have trained and experienced various skills such as huge amount of culture using HEK293 cell lines, purification of various membrane proteins (detergents, amphipol, nanodisc), cryo-EM (grid reparation, microscope operation for data collection), data processing, and other biochemical studies. Now, I have just started to unveil structural mechanism for thermosensing of TRP channels.

1. Lee H, Cha H, Jeong H, Lee S, Lee C, Kim M, Yoo J, Woo J. Conformational changes in the human Cx43/GJA1 gap junction channel visualized using cryo-EM. Nature Communications. 2023 February 18; 14(1). Available from: https://www.nature.com/articles/s41467-023-36593-y DOI: 10.1038/s41467-023-36593-y

2. Lee S, Cho H, Jeong H, Ryu B, Lee H, Kim M, Yoo J, Woo J, Lee H. Cryo-EM structures of human Cx36/GJD2 neuronal gap junction channel. Nature Communications. 2023 March 11; 14(1). Available from: https://www.nature.com/articles/s41467-023-37040-8 DOI: 10.1038/s41467-023-37040-8

3. Lee H, Jeong H, Hyun J, Ryu B, Park K, Lim H, Yoo J, Woo J. Cryo-EM structure of human Cx31.3/GJC3 connexin hemichannel. Science Advances. 2020 August 28; 6(35). Available from: https://www.science.org/doi/10.1126/sciadv.aba4996 DOI: 10.1126/sciadv.aba4996

4. Park J, Chang J, Hwang H, Jeong K, Lee H, Ha H, Park Y, Lim C, Woo J, Kim Y. The pioneer round of translation ensures proper targeting of ER and mitochondrial proteins. Nucleic Acids Research. 2021 December 02; 49(21):12517-12534. Available from: https://academic.oup.com/nar/article/49/21/12517/6439695 DOI: 10.1093/nar/gkab1098

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2024 - Postdoctoral Fellow, Duke University
2023 - 2023 Post Doctoral Research Associate, Korea University

Honors

2019 - 2023 The Global Ph.D. Fellowship, National Research Foundation of Korea
2022 Best Poster Award, The 4th International Symposium of Structure-Based Drug Discovery
2022 Best Paper Award, Korea University

C. Contribution to Science

Until the late 2010s, there were only two determined structures of GJC (Cx26, Cx46) having same “open conformation” or “open state”. Thereby, despite the importance of protein, understanding molecular details have been remained elusive. In 2018, I started this project focused on Cx31.3 hemichannel (half channel) and Cx43 Gap Junction Channel (GJC). Up to now, I have devoted to elucidate the gating mechanism of GJC and I am proud to say that I have achieved some. Details are described below.

First, I solved the structure of Cx31.3 hemichannel at a resolution of 2.3 Å in 2019 (Sci. Adv., 2020). This was the first hemichannel (half channel) structure, and the channel structure with the highest resolution determined in Korea at that time. Cx31.3 hemichannel shows substantial structural changes of highly conserved regions in the connexin family, including entrance-covering N-terminal helix (NTH) conformation with a pore diameter of ~8 Å, and selectively transports chloride ions, which is completely different from the features of previously determined “open conformation”.

a. Lee H, Jeong H, Hyun J, Ryu B, Park K, Lim H, Yoo J, Woo J. Cryo-EM structure of human Cx31.3/GJC3 connexin hemichannel. Science Advances. 2020 August 28; 6(35). Available from: https://www.science.org/doi/10.1126/sciadv.aba4996 DOI: 10.1126/sciadv.aba4996

Second, I mainly focused on the structural study of Cx43 GJC for most of my Ph.D. course and determined over 20 structures with diverse conformations, leading to understand lipid-mediated gating mechanism. Cx43 is the most important connexin (Cx) and over 10,000 papers related to Cx43 have been published. In the past years, I found different NTH conformations of Cx43 GJC within same dataset, which was previously unknown, and the portion of different NTH conformations depend on the various factors such as pH, construct, and cholesteryl hemisuccinate (CHS) (Nat. Commu., 2023). Notably, while NTH shifts towards the “lipid-occluded closed state” in the CHS-rich condition, three different NTH conformations are dynamically mixed in the CHS-low condition. I found that membrane opening is formed between protomers during conformational change of NTH, giving structural insights in the role of lateral lipids movement for the channel gating. These findings elucidate the first detailed gating mechanism in the Gap Junction field which has never been thought previously, and will help accelerate drug developments for whom has malfunction in maintaining intercellular homeostasis such as arrhythmia and cancer.

a. Lee S, Cho H, Jeong H, Ryu B, Lee H, Kim M, Yoo J, Woo J, Lee H. Cryo-EM structures of human Cx36/GJD2 neuronal gap junction channel. Nature Communications. 2023 March 11; 14(1). Available from: https://www.nature.com/articles/s41467-023-37040-8 DOI: 10.1038/s41467-023-37040-8
b. Lee H, Cha H, Jeong H, Lee S, Lee C, Kim M, Yoo J, Woo J. Conformational changes in the human Cx43/GJA1 gap junction channel visualized using cryo-EM. Nature Communications. 2023 February 18; 14(1). Available from: https://www.nature.com/articles/s41467-023-36593-y DOI: 10.1038/s41467-023-36593-y

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/hyuk-joon.lee.1/bibliography/public/

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Won, Jongdae

eRA COMMONS USER NAME (credential, e.g., agency login): jwon01

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
Konkuk University, Seoul	BS	02/2018	Chemistry
Seoul National University, Seoul	PHD	08/2023	Biochemistry
Seoul National University, Seoul	Postdoctoral Fellow	12/2023	Structural Biochemistry

A. Personal Statement

During my graduate school years, I focused on researching the structure of transient receptor potential (TRP) channels, with a specific emphasis on the TRP canonical (TRPC) channels and their regulation using cryo-electron microscopy (cryo-EM). I successfully prepared various TRP channels and recently determined the TRPC5 ion channel structure in complex with G alpha proteins. I declare that I am well prepared to carry out the proposed research program.

1. Kim J, Won J, Chung D, Lee H. FRET analysis of the temperature-induced structural changes in human TRPV3. Scientific Reports. 2023 June 21; 13(1):-. Available from: https://www.nature.com/articles/s41598-023-36885-9 DOI: 10.1038/s41598-023-36885-9
2. Won J, Kim J, Jeong H, Kim J, Feng S, Jeong B, Kwak M, Ko J, Im W, So I, Lee H. Molecular architecture of the Gαi-bound TRPC5 ion channel. Nature Communications. 2023 May 03; 14(1):-. Available from: https://www.nature.com/articles/s41467-023-38281-3 DOI: 10.1038/s41467-023-38281-3

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2024 - Postdoctoral associate, Duke University School of Medicine, Durham, NC
2023 - 2023 Postdoctoral associate, Seoul National University, Seoul

Honors

2023 Best poster presenter award, Korean Society for Structural Biology

C. Contribution to Science

1. G-protein coupled receptors (GPCRs) and ion channels serve as key molecular switches through which extracellular stimuli are transformed into intracellular effects, and it has long been postulated that ion channels are direct effector molecules of the alpha subunit of G-proteins (Gα). However, no complete structural evidence supporting the direct interaction between Gα and ion channels is available. To provide structural insights into the ion channel regulation by direct Gα interactions, I determined the cryo-electron microscopy structures of the human transient receptor potential canonical 5 (TRPC5)-Gαi3 complexes with a 4:4 stoichiometry in lipid nanodiscs. The results demonstrate that ion channels are one of the direct effector molecules of Gα proteins triggered by GPCR activation–providing a structural framework for unraveling the crosstalk between two major classes of transmembrane proteins: GPCRs and ion channels.

a. Won J, Kim J, Jeong H, Kim J, Feng S, Jeong B, Kwak M, Ko J, Im W, So I, Lee H. Molecular architecture of the Gαi-bound TRPC5 ion channel. Nature Communications. 2023 May 03; 14(1):-. Available from: https://www.nature.com/articles/s41467-023-38281-3 DOI: 10.1038/s41467-023-38281-3

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Park, Cheon-Gyu

eRA COMMONS USER NAME (credential, e.g., agency login): CGPARK1

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
Chungbuk National University	BS	02/2013	Biochemistry
Daegu Gyeongbuk Institute of Sci & Tec, Daegu	PHD	02/2020	Brain Sciences
Duke University School of Medicine, Durham, North Carolina	Postdoctoral Fellow	present	Biochemistry

A. Personal Statement

During my Ph.D. degree, I focused on the study of ion channel and receptor modulation by membrane lipid metabolism in neuronal excitability and synaptic transmission. I led project, which used several approaches including optogenetics, FRET, molecular cloning, and electrophysiology that revealed the molecular dissection of the interplay between membrane PIP2 and auxiliary CaV β subunit on CaV channels. My first work identified that net surface charge of the flexible HOOK region of CaV β subunits performs important roles in determining the gating of CaV2.2 channels via dynamic electrostatic interaction with the plasma membrane. I also found that the CaV2.2 channels were regulated by PIP2 through at least two distinct interacting sites, including a nonspecific phospholipid binding motif in the distal I-II loop and the binding pocket in the S4II domain. I am currently working as a postdoctoral researcher, where I am studying regulation mechanism of TRPV1, TRPM3, and TRPM8 channels, incorporating cryo-EM structural studies into my electrophysiological studies.

1. Park C, Yu W, Suh B. Molecular basis of the PIP2-dependent regulation of CaV2.2 channel and its modulation by CaV β subunits. eLife. 2022 November 14; 11:-. Available from: https://elifesciences.org/articles/69500 DOI: 10.7554/eLife.69500
2. Yeon JH, Park CG, Hille B, Suh BC. Translocatable voltage-gated Ca(2+) channel β subunits in α1-β complexes reveal competitive replacement yet no spontaneous dissociation. Proc Natl Acad Sci U S A. 2018 Oct 16;115(42):E9934-E9943. PubMed Central PMCID: PMC6196550.
3. Park CG, Suh BC. The HOOK region of β subunits controls gating of voltage-gated Ca(2+) channels by electrostatically interacting with plasma membrane. Channels (Austin). 2017 Sep 3;11(5):467-475. PubMed Central PMCID: PMC5626366.
4. Park C, Park Y, Suh B. The HOOK region of voltage-gated Ca2+ channel β subunits senses and transmits PIP2 signals to the gate. Journal of General Physiology. 2017 February 01; 149(2):261-276. Available from: https://rupress.org/jgp/article/149/2/261/43587/The-HOOK-region-of-voltage-gated-Ca2-channel DOI: 10.1085/jgp.201611677

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2023 - Postdoctoral Associate, DUKE UNIVERSITY
2020 - 2023 Postdoctoral Researcher, DAEGU GYEONGBUK INSTITUTE/SCIENCE/TECH

C. Contribution to Science

1. Physiological role of CaV2 channel regulation by auxiliary CaV β subunit and membrane PIP2 in synaptic transmission.

Voltage-gated Ca2+ (CaV) channels that mediate Ca2+ influx upon membrane depolarization contribute to various physiological responses, including synaptic transmission, excitation-contraction coupling, and gene transcription. Especially, CaV2 channels are concentrated in the presynaptic nerve terminals and important for the neurotransmitter release. Activities of many ion channels are regulated by membrane phosphatidylinositol 4,5-bisphosphate (PIP2). CaV channels are differentially regulated by PIP2 in an auxiliary CaV β subunit-dependent manner. However, the molecular mechanism by which the CaV β subunits control the PIP2 sensitivity of CaV channels remains unclear. My work showed that net surface charge of the flexible HOOK region of CaV β subunits performs important roles in determining the gating of CaV2.2 channels via dynamic electrostatic interaction with the plasma membrane. The HOOK region of CaV β subunits can be further divided into three domains in accordance with amino acid compositions, poly-serine (S), poly-acidic (A), and poly-basic (B) domains. Acidic residues within the A domain accelerate current inactivation and increase PIP2 sensitivity of CaV2.2 channels, whereas basic residues within the B domain evoke opposite response. My work also investigated the inter-regulatory mechanism of the auxiliary CaV β subunit and membrane PIP2 on CaV2.2 channel gating. Two distinct PIP2-interacting sites were preserved in the CaV2.2 channel: the binding pocket in VSDII and nonspecific phospholipid-biding site in the distal end of the I-II loop. CaV2.2 channels complexed with any β isotype can interact with PIP2 through the binding pocket in the S4II domain. The additional interaction of PIP2 with the phospholipid-biding site in the I-II loop was mainly observed in CaV2.2 channels with the cytosolic β subunit. This converts the channels to a more PIP2-sensitive state. However, PIP2-binding to the I-II loop phospholipid-biding site is selectively disrupted by the lipid anchor of membrane-anchored β subunit. This converts the channels to a less PIP2-sensitive state. Based on this mechanism of CaV channel activity

a. Park C, Yu W, Suh B. Molecular basis of the PIP2-dependent regulation of CaV2.2 channel and its modulation by CaV β subunits. eLife. 2022 November 14; 11:-. Available from: https://elifesciences.org/articles/69500 DOI: 10.7554/eLife.69500

b. Yeon JH, Park CG, Hille B, Suh BC. Translocatable voltage-gated Ca(2+) channel β subunits in α1-β complexes reveal competitive replacement yet no spontaneous dissociation. Proc Natl Acad Sci U S A. 2018 Oct 16;115(42):E9934-E9943. PubMed Central PMCID: PMC6196550.

c. Park CG, Suh BC. The HOOK region of β subunits controls gating of voltage-gated Ca(2+) channels by electrostatically interacting with plasma membrane. Channels (Austin). 2017 Sep 3;11(5):467-475. PubMed Central PMCID: PMC5626366.

d. Park C, Park Y, Suh B. The HOOK region of voltage-gated Ca2+ channel β subunits senses and transmits PIP2 signals to the gate. Journal of General Physiology. 2017 February 01; 149(2):261-276. Available from: https://rupress.org/jgp/article/149/2/261/43587/The-HOOK-region-of-voltage-gated-Ca2-channel DOI: 10.1085/jgp.201611677