



**2023 1st
Structural Biology
LEDARE Workshop
in Sweden**

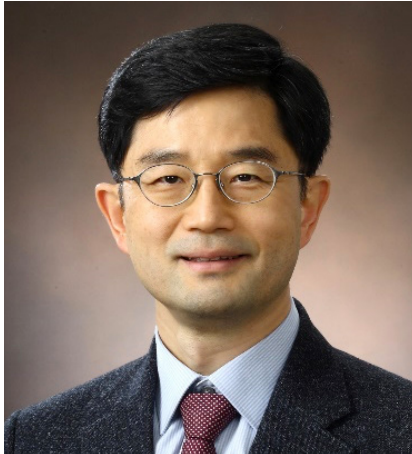
2023.2.8-2.9

Venue: Frösundavik SAS building, Solna

Nordic-Korea Structural Biology Ledare Symposium

Feb. 7		
19:00	Welcome Dinner at Royal Park Hotel, Solna, Stockholm	
Feb. 8		
9:30	Ji-Joon Song (KAIST)	Opening Remarks / Introduce Participants
Session 1 (Chair: Ji-Joon Song)		
9:40	Byung-Ha Oh (KAIST, Korea)	Computational design of functional proteins and structural validation
10:30	Matteo Dal Peraro (EPFL, Switzerland)	New methods for integrative structural biology
11:10	Hee-Jung Choi (Seoul National Univ. Korea)	Structural basis for receptor subtype-specific binding of neuropeptide Y
11:50	Sarah Butcher (University of Helsinki)	Maturation of Tick-Borne Encephalitis Virus
12:30	Lunch	
Session 2 (Chair: Byung-Ha Oh)		
13:30	Hans Hebert (KTH)	Interaction between cyclooxygenase 2 and microsomal prostaglandin E2 synthase 1
14:10	Jae-Sung Woo (Korea Univ., Korea)	Dynamic conformational changes in the human Cx43/GJA1 gap junction channel
14:50	Luca Jovine (Karolinska Institute)	From Egg-Sperm Interaction to Bacterial Infections on the Trail of the ZP Domain
15:50	FIKA- Coffee Break	
Session 3 (Chair: Hans Hebert)		
15:50	Myung Hee Kim (KRIBB)	Invasio mechanisms of bacterial MARTX toxin effectors
16:30	Carsten Mim (KTH)	The role of BAR domains in membrane and actin dynamics
17:10	Ji-Joon Song (KAIST)	Integrative Structural Study on Huntington's disease protein to reveal Huntingtin as a modular scaffolding machine
17:50	Closing Remarks	
18:30	Dinnar at Royal Park Hotel, Solna, Stockholm	
Feb. 9		
8:00	Breakfast & Discussion at Royal Park Hotel, Solna, Stockholm	

Byung-Ha Oh



Professor at the Department of Biological Sciences,
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Short Biography and Research Interest

Byung-Ha Oh is a Biochemist and Structural Biologist, doing protein design to create proteins for unmet biomedical or biotechnological needs. He completed his undergraduate studies at Seoul National University in Korea. For his Ph.D., he worked with Prof. John L. Markley at the University of Wisconsin-Madison in the USA, developing NMR methods for protein structure determination. For his postdoctoral training, he worked with Prof. Sung-Hou Kim at the University of California-Berkeley in the USA, studying the structural mechanisms underlying the transport of amino acids into bacterial cells. In 1994, he started his own laboratory at Pohang University of Science & Technology as an assistant professor. He moved to KAIST in 2009 at the Department of Biological Sciences, where he is currently working. His laboratory has developed a computational pipeline to discover antibodies that bind to a pre-defined surface of target proteins. This approach is showcased by discovering and developing a neutralizing antibody that binds to the receptor-binding domain (RBD) of the SARS-CoV-2 spike glycoprotein of all currently circulating variants of the virus, including Omicron, with potent affinity (pico- to femtomolar dissociation constants). Based on physics-based calculations and learning-based computations, he continues to design therapeutic proteins (including monoclonal antibodies) for cancer immunotherapy and neuropathological diseases.

Selected Publications

1. Structural basis for effector protein recognition by the Dot/Icm Type IVB coupling protein complex. Kim H, Kubori T, Yamazaki K, Kwak MJ, Park SY, Nagai H, Vogel JP, Oh BH. *Nat Commun.* 2020 May 26;11(1):2623.
2. De novo design of modular and tunable protein biosensors. Quijano-Rubio A, Yeh HW, Park J, Lee H, Langan RA, Boyken SE, Lajoie MJ, Cao L, Chow CM, Miranda MC, Wi J, Hong HJ, Stewart L, Oh BH*, Baker D*. *Nature.* 2021 Mar;591(7850):482-487. [*Corresponding authors]
3. Computational design of a neutralizing antibody with picomolar binding affinity for all concerning SARS-CoV-2 variants. Jeong BS, Cha JS, Hwang I, Kim U, Adolf-Bryfogle J, Coventry B, Cho HS, Kim KD, Oh BH. *MAbs.* 2022 Jan-Dec;14(1):2021601.
4. Computational design of an apoptogenic protein that binds BCL-xL and MCL-1 simultaneously and potently. Kim S, Park HS, Oh BH. *Comput Struct Biotechnol J.* 2022 Jun 14;20:3019-3029.
5. Structural basis for the broad and potent cross-reactivity of an N501Y-centric antibody against sarbecoviruses. Jeong BS, Jeon JY, Lai CJ, Yun HY, Jung JU, Oh BH. *Front Immunol.* 2022 Nov 17;13:1049867.

Abstract

Computational design of functional proteins and structural validation

In the endless protein fold space, nature has sampled only a “spot” of the space. Computational protein design enables the sampling of enormous protein fold space that has not been explored by nature. Since the function of a protein is determined by the three-dimensional structure of the protein, billions of new proteins with a novel function, in principle, can be generated by designing new protein folds. I will introduce examples of de novo protein design and protein-protein interface design with an aim to create novel proteins for therapy or diagnosis. In particular, I will talk about computational antibody design, which involves amino acid and protein docking and explores the amino acid sequences of the ‘complementary determining regions’ of antibodies. Combined with experimental validation and yeast surface display, the computational approach enabled the discovery of antibody against the spike protein of all circulating SARS-CoV-2 variants with pico- to femto-molar binding affinity.

Matteo Dal Peraro



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Short Biography and Research Interest

Matteo Dal Peraro graduated in Physics at the University of Padua in 2000. He obtained his Ph.D. in Biophysics at the International School for Advanced Studies (SISSA, Trieste) in 2004. He then received postdoctoral training at the University of Pennsylvania (Philadelphia). He joined EPFL School of Life Sciences in late 2007, where he is now Associate Professor. He served as Director of the Doctoral Programs in Biotechnology and Bioengineering (EDBB) and in Computational and Quantitative Biology (EDCB) and currently is the Associate Director of the Institute of Bioengineering (IBI).

His research at the Laboratory for Biomolecular Modeling (LBM), within the Institute of Bioengineering (IBI), now focuses on integrative structural biology and nanopore sensing. One of the main aims is understanding the physical and chemical properties of complex biological systems, in particular their function emerging from structure and dynamics using a broad spectrum of innovative computational methods fully integrated with experimental data. Multiscale simulations, dynamic integrative modeling and biophysical and structural studies are thus used to investigate the assembly and function of molecular complexes, mimicking the conditions of the native cellular environment. The functional knowledge acquired using this approach is eventually used to engineering biological systems for biotechnological applications, like using biological nanopores as single-molecule sensing devices for molecular detection.

Selected Publications

1. L Abrami, M Audagnotto, S Ho, MJ Marcaida, FS Mesquita, MU Anwar, PA Sandoz, G Fonti, F Pojer, M Dal Peraro, FG van der Goot, Molecular mode of action of an acyl protein thioesterase, *Nature Chemical Biology*, 17 (4), 438-447, 2021.
2. C Cao, L Krapp, A Al Ouahabi, N Konig, N Cirauqui, A Radenovic, J-F Lutz, M Dal Peraro, Aerolysin nanopores decode digital information stored in tailored macromolecular analytes, *Science Advances*, 6(50), eabc2661, 2020.
3. MJ Marcaida; A Kauzlaric; A Duperrex; J Sülzle; M Moncrieffe; D Adebajo; S Manley; D Trono; M Dal Peraro, The human RNA helicase DDX21 presents a dimerization interface necessary for helicase activity, *iScience*, 23(12), 101811, 2020.
4. T Yung, B Shin, G Tamo, H Kim, R Vijayvargia, A Leitner, MJ Marcaida, J Astorga-Wells, R Jung, R Aebbersold, M Dal Peraro, H Hebert, IS Seong, J-J Song, The polyglutamine expansion at the N-terminal of huntingtin modulates the dynamic configuration and phosphorylation of the C-terminal HEAT domain, *Structure*, i28(9):1035-1050, 2020.
5. LA Abriata, GE Tamò, M Dal Peraro, A further leap of improvement in tertiary structure prediction in CASP13 prompts new routes for future assessments, *Proteins: Structure, Function, and Bioinformatics*, 87 (12), 1100-1112, 2019
6. C Cao, N Cirauqui, MJ Marcaida, E Buglakova, A Duperrex, A Radenovic, M Dal Peraro, Single-molecule sensing of peptides and nucleic acids by engineered aerolysin nanopores, *Nature Communications*, 10(1):1-11, 2019

Abstract

Proteins are the major molecular building blocks of life, dictating the spatial and temporal occurrence of most biological functions. They ultimately encode the genetic information of every organism and translate it into the physical and chemical mechanisms at the basis of all the molecular processes sustaining living organisms. They have evolved to do so by specifically interacting with other proteins, nucleic acids, metabolites, membranes in order to form supramolecular complexes whose structural architecture is at basis of their biological function. In my lab we study the emergence of macromolecular function from its structural organization and native dynamics by integrating experimental data with molecular models and simulations. Recently, leveraging advances in computer vision and artificial intelligence, we have developed methods to efficiently address the outstanding problems of fitting molecular models into low-resolution cryo-electron microscopy data and predicting protein interacting interfaces.

Hee-Jung Choi



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Short Biography and Research Interest

Hee-Jung Choi majored in biochemistry and structural biology. She received her Ph.D. at the department of Chemistry, Seoul National University in 1997, and continued her research at Stanford University as a postdoctoral fellow and then as a research associate. During her stay at Stanford University, she studied beta2-adrenergic receptor, which is a target for asthma drug, and solved the crystal structures of the inactive and active states of the beta2-adrenergic receptor for the first time under supervision of Prof. Brian Kobilka (Nature 2007, Nature 2011). She was also involved in several structural projects on cell-cell adhesion and the Wnt signaling pathway under supervision of Prof. William Weis. Hee-Jung Choi started her own lab at Seoul National University in 2012. Hee-Jung Choi's research has focused on understanding the molecular mechanisms of (1) Wnt signaling and (2) G protein coupled receptor (GPCR) signaling through biochemical and structural analyses using X-ray crystallography and cryo-electron microscopy. As both Wnt and GPCR signaling pathways are implicated in various human diseases, and especially, GPCRs have been intensively studied as drug targets, structural information is expected to be utilized for drug development.

Selected Publications

1. Ko S.-B., Mihara E., Park Y., Roh K., Kang C., Takagi J., Bang I.*, Choi H.-J.* (2022). Functional role of the Frizzled linker domain in the Wnt signaling pathway. *Commun. Biol.*, 5(421). (*corresponding author)
2. Choi H.-K.†, Kang H.†, Lee C., Kim H.G., Phillips B.P., Park S., Tumescheit C., Kim S.A., Lee H., Roh S.-H., Hong H., Steinegger M., Im W., Miller E.A.*, Choi H.-J.*. Yoon T.-Y.* Evolutionary balance between foldability and functionality of a glucose transporter. (2022) *Nat. Chem. Biol.* 18:713-723. (*corresponding author)
3. Park C. †, Kim J. †, Ko S.-B., Choi Y.K., Jeong H., Woo H., Kang H., Bang I., Kim S.A., Yoon T.-Y., Seok C., Im W., Choi H.-J.* Structural basis of neuropeptide Y signaling through Y1 receptor. (2022) *Nat. Commun.* 13, 853. (*corresponding author)
4. Kim Jinuk, Han W., Park T., Kim E.J., Bang I., Lee H.S., Jeong Y., Roh K., Kim Jeesoo, Kim J.-S., Kang C., Seok C., Han J.-K., Choi H.-J.* Sclerostin inhibits Wnt signaling through tandem interaction with two LRP6 ectodomains. (2020) *Nat. Commun.* 11, 5357. (*corresponding author)
5. Choi, H.-K., Min, D., Kang, H., Shon, M. J., Rah, S.-H., Kim, H. C., Jeong, H., Choi, H.-J.*, Bowie, J. U.*, Yoon, T.-Y.* (2019) Watching helical membrane proteins fold reveals a common N-to-C-terminal folding pathway. *Science* 366, 1150–1156. (*corresponding author)

Abstract

Structural basis for receptor subtype-specific binding of neuropeptide Y

Neuropeptide Y (NPY) and its receptors play important roles in regulating appetite and emotion. Upon NPY stimulation, both the neuropeptide Y1 and Y2 receptors (Y1R and Y2R) activate the inhibitory G-protein signaling pathway, but their physiological responses to appetite control are reported to be quite different. That is, NPY binding to Y1R increases food intake, whereas NPY binding to Y2R decreases appetite. In addition, deletion of the N-terminal two amino acids of NPY significantly reduced Y1R-mediated signaling but not Y2R-mediated signaling, suggesting that Y1R and Y2R may have distinct NPY binding modes. Here, we report the cryo-electron microscopy (cryo-EM) structures of the NPY-Y1R-Gi and NPY-Y2R-Gi complexes at 3.2 and 3.1 Å resolution, respectively. Structural comparison between NPY-bound Y1R and Y2R, along with mutagenesis studies, provides the molecular basis for receptor subtype-specific interactions of NPY.

Sarah Butcher



Professor at University of Helsinki

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Short Biography and Research Interest

Prof Sarah Butcher has over 30 years' experience in cryoEM, structural biology and antiviral drug discovery primarily in academia. Currently, she is Professor of Microbiology, in a joint position between the Faculty of Biological and Environmental Sciences and the HiLIFE Institute of Biotechnology, University of Helsinki, Finland where she focusses on the structure and function of neglected and emerging viruses. She gained her PhD for work done in EMBL, Heidelberg, Germany on the cryoEM structures of lipid-containing bacteriophage, carried out a postdoctoral fellowship in the MRC Virology Unit in Glasgow, UK, and then moved to Finland where she started the country's first cryoEM unit in the late 1990's. She is an elected fellow of EMBO and the Finnish Society of Sciences and Letters. Currently she leads the Finnish Instruct Centre and is vice-chair of the Instruct-ERIC Council, which coordinates access to structural cell biology infrastructure across Europe.

Selected Publications

Pulkkinen, L. I. A. , Barrass, S. V. , Lindgren, M., Pace, H., Överby, A.K., Anastasina, M., Bally, M., Lundmark, R., Butcher, S.J. Simultaneous membrane and RNA binding by tick-borne encephalitis virus capsid protein. *PLOS Pathogens* (accepted)

Flatt, J.W., Domanska, A., Seppälä, A.L., Butcher, S.J. (2021) Identification of a conserved virion-stabilizing network inside the interprotomer pocket of enteroviruses. *Commun Biol* 4:250 <https://doi.org/10.1038/s42003-021-01779-x>

Cantuti-Castelvetri, L., Ojha, R., Pedro, L.D., Djannatian, M., Franz, J., Kuivanen, S., van der Meer, F., Kallio, K., Kaya, T., Anastasina, M., Smura, T., Levanov, L., Szivovics, L., Tobi, A., Kallio-Kokko, H., Österlund, P., Joensuu, M., Meunier, F.A., Butcher, S.J., Winkler, M.S., Mollenhauer, B., Helenius, A., Gokce, O., Teesalu, T., Hepojoki, J., Vapalahti, O., Stadelmann, C., Balistreri, G., Simons M. (2020) Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. *Science* 370:856-860 doi: 10.1126/science.abd2985

Abdelnabi, R., Geraets, J.A., Ma, Y, Mirabelli, C., Flatt, J.W. , Domanska, A., Delang, L., Jochmans, D., Jayaprakash, V., Sinha, B.N., Leyssen, P., Butcher, S.J., Neyts, J. (2019) A novel druggable interprotomer pocket in the capsid of rhino- and enteroviruses. *PLoS Biology* 17(6):e3000281.

Shakeel, S., Dykeman, E.C., White, S.J., Ora, A., Cockburn, J., Butcher, S.J., Stockley, P.G., Twarock, R. (2017) Genomic RNA folding mediates assembly of human parechovirus. *Nature Communications* 8:5. doi: 10.1038/s41467-016-0011-z. Direct link to the paper: <http://rdcu.be/pybT>

Abstract

Maturation of Tick-Borne Encephalitis Virus

Flaviviruses such as Dengue (DENV) or tick-borne encephalitis virus (TBEV) assemble into an immature form within the endoplasmic reticulum (ER), and are then processed by furin protease in the trans-Golgi. To understand flavivirus maturation, we carried out cryo-EM reconstructions of the immature and mature TBEV. By employing asymmetric localised reconstruction we were able to resolve the structures to 4 and 3 Å respectively, enabling us to model the crucial furin protease recognition site in the immature form, and critical residues for virion stability. We identify ordered lipids that are present only in the mature form, binding as a consequence of rearranging the membrane helices of the two membrane proteins, E and M during maturation.

Hans Hebert



Senior Professor at KTH

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Short Biography and Research Interest

Hans Hebert is a senior professor at School of Engineering Sciences in Chemistry, Biotechnology and Health, KTH Royal Institute of Technology in Stockholm. He received his PhD at Department of Biohysics, Karolinska Institutet (KI), formed his own group and moved to Department of Biosciences at KI. In between he spent two post-doc periods, the latter one as a Humboldt scholarship holder, at the Max Planck Institute of Biochemistry in Martinsried, Munich. Hans Hebert has been a professor at KTH since 2005 and dean at the KTH School of Technology and Health during 2013 -2017. His main research interest has mainly been related to membrane proteins. He moved early from X-ray crystallography to electron microscopy as the main technique for structural studies. Insights into the structure of P-type ATPases and the first structure of a membrane associated protein in eicosanoid and glutathione metabolism were results of EM-data from two-dimensional crystals. More recently single particle cryoEM has been applied to a variety of protein complexes.

Selected Publications

Kim H, Lenoir S, Helfricht A, Jung T, Karneva ZK, Lee Y, Beumer W, van der Horst GB, Anthonijsz H, Buil LCM, van der Ham F, Platenburg GJ, Purhonen P, Hebert H, Humbert S, Saudou F, Klein P, Song JJ (2022) A pathogenic proteolysis-resistant huntingtin isoform induced by an antisense oligonucleotide maintains huntingtin function, *JCI Insight* 7 (17).

Jung T, Shin B, Tamo G, Kim H, Vijayvargia R, Leitner A, Marcaida MJ, Astorga-Wells J, Jung R, Aebersold R, Dal Peraro M, Hebert H, Seong IS, Song JJ. (2020) The polyglutamine expansion at the N-terminal of Huntingtin protein modulates the dynamic configuration and phosphorylation of the C-terminal HEAT domain, *Structure* 28 (9), 1035-1050. e8.

Hebert H (2019) CryoEM: A crystals to single particles round-trip. *Curr. Opin. Struct. Biol.* 58, 59-67.

Trillo-Muyo S, Nilsson HE, Recktenwald CV, Ermund A, Ridley C, Meiss LN, Bähr A, Klymiuk N, Wine JJ, Koeck PJB, Thornton DJ, Hebert H, Hansson GC (2018) Granule-stored MUC5B mucins are packed by the non-covalent formation of N-terminal head-to-head tetramers, *J. Biol. Chem.* 293 (15), 5746-5754.

Söderberg CAG, Månsson C, Bernfur K, Rutsdottir G, Härmark J, Rajan S, Al-Karadaghi S, Rasmussen M, Höjrup P, Hebert H, Emanuelsson C (2018) Structural modelling of the DNAJB6 oligomeric chaperone shows a peptide-binding cleft lined with conserved S/T-residues at the dimer interface, *Sci. Rep.* 8 (1), 1-15.

Chen G, Abelein A, Nilsson HE, Leppert A, Andrade-Talavera Y, Tambaro S, Hemmingsson L, Roshan F, Landreh M, Biverstål H, Koeck PJB, Presto J, Hebert H, Fisahn A, Johansson J (2017) Bri2 BRICHOS client specificity and chaperone activity are governed by assembly state. *Nat. Commun.* 8 (1), 1-14.

Kuang Q, Purhonen P, Hebert H (2015) Structure of potassium channels. *Cell. Mol. Life Sci* 72 (19), 3677-3693.

Abstract

Interaction between cyclooxygenase 2 and microsomal prostaglandin E2 synthase 1

Cyclooxygenase and prostaglandin synthases play key roles in the cascade of events from inflammatory stimuli to pro-inflammatory response. Microsomal prostaglandin E2 synthase 1 (MPGES1) is an inducible enzyme integrated in ER and perinuclear membranes that takes the product from the monotopic cyclooxygenases (isoforms COX-1 or COX-2), prostaglandin H₂, and converts it into prostaglandin E₂. Previously we have determined the structure of MPGES1 in membrane bound form using electron crystallography. A large number of atomic models of cyclooxygenases are available. In the present work we have studied the complex of COX-2 and MPGES1 in nanodiscs using single particle cryoEM. Interestingly there is a symmetry mismatch since cyclooxygenases form dimers while MPGES1 like other members of the MAPEG (membrane associated proteins in eicosanoid and glutathione metabolism) superfamily are known to be trimers. A model of the assembly has been obtained that shed light on how the substrates are shuffled in the complex and on alternatives for specific inhibition at the terminal step of pro-inflammatory mediator production.

Jae-Sung Woo



Jae-Sung Woo, Ph.D.

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Short Biography and Research Interest

Dr. Woo is an associate professor in the Department of Life Sciences, Korea University. He received his PhD from POSTECH in 2007. During his PhD and postdoctoral training in POSTECH and ETH Zurich, he studied the structures and functions of anti-apoptotic proteins, E3 ubiquitin ligases, condensins, and ABC transporters. He started running an independent research group as a research fellow at the Center for RNA Research in IBS in 2013, and elucidated the structure of human Microprocessor, a key enzyme of microRNA biogenesis (2015 Cell and 2016 Cell). He further revealed the molecular mechanism underlying the single-nucleotide precision of this enzyme (2018 Mol. Cell).

After he joined Korea University in 2017, he started working on the structures and gating mechanisms of gap junction intercellular channels (GJICs). Direct intercellular communication through GJICs plays crucial roles in numerous biological processes including synchronized cardiac contraction, tissue development, and neurotransmission. While the regulation of channel activity by various cellular signals has been known for a long time, the underlying mechanism is still elusive. His group recently determined the structure of Cx31.3 gap junction hemichannel at 2.3 Å resolution by cryo-electron microscopy (2020 Sci. Adv.), which revealed a pore conformation impermeable to ATP but selectively permeable to anions. His group is currently dedicated to the study on Cx43 and Cx36 GJICs to understand the conformational changes required for channel gating.

Selected Publications

- Jeong YK, Lee SH, Hwang G-H, Hong S-A, Park S-E, Kim J-S, Woo J-S*, Bae S* (2021), Adenine base editor engineering reduces editing of bystander cytosines, *Nature Biotechnology* DOI: 10.1038/s41587-021-00943-2
- Lee HJ, Jeong H, Hyun J, Ryu B, Park K, Lim HH, Yoo J, Woo JS (2020), Cryo-EM structure of human Cx31.3/GJC3 connexin hemichannel, *Science Advances* 6(35):1–16
- Kwon SC, Baek SC, Choi Y-G, Yang J, Lee Y, Woo J-S*, Kim VN* (2019), Molecular Basis for the Single-Nucleotide Precision of Primary microRNA Processing, *Molecular Cell* 73:1–14
- Kwon SC, Nguyen TA, Choi YG, Jo MH, Hohng S, Kim VN*, Woo JS* (2016), Structure of Human DROSHA, *Cell* 164(1–2):81–90
- Nguyen TA, Jo MH, Choi Y-G, Park J, Kwon SC, Hohng S, Kim VN*, Woo J-S* (2015), Functional Anatomy of the Human Microprocessor, *Cell* 161(6):1374–1387

Abstract

Dynamic conformational change of Cx43 gap junction intercellular channel visualized by cryo-EM

Connexin family proteins assemble into hexameric hemichannels in a cell membrane, which dock together between two adjacent membranes to form gap junction intercellular channels (GJCs).

The most ubiquitously expressed connexin Cx43 plays important roles in numerous biological processes. We determined cryo-EM structures of Cx43 GJCs at 3.1-3.6 Å resolutions, which showed dynamic conformational changes of N-terminal helices (NTHs) caused by pH change or C-terminal truncation.

Cx43 GJC with gate-covering NTHs (GCNs) was closed by pore-occluding lipids, whereas those with varying compositions of GCNs and pore-lining NTHs (PLNs) showed various pore dimensions and electrostatic surface potentials. GCN-to-PLN transition accompanies π -helix formation in the first transmembrane helix (TM1), movement of TM2-4 that creates a side opening to the membrane, and structural stabilization of the cytoplasmic loop. Our study provides structural insights into the intercellular ion/metabolite transfer and the lateral lipid diffusion through Cx43 GJC.

Luca Jovine



Professor of Structural Biology, Karolinska Institutet
Member of EMBO and the Nobel Assembly

Short Biography and Research Interest

After studying molecular biology at the University of Milan, Italy, Luca Jovine was a Ph.D. student in the group of Dr. Kiyoshi Nagai at the MRC Laboratory of Molecular Biology in Cambridge. Here, he used molecular modeling and X-ray crystallography to study RNA and RNA-protein interactions of relevance to pre-mRNA splicing and the signal recognition particle. He then completely changed research direction by moving to the laboratory of Prof. Paul Wassarman at Mount Sinai School of Medicine in New York, where he began working on biochemical and cell biological aspects of mammalian fertilization proteins - a topic that deeply fascinated him since university. Upon starting his own group at Karolinska Institutet in 2005, Jovine combined his different expertise to launch a long-term investigation of the structural basis of egg-sperm interaction at fertilization. Through the determination of the first structures of egg coat proteins and egg coat-sperm protein complexes, this revealed an unexpected evolutionary conservation of the molecules that mediate animal gamete recognition. In parallel with these studies and investigations of gamete fusion, the group has also been focusing on human proteins of biomedical interest that are structurally similar to egg coat proteins but involved in completely different biological processes.

Selected Recent Publications

Stsiapanava A., Xu C., Nishio S., Han L., Carroni M., Tunyasuvunakool K., Jumper J., de Sanctis D., Wu B. and Jovine L.

Structure of the decoy module of human glycoprotein 2 and uromodulin and its interaction with bacterial FimH
Nat. Struct. Mol. Biol. 29:190-193 (2022)

Stsiapanava A., Xu C., Brunati M., Zamora-Caballero S., Schaeffer C., Bokhove M., Han L., Hebert H., Carroni M., Yasumasu S., Rampoldi L., Wu B. and Jovine L.

Cryo-EM structure of native human uromodulin, a zona pellucida module polymer
EMBO J. e106807 (2020) [bioRxiv 10.1101/2020.05.28.119206]

Raj I., Sadat Al Hosseini H., Dioguardi E., Nishimura K., Han L., Villa A., De Sanctis D. and Jovine L.

Structural basis of egg coat-sperm recognition at fertilization
Cell 169:1315-1326 (2017)

Han L., Monné M., Okumura H., Schwend T., Cherry A. L., Flot D., Matsuda T. and Jovine L.

Insights into egg coat assembly and egg-sperm interaction from the X-ray structure of full-length ZP3
Cell 143:404-415 (2010)

Monné M., Han L., Schwend T., Burendahl S. and Jovine L.

Crystal structure of the ZP-N domain of ZP3 reveals the core fold of animal egg coats
Nature 456:653-657 (2008)

From Egg-Sperm Interaction to Bacterial Infections on the Trail of the ZP Domain

What connects the union of gametes at fertilization, a fundamental process that ensures the transmission of genetic material through the generations, to the defense against pathogens causing urinary tract infection (UTI) — the most common type of non-epidemic bacterial infection in humans? In my talk, I will describe how our work on reproductive proteins led us to visualize uromodulin, the most abundant protein in human urine, as well as glycoprotein 2, a related defense molecule acting at the level of our gastrointestinal tract. By integrating cryo-EM, X-ray crystallography and AlphaFold modeling, these studies ultimately allowed us to shed light on the molecular basis of UTI prevention.

Myung Hee Kim



Director & Principal Research Scientist at the Microbiome Convergence Research Center, Korea Research Institute of Bioscience and Biotechnology (KRIBB)

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Short Biography and Research Interest

Myung Hee Kim is a Biochemist and Structural Biologist, studying the host-microbe/microbiome interactions. She completed her undergraduate studies in Food and Nutrition at Chungnam National University, Korea. She received her master`s and PhD degrees in Food Microbiology from the same university. Then, she moved to the US to pursue postdoctoral training at the University of Virginia, Charlottesville, Virginia, US. She worked with Prof. Zygmunt Derewenda at Department of Molecular Physiology and Biological Physics, studying the molecular mechanisms of neuronal migration. In 2006, she started her own lab at the Systems Microbiology Research Center in KRIBB. Currently, she is a Director and Principal Research Scientist at the Microbiome Convergence Research Center in KRIBB. Her lab has explored the cell signaling mechanisms underlying the pathogenesis of infection and the immune defense using a multidisciplinary approach involving structural biology, biochemistry, cell biology and immunology, as well as animal models. She has been also focused on the inter-kingdom signaling between gut microbiota and host immune, in particular, mediated by aminoacyl-tRNA synthetases.

Selected Publications (*Co-corresponding author)

1. Lee EY*, Kim SM, Hwang JH, Jang SY, Park S, Choi S, Lee GS, Hwang J, Moon JH, Fox PL, Kim S, Lee CH, Kim MH* (2022) Glutamyl-prolyl-tRNA synthetase 1 coordinates early endosomal anti-inflammatory AKT signaling. *Nature Communications* 13(1):6455
2. Lee Y, Kim BS, Choi S, Lee EY, Park S, Hwang J, Kwon Y, Hyun J, Lee C, Kim J, Eom S, Kim MH (2019) Makes caterpillars floppy-like effector-containing MARTX toxins require host ADP-ribosylation factor (ARF) proteins for systemic pathogenicity. *PNAS* 116(36):18031-18040
3. Jeong SJ, Park S, Nguyen LT, Hwang J, Lee EY, Giong HK, Lee JS, Yoon I, Lee JH, Kim JH, Kim HK, Kim D, Yang WS, Kim SY, Lee CY, Yu K, Sonenberg N, Kim MH*, Kim S* (2019) A threonyl-tRNA synthetase-mediated translation initiation machinery. *Nature Communications* 10(1):1357
4. Lee EY, Lee HC, Kim HK, Jang SY, Park SJ, Kim YH, Kim JH, Hwang J, Kim JH, Kim TH, Arif A, Kim SY, Choi YK, Lee C, Lee CH, Jung JU, Fox PL, Kim S, Lee JS*, Kim MH* (2016) Infection-specific phosphorylation of glutamyl-prolyl tRNA synthetase induces antiviral immunity. *Nature Immunology* 17(11):1252-1262
5. Hwang J, Suh HW, Jeon YH, Hwang E, Nguyen LT, Yeom J, Lee SG, Lee C, Kim KJ, Kang BS, Jeong JO, Oh TK, Choi I, Lee JO, Kim MH (2014) The structural basis for the negative regulation of thioredoxin by thioredoxin-interacting protein. *Nature Communications* 5:2958

Abstract

Invasion mechanisms of bacterial MARTX toxin effectors

Bacterial pathogens have the ability to deliver “effector” proteins into host cells to dysregulate a multitude of cell functions, thereby causing severe disease. In addition to the typical effector transfer systems, known as type III and IV secretion systems, many Gram-negative pathogenic bacteria utilize distinct effector transfer machineries, namely, multifunctional auto-processing repeats-in-toxin (MARTX) toxins. These toxins present across multiple bacterial genera are large proteins composed of approximately 3,500–5,300 amino acid residues that make up four distinct regions: the N-terminal repeat domain, the modularly structured multi-effector-containing domain, the cysteine protease domain (CPD), and the C-terminal repeat domain. Once secreted, MARTX toxins translocate to host cells via an unknown mechanism and undergo an event that releases functionally discrete effector domains in the cytosol. My lab has been exploring mechanisms by which the effectors circumvent host immunity and promote infection. In this talk, I will present our recent data showing molecular mechanisms underlying the role of the effectors in dysregulating signaling pathways critical for host defense and activating pathogenesis.

Carsten Mim



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Short Biography and Research Interest

Carsten Mim is an associate professor at the Royal Institute of Technology (KTH). He has a longstanding interest in processes at the membrane interface. He started his research as a PhD student in electrophysiology, in the lab of Christof Grever at the Max Planck Institute of Biophysics. They discovered a voltage sensitive step in EAAT4 that slows the turnover rate at a hyperpolarized membrane potential and increases EAAT4's apparent affinity. Those studies imply that EAAT4 acts as a glutamate sink in the periphery of the synapse.

To complement his skills, he learned electron microscopy from Dr. Vinzenz Unger at Northwestern University/ Yale University. There, he studied the molecular mechanisms of membrane remodelling by the BAR domain 'endophilin. This research demonstrated that the membrane is bent by a scaffold of degenerate protein interactions. Since starting his lab has been interested in the mechanisms that control the recruitment of membrane remodeling proteins and the interplay between membrane bending and actin dynamics.

Selected Publications

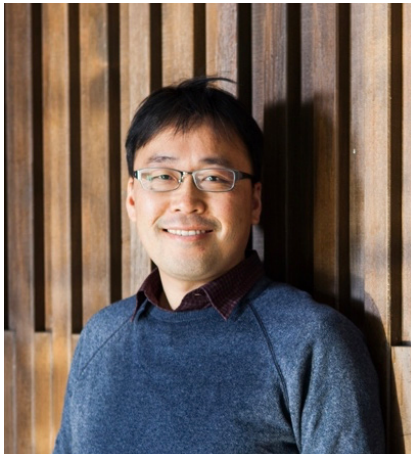
1. Wang Z, Mim C ‘CryoEM reveals BIN1 (isoform 8) does not bind to single actin filaments in vitro’ Micropublication Biology (2021)
2. Gowrisankaran S, Wang Z, Morgan DG, Milosevic I, Mim C ‘Cells Control BIN1-Mediated Membrane Tubulation by Altering the Membrane Charge.’ J Mol Biol. 432(4):1235-1250. (2019).
3. Farsi Z, Gowrisankaran S, Krunic M, Rammner B, Woehler A, Lafer E M, Mim C, Jahn R, Milosevic I, ‘Clathrin coat controls vesicle acidification by blocking vacuolar ATPase activity’ Elife. 2018 Apr 13;7 (2018)
4. Mim C, Cui H, Gawronski-Salerno JA, Frost A, Lyman E, Voth GA, Unger VM. ‘Structural basis of membrane bending by the N-BAR protein endophilin.’ Cell 149 (1), 137-145 (2012)
5. Mim C, Tao Z, Grewer C. ‘Two conformational changes are associated with glutamate translocation by the glutamate transporter EAAC1.’ Biochemistry. 2007 Aug 7;46(31):9007-18. (2007).

Abstract

The role of BAR domains in membrane and actin dynamics

Cell morphology and cell motility are basic properties of cells. Both phenomena require that cells undergo changes in membrane protein composition, as well as a manipulation of the membrane's shape and the underlying actin cytoskeleton. These processes are not only fundamental for cell biology but are particularly important in neuronal development and cancer. One of the cell's most versatile tools to achieve these tasks is the BIN1/Amphiphysin/Rvs (BAR) domain protein (BAR protein) family, which sense/induce membrane curvature. Interestingly, BAR proteins can control actin dynamics either by binding directly to actin or through recruitment of actin modulating proteins. We will present data to show how recruitment of these proteins is regulated and their action on membranes.

Ji-Joon Song



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Short Biography and Research Interest

Ji-Joon Song is a Professor in the Department of Biological Sciences at KAIST. He received his B.S. at Seoul National University, and his Ph.D. in structural biology with Leemor Joshua-Tor at Watson School of Biological Science, Cold Spring Harbor Laboratory. During his Ph.D., he determined the first structure of Argonaute involved in RNAi identifying the catalytic enzyme in RNAi. He then joined in Bob Kingston group as a research fellow at Massachusetts General Hospital, Harvard Medical School. The research in Song Lab at KAIST focuses on understanding the molecular mechanisms of epigenetic gene regulation using cryo-EM and other integrative structural approaches.

Selected publication

1. Kim, H., Lenoir, S., Helfricht, A., Jung, T., Karneva, Z.K., Lee, Y., Beumer, W., van der Horst, G.B., Anthonijsz., H., Buil, L., van der Ham, F., Platenburg, G.J., Purhonen, P., Hebert, H., Humbert, S., Saudou, F., Klein, P., Song, J.J., A pathogenic proteolysis-resistant huntingtin isoform induced by an antisense oligonucleotide maintains huntingtin function in mice. *JCI Insight* (2022).
2. Heo, Y., Yoon, E., Jeon, Y.-E., Yun, J.-H., Ishimoto, N., Woo, H., Park, S.-Y., *Song, J.J., *Lee, W., Cryo-EM structure of the human somatostatin receptor 2 complex with its agonist somatostatin delineates the ligand binding specificity. *eLife* (2022) (*Co-corresponding authors)
3. Jung, T.*, Shin, B.*, Tamo, G.*, Kim, H.*, Vijayvargia, R., Leitner, A., Marcaida, M.J., Astrorga-Wells, J., Jung, R., Aebersold, R., Dal Peraro, M., Hebert, H., Seong I.S., Song, J.J., The polyglutamine expansion at the N-terminal of huntingtin modulates the dynamic configuration and phosphorylation of the C-terminal HEAT domain. *Structure* (2020) (*equally contributed)
4. Cho, C., Jang, J., Kang, Y., Watanabe, H., Uchihashi, T., Kim, S.J., Kato, K., Lee, J.Y., Song, J.J., Structural basis of nucleosome assembly by the Abo1 AAA+ ATPase histone chaperone. *Nature Communications* (2019)
5. Kim G.J., Azmi, L.B., Jang, S., Jung, T., Hebert, H., Roe, A., Byron, O., Song, J.J., Aldehyde-alcohol dehydrogenase forms a high-order spirosome architecture critical for its activity. *Nature Communications* (2019)
6. Jang, S., Kang, C., Yang, H.-S., Jung, T., Hebert, H., Chung, K.Y., Kim, S.J., Hohng, S., Song, J.J., Structural basis of recognition and destabilization of histone H2B ubiquitinated nucleosome by DOT1L histone H3 Lys79 methyltransferase. *Genes & Development* (2019)
7. Song, J. J., Smith, S. K., Hannon, G. J., Joshua-Tor, L., Crystal structure of Argonaute and its implications for RISC Slicer activity. *Science* 305, 1434-1437(2004).

Abstract

Integrative Structural Study on Huntington's disease protein to reveal Huntingtin as a modular scaffolding machine.

Huntington's disease (HD) is a dominantly inherited neurodegenerative disease. The occurrence is 1 in 10,000 population and HD patients suffer the decade period of degeneration before deaths. This devastating disease is caused by the expansion of CAG repeats in HTT gene leading to polyglutamine (polyQ) expansion in Huntington's disease protein (HTT). HTT protein is shown to be required for proper development and neuronal homeostasis. However, despite the importance of HTT protein, little is known about the biological function of HTT protein. We have been investigating the biological function of HTT protein via integrative structural and biochemical approaches. We have shown that the polyQ expansion at the N-terminus of HTT leads to conformational change of the entire HTT protein and the phosphorylation patterns of HTT. In addition, we showed that HTT protein physically interacts with cytoskeleton protein and alters the organization of cytoskeleton. Furthermore, we determined the complex structure of HTT protein bound to cytoskeleton via cryo-electron tomography subtomogram averaging and revealed that HTT protein functions as a modular scaffolding machine. In this presentation, we will discuss our recent findings on the structure and function of HTT and our discovery of a means to control HD pathology.