BIOGRAPHICAL SKETCH

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NAME: Xiangdong Zheng

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

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)*	Completion Date MM/YYYY	FIELD OF STUDY
Harbin Institute of Technology, Weihai, China	B.S.	7/2008	Biochemistry
Tsinghua University, Beijing, China	M.S.	7/2011	Crystallography
Tsinghua University, Beijing, China	Ph.D.	6/2015	Crystallography
Tsinghua University, Beijing, China	Postdoctor	9/2018	Cryo-EM, Epigenetics
Columbia University, New York, NY, US	Postdoctor	12/2020	Cryo-EM, Ion Channel

A. Personal Statement

I have been working on protein structural biology since 2008 when I began my graduate study in the School of Medicine at Tsinghua University. My master thesis was on the crystal structure of esterase Rv0045c from *Mycobacterium tuberculosis* and my Ph.D. thesis was on the structural basis of the function of the centrosomal protein Sas-4/CPAP in centrosome duplication, through which I obtained extensive training and experience in protein crystallography and became proficient in all procedures in this field, including protein expression, purification and crystallization, X-ray diffraction data collection, phasing, model building and refinement, and structure analysis and presentation. During my Ph.D. training, I sought to illustrate two fundamental questions: how pericentriolar material (PCM) components were tethered, and how centriolar/ciliary-microtubule length was controlled by Sas4/CPAP during centrosome biogenesis. I solved the crystal structure of the TCP domain of Sas-4 and of the CPAP PN2-3 domain bound to an alpha/beta-tubulin dimer, which provided structural insights into the functions of Sas-4/CPAP in centrosome biogenesis.

After Ph.D training, I began to learn cryo-electron microscopy (cryo-EM) in the Center for Structural Biology at Tsinghua University, and I did a short period of postdoctoral research in the same lab. I worked on the project of determination of the structure of the *Saccharomyces cerevisiae* acetyltransferase SAGA complex. Through these years of training, I learned the technique of single particle analysis (SPA) and gained valuable experiences on negative staining, cryogenic specimen-preparation, data acquisition, image processing and 3D reconstruction. I purified the endogenous holoenzyme of the SAGA complex from *S. cerevisiae*, which is 1.8 MDa and composed of 19 subunits. Using SPA, we solved the cryo-EM structure of the SAGA complex at 6.9 Å resolution, with the largest subunit Tra1 resolved at 4.6 Å.

In September 2018, I joined Dr. Jian Yang's lab in the Department of Biological Sciences at Columbia University. From then on, I have been mainly focusing on the project about the structure, function and disease mechanisms of cyclic nucleotide-gated (CNG) channels and also participated in projects on structural studies of TRPML channels. During this period, I purified the full-length recombinant *Caenorhabditis elegans* CNG channel TAX-4, and reconstituted it in nanodiscs with or without cGMP. Collaborating with Dr. Joachim Frank's lab, we solved the cryo-EM structures of TAX-4 reconstituted in lipid nanodiscs in a cGMP-unbound closed state and a cGMP-bound open state at 2.6 Å and 2.7 Å resolutions, respectively. Our work observed a single double-barrier activation gate in the central cavity and a complete conformational trajectory from cGMP binding to the opening of the cavity gate. In the past year I have taken classes on cryo-EM, mastered all the essential

techniques of cryo-EM data collection and analyses, carried out cryo-EM experiments and analyses fully independently, and obtained ~10 high-resolution cryo-EM structures of TAX4 and TRPML channels.

Ongoing and recently completed projects that I would like to highlight include:

RO1 GM085234
Yang (PI)
09/04/19-08/31/23
Molecular physiology of TRPML channels

R01 EY027800
Yang (PI)
04/01/17-03/31/20
Molecular physiology of cyclic nucleotide-gated channels

Citations: (* indicates equal-contribution first authors; # indicates co-corresponding authors)

1. **Zheng X***, Gooi LM*, Wason A, Gabriel E, Mehrjardi NZ, Yang Q, Zhang X, Debec A, Basiri ML, Avidor-Reiss T, Pozniakovsky A, Poser I, Saric T, Hyman AA, Li H# & Gopalakrishnan J#. (2014) Conserved TCP domain of Sas-4/CPAP is essential for pericentriolar material tethering during centrosome biogenesis. ***Proc Natl Acad Sci U S A*** 111(3):E354-363. (PMCID: PMC3903230)
2. **Zheng X***, Ramani* A, Soni K, Gottardo M, Zheng S, Ming Gooi L, Li W, Feng S, Mariappan A, Wason A, Widlund P, Pozniakovsky A, Poser I, Deng H, Ou G, Riparbelli M, Giuliano C, Hyman AA, Sattler M, Gopalakrishnan J# & Li H#. (2016) Molecular basis for CPAP-tubulin interaction in controlling centriolar and ciliary length. ***Nat Commun*** 7:11874. (PMCID: PMC4912634)
3. Liu G*, **Zheng X***, Guan H*, Cao Y, Kang J, Qu H, Ren X, Lei J, Dong M, Li X & Li H. (2019) Architecture of *Saccharomyces cerevisiae* SAGA complex. ***Cell Discov*** 5:25. (PMCID: PMC6502868)
4. **Zheng X***, Fu Z*, Su D*, Zhang Y, Li M, Pan Y, Li H, Li S, Grassucci RA, Ren Z., Hu Z., Li X, Zhou M, Li G#, Frank J#, and Yang J#. (2020). Mechanism of ligand activation of a eukaryotic cyclic nucleotide-gated channel. ***Nat. Struc. Mol. Biol.*** 27, 625-634. (PMCID: PMC7354226)

B. Positions, Scientific Appointments, and Honors

Positions

12/20-present Associate Research Scientist, Columbia University, Dept. of Biological Sciences

C. Contribution to Science

1. During my master training, I primarily worked on the enzymatic and structural study of *M. tuberculosis* esterase Rv0045c. I contributed to expression, purification and crystallization of esterase Rv0045c (Xu et al., 2010), and determination of optimal catalytic condition and potential substrates for this enzyme (Guo et al., 2010). Beyond the biochemical study, I solved the crystal structure of esterase Rv0045c at 2.8 Å resolution, using the method of molecular replacement (Zheng et al., 2011). Combining docking analysis, I proposed that Rv0045c probably adopts two kinds of enzymatic mechanisms when hydrolyzing C-O ester bonds within substrates (Zheng et al., 2011). Our work provided structural insights into the hydrolysis mechanism of C-O ester bond, and will be helpful for understanding the ester/lipid metabolism in *M. tuberculosis*. I also contributed to crystallization of a novel cationic antimicrobial peptide cecropin B from *Bombyx mori* (Liu et al., 2010).
    a. Xu L, Guo J, **Zheng X**, Wen T, Sun F, Liu S & Pang H. (2010) Crystallization and preliminary X-ray analysis of a novel esterase Rv0045c from *Mycobacterium tuberculosis*. ***Acta Crystallogr Sect F*** 66(Pt 12):1579-1582. (PMCID: PMC2998358)
    b. Guo J*, **Zheng X***, Xu L, Liu Z, Xu K, Li S, Wen T, Liu S & Pang H. (2010) Characterization of a novel esterase Rv0045c from *Mycobacterium tuberculosis*. ***PLoS One*** 5(10):e13143. (*equal contribution) (PMCID: PMC2948520)

c. **Zheng X***, Guo J*, Xu L, Li H, Zhang D, Zhang K, Sun F, Wen T, Liu S & Pang H. (2011) Crystal structure of a novel esterase Rv0045c from *Mycobacterium tuberculosis*. ***PLoS One*** 6(5):e20506. (*equal contribution) (PMCID: PMC3102732)
d. Liu Z, Zhou Q, Mao X, **Zheng X**, Guo J, Zhang F, Wen T & Pang H. (2010) Crystallization and preliminary X-ray analysis of cecropin B from *Bombyx mori*. ***Acta Crystallogr Sect F*** 66(Pt 7):851-853. (PMCID: PMC2898478)

2. During my Ph.D. thesis, I worked on the molecular basis for function of Sas-4/CPAP in centrosome duplication. Sas-4/CPAP is one of over hundred centrosomal proteins that contribute to centrosome biogenesis. Two major functions have been explored for Sas-4/CPAP during centrosome biogenesis: one is to scaffold and tether PCM components to newly assembled centrioles, and the other one is to control the length of centriolar and ciliary microtubules. By solving the crystal structure of TCP domain of Sas-4 (Zheng et al., 2014) and the complex structure of CPAP PN2-3 domain bound to alpha/beta-tubulin dimer (Zheng et al., 2016), we are one of the two groups that simultaneously illustrated the molecular basis for Sas-4 TCP domain in PCM tethering and CPAP-tubulin interaction in centriolar/ciliary-microtubule length control. I performed total internal reflection fluorescence (TIRF) microscopy assay to analyze the PN2-3's bound-tubulin releasing ability and CPAP's microtubule polymerization ability *in vitro*. We are the first to discover two distinct mutations in PN2-3 domain that exhibit opposite effects on centriolar/ciliary-microtubule length (Zheng et al., 2016), which complemented our structural work and enabled us to probe into the molecular mechanism for CPAP-tubulin interaction in controlling centriolar and ciliary length. Moreover, I have contributed to structure determination of histone N-terminal methyltransferase NRMT1 (Wu et al., 2015) and methyltransferase SETD2 (Yang et al., 2016).
    a. **Zheng X***, Gooi LM*, Wason A, Gabriel E, Mehrjardi NZ, Yang Q, Zhang X, Debec A, Basiri ML, Avidor-Reiss T, Pozniakovsky A, Poser I, Saric T, Hyman AA, Li H & Gopalakrishnan J. (2014) Conserved TCP domain of Sas-4/CPAP is essential for pericentriolar material tethering during centrosome biogenesis. ***Proc Natl Acad Sci U S A*** 111(3):E354-363. (*equal contribution) (PMCID: PMC3903230)
    b. **Zheng X***, Ramani* A, Soni K, Gottardo M, Zheng S, Ming Gooi L, Li W, Feng S, Mariappan A, Wason A, Widlund P, Pozniakovsky A, Poser I, Deng H, Ou G, Riparbelli M, Giuliano C, Hyman AA, Sattler M, Gopalakrishnan J & Li H. (2016) Molecular basis for CPAP-tubulin interaction in controlling centriolar and ciliary length. ***Nat Commun*** 7:11874. (*equal contribution) (PMCID: PMC4912634)
    c. Wu R, Yue Y, **Zheng X** & Li H. (2015) Molecular basis for histone N-terminal methylation by NRMT1. ***Genes Dev*** 29(22):2337-2342. (PMCID: PMC4691888)
    d. Yang S, **Zheng X**, Lu C, Li GM, Allis CD & Li H. (2016) Molecular basis for oncohistone H3 recognition by SETD2 methyltransferase. ***Genes Dev*** 30(14):1611-1616. (PMCID: PMC4973290)

3. During my postdoctoral research in Center for Structural Biology at Tsinghua University, I mainly focused on cryo-EM architecture of *S. cerevisiae* SAGA complex. SAGA complex is one of the acetyltransferases in yeast and vertebrates, which is about 1.8 MDa and contains at least 19 subunits. The acetyltransferase SAGA plays important role in gene transcription by RNA polymerase II and was determined to be a general coactivator. We purified the intact SAGA holoenzyme from *S. cerevisiae* and solved the cryo-EM structure of SAGA at 6.9 Å resolution using the method of single particle analysis (Zheng et al., 2018). We also resolved the cryo-EM structure of the largest subunit Tra1 at 4.7 Å resolution. Our work depicted the overall spatial arrangement of SAGA components and provided insights into the molecular architecture and functional model of SAGA complex.

    Besides, I was able to prepare native histone proteins (H2A, H2B, H3 and H4), K9 tri-methylated H3 histone protein and chromatin DNA template with high purity and quality, and to reconstitute chromatin fibers containing twelve nucleosome repeats which was determined by negative staining. The high quality of chromatin fibers is crucial to perform phase separation assays with reliable and repeatable results *in vitro*. By doing so, I contributed to phase separation studies of heterochromatin formation by ADCP1 in plant (Zhao et al., 2019) and HP1 in animals (Wang et al., 2019).
    a. Liu G*, **Zheng X***, Guan H*, Cao Y, Kang J, Qu H, Ren X, Lei J, Dong M, Li X & Li H. (2019) Architecture of *Saccharomyces cerevisiae* SAGA complex. ***Cell Discov*** 5:25. (*equal contribution) (PMCID: PMC6502868)

b. Zhao S, Cheng L, Gao Y, Zhang B, **Zheng X**, Wang L, Li P, Sun Q, Li H. (2019) Plant HP1 protein ADCP1 links multivalent H3K9 methylation readout to heterochromatin formation. ***Cell Res*** 29(1):54-66. (PMCID: PMC6318295)
c. Wang L*, Gao Y*, **Zheng X***, Liu C, Dong S, Li R, Zhang G, Wei Y, Qu H, Li Y, Allis CD, Li G, Li H & Li P. (2019) Histone modifications regulate chromatin compartmentalization by contributing to a phase separation mechanism. ***Mol Cell*** Under revision. (*equal contribution)

4. During my postdoctoral research in Dr. Jian Yang's lab in the Department of Biological Sciences at Columbia University. I focused on investigating the molecular mechanisms of ion permeation, gating and channelopathy of CNG channels. I figured out the key points for nanodisc reconstitution of full-length *C. elegans* CNG channel TAX-4, and prepared TAX-4-nanodisc complexes with/without cGMP. With collaboration of Dr. Joachim Frank's lab, we solved the cryo-EM structures of TAX-4 reconstituted in lipid nanodiscs in a cGMP-unbound closed state and a cGMP-bound open state at 2.6 Å and 2.7 Å resolutions, respectively. Our work observed a single double-barrier activation gate in the central cavity and a complete conformational trajectory from cGMP binding to the opening of the cavity gate. Through this project, I mastered the basics of single particle cryo-EM experiments, including data collection, image processing and 3D reconstruction, and accordingly, was able to carry out cryo-EM experiments independently. I have also been involved in projects to solve the cryo-EM structures of TRPML channels. In the past two years I have taken classes on cryo-EM, mastered all the essential techniques of cryo-EM data collection and analyses, carried out cryo-EM experiments and analyses fully independently, and obtained ~10 high-resolution cryo-EM structures of TAX4 and TRPML channels. Two papers are in preparation.
    a. **Zheng X***, Fu Z*, Su D*, Zhang Y, Li M, Pan Y, Li H, Li S, Grassucci RA, Ren Z., Hu Z., Li X, Zhou M, Li G, Frank J, and Yang J. (2020). Mechanism of ligand activation of a eukaryotic cyclic nucleotide-gated channel. ***Nat. Struc. Mol. Biol.*** 27, 625-634. (*equal contribution) (PMCID: PMC7354226)

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https://www.ncbi.nlm.nih.gov/myncbi/xiangdong.zheng.1/bibliography/public/

BIOGRAPHICAL SKETCH

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NAME: Jian Yang

eRA COMMONS USER NAME (credential, e.g., agency login): jianyang160

POSITION TITLE: Professor of Biological Sciences

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
Peking University, Beijing, China	B.S.	06/1982	Biophysics
Shanghai Brain Research Institute, China	M.S.	07/1985	Neurophysiology
University of Washington, Seattle, WA	Ph.D.	06/1991	Physiol. & Biophy.
Stanford University, Stanford, CA	Postdoctor	12/1993	Ca^{2+} Channels
UCSF, San Francisco, CA	Postdoctor	12/1996	K^+ Channels

A. Personal Statement

I have been working on ion channels since graduate school. For my PhD thesis in Bertil Hille's lab, I characterized the biophysical properties of 5-HT3 receptor channels. My postdoc work in Dick Tsien's lab was focused on figuring out "what makes a calcium channel a calcium channel", as we used to say in the Tsien lab. During my second postdoc in Lily Jan's lab, I learned much more ion channel molecular biology and worked on the subunit stoichiometry of inward rectifier potassium (Kir) channels and the molecular determinants of inward rectification and ion permeation. After establishing my own lab at Columbia in 1997, I initially continued to work on Kir channels, primarily by using mutagenesis and patch clamp. In 2000, I returned to work on voltage-gated calcium channels (VGCCs), and in 2004, we also started to work on TRP channels. In 2002, spurred by the spectacular crystallographical studies of Rod MacKinnon on potassium channels, I decided to do X-ray crystallography in my own lab, which we have been doing ever since. In 2014, we began to do cryo-EM, this time inspired by the stunning success of the TRPV1 cryo-EM structure obtained by David Julius and Yifan Cheng and frustrated by many years of failure to get a crystal structure of a full-length channel. I consider these career moves important, timely, exciting and rewarding. In 2011, in collaboration with the Kunming Institute of Zoology (KIZ) of the Chinese Academy of Sciences, and with approval and support of my department, I set up an Ion Channel Research and Drug Development Center (ICDC) at KIZ, with the main goal of discovering natural products of therapeutic potential and/or as research tools that target ion channels. I collaborate with ICDC as a visiting investigator with strict adherence to NIH and Columbia University policies. No NIH funds have been or will be used at ICDC, and no grant at ICDC overlaps with my past and present NIH-sponsored projects.

My research focuses on the structure, function, regulation, disease mechanisms and drug discovery of calcium-conducting channels, including VGCCs, TRP channels and cyclic nucleotide-gated (CNG) channels. We strive to better understand how these channels work as molecular machines and how they control and regulate diverse physiological and pathological processes. Our past work touched upon the pore architecture of VGCCs, the location of the activation gate, the crystal structure of VGCC β subunits, the identification of novel $Ca_V\beta$ interacting proteins, the molecular mechanisms of regulation of VGCCs by PIP_2, G proteins, RGK proteins and proteolysis, the molecular mechanisms of the assembly of TRPP/PKD complexes, the structural basis of regulation and function of TRPML channels, and the structure, function and disease mechanisms of

CNG channels. We use various approaches in our research, including molecular biology, biochemistry, cell biology, electrophysiology, calcium imaging, confocal microscopy, X-ray crystallography and cryo-EM. We have the necessary motivation, expertise, tools and collaboration to carry out the proposed projects. This is further demonstrated by the large amount of preliminary data we have gathered for this application. I have over 38 years of research experience (starting when I was a M.S. student). I have had continuous NIH grant support since establishing my own lab, and I am the PI of an ongoing and eight completed RO1s. Thus, I have the required leadership skill and experience in organizing, executing and completing research projects.

Ongoing and recently completed projects that I would like to highlight include:

RO1 GM085234
Yang (PI)
09/04/19-08/31/23
Molecular physiology of TRPML channels

R01 EY027800
Yang (PI)
04/01/17-03/31/20
Molecular physiology of cyclic nucleotide-gated channels

Citations: (* indicates equal-contribution first authors; #indicates co-corresponding authors)

1. Zheng, X.*, Fu, Z.*, Su, D.*, Zhang Y., Li, M., Pan, Y., Li, H., Li, S., Grassucci, R.A., Ren, Z, Hu, Z., Li, X., Zhou, M., Li, G.#, Frank, J.#, and **Yang, J.#** (2020). Mechanism of ligand activation of a eukaryotic cyclic nucleotide-gated channel. ***Nat. Struc. Mol. Biol.*** 27, 625-634. (PMCID: PMC7354226)
2. Li, M-h.*, Zhou, X.*, Wang, S.*, Michailidis, I.E., Gong, Y., Su, D., Li, H., Li, X.#, and **Yang, J.#** (2017). Structure of a eukaryotic cyclic nucleotide-gated channel. **Nature** 542, 60-65. (PMCID: PMC5783306)
3. Michailidis, I.E., Abele, K., Zhang, W.K., Lin, B., Yu, Y., Geyman, L., Ehlers, M.D., Pnevmatikakis, E.A., and **Yang J.** (2014). Age-related homeostatic midchannel proteolysis of L-type voltage-gated Ca^{2+} channels. ***Neuron*** 82, 1045-1057. (PMCID: PMC4052215)
4. Wu, L.*, Bauer, C*., Zhen, X-G., Xie, C., and **Yang, J.** (2002). Dual regulation of voltage-gated calcium channels by PIP_2. ***Nature*** 419, 947-952.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2015 – present	Editorial Board, Journal of Physiology (London)
2015 – present	Editorial Board, Channels (Canada)
2015	NIH NTRC Study Section, ad hoc reviewer
2014 – 2017	Editorial Board, Zoological Research (Kunming, China)
2011 – present	Visiting Investigator, Ion Channel Research and Drug Development Center, Kunming Institute of Zoology, Chinese Academy of Sciences, Kunming, China
2009 – present	Professor, Columbia University, Dept. of Biological Sciences, New York, NY
2004 – 2008	NIH NTRC Study Section, Regular member
2004 – 2010	Editorial Board, Biophysical Journal
2004	NIH NTRC Study Section, ad hoc reviewer
2003	NIH NTRC Study Section, ad hoc reviewer
2002 – 2009	Associate Professor, Columbia University, Dept. of Biological Sciences, New York, NY
1997 – 2002	Assistant Professor, Columbia University, Dept. of Biological Sciences, New York, NY
1985 – 1987	Visiting Scholar, Colorado State University, Dept. of Neurobiology & Anatomy, Ft. Collins, CO

Honors

1997-1999 Sloan Research Fellow, Alfred P. Sloan Foundation
2000-2003 McKnight Scholar Award, The McKnight Endowment Fund for Neuroscience
2002-2004 EJLB Scholar, The EJLB Foundation
2004-2008 Established Investigator Award, The American Heart Association

C. Contribution to Science

5. My early work as an independent junior PI centered on inward rectifier potassium (Kir) channels. It was an exciting time to work on potassium channels, especially after the publication of the first crystal structure of an ion channel by Rod MacKinnon. Compared to what was known about voltage-gated potassium channels, much less was known about the assembly, pore architecture and location of the activate gate in Kir channels. Using cysteine chemical modification, we discovered that the Kir channel pore is 12 Å wide (Lu et al., 1999a). We also demonstrated that the cytoplasmic domains of Kir channels form a long and wide intracellular vestibule that protrudes beyond the membrane into the cytoplasm (Lu et al., 1999b), a finding later confirmed by crystal structures of Kir channels obtained by other laboratories. Moreover, using the cutting-edge technology of unnatural amino acid mutagenesis, we engineered artificial amino acids into Kir channels and demonstrated directly that the K^+ selectivity filter is dynamic and regulates Kir channel gating (Lu et al., 2001). This work indicates that the selectivity filter of Kir channels can function as a gate, a conclusion further supported by our later work showing the lack of state-dependent modification of cysteines residues engineered below the selectivity filter by intracellular thiol-specific reagents (Xiao et al., 2003).
    a. Lu, T., Zhang, X-M., Nguyen, B., and **Yang, J.** (1999). Architecture of a K^+ channel inner pore revealed by stoichiometric covalent modification. ***Neuron*** 22, 571-580.
    b. Lu, T., Zhu, Y-G., and **Yang, J.** (1999). Cytoplasmic amino and carboxyl domains form a wide internal vestibule in an inwardly rectifying K^+ channel. ***Proc. Natl. Acad. Sci.*** 96, 9926-9931.
    c. Lu, T., Ting, A.Y., Mainland, J., Jan, L.Y., Schultz, P.G., and **Yang, J**. (2001). Probing ion permeation and gating in a K^+ channel with backbone mutations in the selectivity filter. ***Nature Neurosci.*** 4, 239-246.
    d. Xiao, J., Zhen, X-G., and **Yang, J.** (2003). Localization of PIP_2 activation gate in inward rectifier K^+ channels. ***Nature Neurosci.*** 6, 811-818.

6. We have made three major discoveries in the study of voltage-gated calcium channels (VGCCs): (1) We are the first to discover that VGCCs are regulated by PIP_2 (Wu et al., 2002), providing mechanistic insights into the regulation of VGCCs by Gq-coupled receptors; (2) We are one of the three groups that simultaneously solved the first crystal structure of the beta subunit of VGCCs (Chen et al., 2004), which is essential for trafficking the channel complex to the plasma membrane and fine-tuning channel biophysical properties. The structure overturns a then widely accepted and long-held doctrine regarding where and how the alpha 1 and beta subunits interact; (3) We discovered that the alpha 1 subunit of neuronal L-type VGCCs undergoes a novel form of age- and activity-dependent proteolysis (called midchannel proteolysis) in the pore-forming core region (Michailidis et al., 2014), providing novel molecular insights into neuronal calcium homeostasis and neuroprotection. Each of these discoveries leads to new concepts and new research areas.
    a. Wu, L.*, Bauer, C*., Zhen, X-G., Xie, C., and **Yang, J.** (2002). Dual regulation of voltage-gated calcium channels by PIP_2. ***Nature*** 419, 947-952.
    b. Chen, Y-h., Li, M-h., Zhang, Y., He., L-l., Yamada, Y., Fitzmaurice, A., Shen, Y., Zhang, H., Tong, L., and **Yang, J.** (2004). Structural basis of the α_1–β interaction of voltage-gated Ca^{2+} channels. ***Nature*** 429, 675-680.
    c. Michailidis, I.E., Abele, K., Zhang, W.K., Lin, B., Yu, Y., Geyman, L., Ehlers, M.D., Pnevmatikakis, E.A., and **Yang J.** (2014). Age-related homeostatic midchannel proteolysis of L-type voltage-gated Ca^{2+} channels. ***Neuron*** 82, 1045-1057. (PMCID: PMC4052215)

7. In recent years, we have made significant contributions to the understanding of the structure and function of TRPP/PKD complexes. These ion channel/receptor complexes play critical roles in calcium signaling in cells. They are relatively new, and much is unknown about them. Mutations in these complexes cause human diseases, such as autosomal dominant polycystic kidney disease (ADPKD), one of the most

common genetic diseases in humans. Using a multipronged approach that includes biochemistry, electrophysiology, single molecule optical imaging, X-ray crystallography and computational modeling, we have elucidated the molecular mechanisms of the assembly of the TRPP2/PKD1 and TRPP3/PKD1L3 complexes (Yu et al., 2009; Jiang et al., 2011; Yu et al., 2012). A prevailing view in the PKD field was that PKD proteins are membrane receptors, not ion channels, and that they play a regulatory role in TRPP/PKD complexes. Our work indicates that PKD1L3 is in fact a channel-forming protein, directly lining the pore of the TRPP3/PKD1L3 complex (Yu et al., 2012). Our studies have significant implications for the regulation and function of TRPP/PKD complexes and for the pathogenic mechanisms of ADPKD.

a. Yu, Y., Ulbrich, M.H., Li, M-h., Chen, X-Z., Ong, A.C.M., Tong, L., Isacoff, E.Y., and **Yang, J.** (2009). Structural and molecular basis of the assembly of the TRPP2/PKD1 complex. ***Proc. Natl. Acad. Sci.*** 106, 11558-11563. (PMCID: PMC2710685)
b. Zhu, J.*, Yu, Y.*, Ulbrich, M.H., Li, M-h., Isacoff, E.Y., Honig, B., and **Yang, J**. (2011). A structural model of the TRPP2/PKD1 C-terminal coiled-coil complex produced by a combined computational and experimental approach. ***Proc. Natl. Acad. Sci.*** 108, 10133-10138. (PMCID: PMC3121833)
c. Yu, Y., Ulbrich, M.H., Dobbins, S. Li, M-h., Zhang, W.K., Tong, L., Isacoff, E.Y., and **Yang, J.** (2012). Molecular mechanism of the assembly of an acid-sensing receptor/ion channel complex. ***Nat. Commun.*** 3:1252. doi: 10.1038/ncomms2257. (PMCID: PMC3575195)

8. In 2017 we obtained a 3.5 Å-resolution cryo-EM structure of a full-length eukaryotic cyclic nucleotide-gated (CNG) channel (Li et al., 2017a). This was the first high-resolution structure of this distinct subfamily of ion channels. We have recently obtained high-resolution structures of both closed and open states of the same CNG channel (Zheng et al., 2020). These structures provide insights into CNG channel ion permeation, gating and channelopathy. In recent years we have also been working on the structure, function and regulation of TRPML1 and TRPML3 channels. These channels function as calcium channels in endosomes and lysosomes and are crucial for cellular physiology. Mutations in TRPML1 cause mucolipidosis type IV, a rare but devastating lysosomal storage disorder in humans, and mutations in TRPML3 cause deafness and pigmentation defects in mice. We have determined high-resolution structures of a functionally important luminal domain of TRPML1 (Li et al., 2017b) and the full length TRPML3 (Zhou et al., 2017) under various pH conditions or in different states.
    a. Li, M-h.*, Zhou, X.*, Wang, S.*, Michailidis, I.E., Gong, Y., Su, D., Li, H., Li, X.[#], and **Yang, J.**[#] (2017a). Structure of a eukaryotic cyclic nucleotide-gated channel. ***Nature*** 542, 60-65.(PMCID: PMC5783306)
    b. Li, M-h.*, Zhang, W,K.*, Benvin, N*., Zhou, X., Su, D., Wang, S., Michailidis, I.E., Tong, L., Li, X.[#], and **Yang, J**.[#] (2017b). Structural basis of Ca^{2+}/pH dual regulation of the endolysosomal Ca^{2+} channel TRPML1. ***Nat. Struc. Mol. Biol.*** 24, 205-213. (PMCID: PMC5336481)
    c. Zhou, X.*, Li, M-h.*, Su, D.*, Li, H., Jia, Q., Li, X.[#], and **Yang, J.**[#] (2017). Cryo-EM structures of the human endolysosomal TRPML3 channel in three distinct states. ***Nat. Struc. Mol. Biol.*** 24, 1146-1154. (PMCID: PMC5747366)
    d. Zheng, X.*, Fu, Z.*, Su, D.*, Zhang Y., Li, M., Pan, Y., Li, H., Li, S., Grassucci, R.A., Ren, Z, Hu, Z., Li, X., Zhou, M., Li, G.[#], Frank, J.[#], and **Yang, J.**[#] (2020). Mechanism of ligand activation of a eukaryotic cyclic nucleotide-gated channel. ***Nat. Struc. Mol. Biol.*** 27, 625-634. (PMCID: PMC7354226)

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