BIOGRAPHICAL SKETCH

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NAME: Yuan, Peng

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

POSITION TITLE: Professor of Pharmacological 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
University of Science & Technology of China	B.S.	07/1997	Physics
University of Pennsylvania, Philadelphia, PA	Ph.D.	08/2008	Biochemistry and Molecular Biophysics
The Rockefeller University, New York, NY	Postdoctoral	08/2013	Molecular Neurobiology and Biophysics

A. Personal Statement

I am a structural biologist and membrane biophysicist, and my expertise includes X-ray crystallography, single-particle cryo-electron microscopy, membrane protein biochemistry and biophysics, and ion channel electrophysiology. Selective transport of ions, drugs and folded proteins across cell membranes, mediated by membrane transport proteins, is a fundamental biological process. As an independent investigator since 2013, my research interest is in developing new approaches and tools to study molecular mechanisms of ion channels and transporters and membrane enzymes that play central roles in physiology and disease. How do ion channels and transporters recognize their specific substrate ions? How do channels open and close their ion conduction pores in response to environmental cues and cellular stimuli, including chemicals, temperature, membrane voltage and mechanical force? To answer these fundamental questions, my lab uses multidisciplinary approaches, including electrophysiology, biochemical and biophysical assays, and structural techniques including X-ray crystallography and cryo-electron microscopy. Dysfunction of these membrane proteins leads to a wide range of diseases, including neurodegeneration, asthma, hypertension, cancer, diabetes, heart failure, and chronic pain. My long-term goal is to advance our understanding of structure and function of these essential membrane proteins at the atomic level and establish new foundations for rational therapies. My laboratory, combining multidisciplinary approaches, is capable of providing an integrative understanding of structure and function of challenging membrane proteins. Recently, my laboratory has advanced understanding of structure and mechanism of a number of important membrane proteins, including transient receptor potential (TRP) channels, bacterial outer-membrane pilus assembly machinery, copper transporters, proton-activated chloride channels, pannexin channels, and mechanosensitive channels. My experience and qualifications are highlighted in the following representative projects and publications.

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

R01 NS099341
Yuan (PI)
06/15/17 - 01/17/23
Structure and mechanism of a polymodal TRP ion channel

R01 NS109307

Yuan (PI)
09/30/18 - 06/30/24
Molecular mechanisms of copper transport

R01 GM143440
Yuan (PI)
09/01/22 - 06/30/26
Structural Mechanism for Gating of Mechanosensitive Channels

Citations:

1. Deng Z, Maksaev G, Rau M, Xie Z, Hu H, Fitzpatrick JAJ, **Yuan P**. Gating of human TRPV3 in a lipid bilayer. *Nature Structural & Molecular Biology* **27**:635-644 (2020). PMCID: PMC7354234.
2. Bitter RM, Oh S, Deng Z, Rahman S, Hite RK, **Yuan P**. Structure of the Wilson disease copper transporter ATP7B. *Science Advances* **8**:eabl5508 (2022). PMCID: PMC8896786.
3. Mount J, Maksaev G, Summers BT, Fitzpatrick JAJ, **Yuan P**. Structural basis for mechanotransduction in a potassium-dependent mechanosensitive ion channel. *Nature Communications* **13**:6904 (2022). PMCID: PMC9653487.
4. Zhang J, Maksaev G, **Yuan P**. Open structure and gating of the Arabidopsis mechanosensitive ion channel MSL10. *Nature Communications* **14**:6284 (2023). PMCID: PMC10560256.

I confirm that I have not published under a different name.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2023	NIH Special Emphasis Panel/Scientific Review Group ZRG1 F04-S, *ad hoc* reviewer
2023 -	Professor, Department of Pharmacological Sciences (primary appointment) Professor, Department of Neuroscience (secondary appointment), Icahn School of Medicine at Mount Sinai, New York, NY
2021	NIH NCI K99/R00 Review Committee, *ad hoc* reviewer
2020 - 2023	Associate Professor, Department of Cell Biology & Physiology, Washington University School of Medicine, St. Louis, MO
2016 - 2023	Member, American Heart Association
2013 - 2023	Member, Center for the Investigation of Membrane Excitability Diseases, Washington University School of Medicine
2013 - 2020	Assistant Professor, Department of Cell Biology & Physiology, Washington University School of Medicine, St. Louis, MO
2011 - Present	Member, Biophysical Society
2011 - 2023	Member, American Physiological Society

Honors

2017	National Scientist Development Award, American Heart Association
2016	Mallinckrodt Grant for New Investigators, Mallinckrodt Foundation

C. Contributions to Science

1. Structure and mechanism of mechanosensitive channels

Mechanosensitive (MS) ion channels transduce physical force into electrochemical signaling that underlies an array of fundamental physiological processes, including hearing, touch, proprioception, osmoregulation, and morphogenesis. Because we cannot apply mechanical force, the physiological stimulus that activates MS channels, in structural biology approaches, it is extremely difficult to illuminate distinct functional states during gating, especially the open conformations. Thus, it remains a long-standing central question how MS channels perceive mechanical force and transition to conductive states. Through innovative functional identification and structural biology, we have elucidated a potentially unifying mechanotransduction

mechanism, for the first time at the near-atomic level, in ion channel proteins depicted as 'flattening and expansion' of an intrinsically curved transmembrane domain. We have first revealed the 'flattening and expansion' gating mechanism in MSL1, and further corroborated this elegant mechanism in other MS channels including a ligand- and force-activated channel MscK. Notably, the shared structural feature between unrelated MS channels suggests the possibility of a universal mechanical gating mechanism originated from membrane deformation. We have been further testing this central hypothesis by innovative structural and functional studies of MS channels with distinct architectures that underly numerous mechanotransduction events in all kingdoms of life.

a. Deng Z, Maksaev G, Schlegel AM, Zhang J, Rau M, Fitzpatrick JAJ, Haswell ES, **Yuan P**. Structural mechanism for gating of a eukaryotic mechanosensitive channel of small conductance. *Nature Communications* **11**:3690 (2020). PMCID: PMC7378837.
b. Mount J, Maksaev G, Summers BT, Fitzpatrick JAJ, **Yuan P**. Structural basis for mechanotransduction in a potassium-dependent mechanosensitive ion channel. *Nature Communications* **13**:6904 (2022). PMCID: PMC9653487.
c. Zhang J, Maksaev G, **Yuan P**. Open structure and gating of the Arabidopsis mechanosensitive ion channel MSL10. *Nature Communications* **14**:6284 (2023). PMCID: PMC10560256.

2. Structure and mechanism of the TRPV ion channels

The calcium-permeable, non-selective and thermosensitive vanilloid subfamily of TRP channels play important roles in multiple physiological processes, including thermoregulation, osmoregulation and nociception. We have determined a cryo-EM structure of TRPV4 at 3.8 Å resolution and used X-ray crystallography to identify ion-binding sites in the selectivity filter, offering explanation for non-selectivity. We have determined multiple cryo-EM structures of human TRPV3 in lipid nanodiscs, representing distinct functional states during the gating cycle. In combination with electrophysiological characterization, structures of TRPV3 in distinct functional states embedded in a lipid membrane environment provide unique insights into channel activation and inactivation mechanisms. In collaboration with the Scheuring lab, we have discovered a non-canonical pentameric TRPV3 channel assembly, laying the foundation for new directions in TRP channel research.

a. Deng Z, Paknejad N, Maksaev G, Sala-Rabanal M, Nichols CG, Hite RK, and **Yuan P**. Cryo-EM and X-ray structures of TRPV4 reveal insight into ion permeation and gating mechanisms. *Nature Structural & Molecular Biology* **25**:252-260 (2018). PMCID: PMC6252174.
b. **Yuan P**. Structural biology of thermoTRPV channels. *Cell Calcium* **84**: 102106 (2019). PMCID: PMC6893863.
c. Deng Z, Maksaev G, Rau M, Xie Z, Hu H, Fitzpatrick JAJ, **Yuan P**. Gating of human TRPV3 in a lipid bilayer. *Nature Structural & Molecular Biology* **27**:635-644 (2020). PMCID: PMC7354234.
d. Lansky S, Betancourt JM, Zhang J, Jiang Y, Kim ED, Paknejad N, Nimigean CM, **Yuan P**, Scheuring S. A pentameric TRPV3 channel with a dilated pore. *Nature* **621**:206-214 (2023). PMCID: PMC10584365.

3. Structure and function of additional ion channels

The pannexin family of ion channels comprises three paralogs, PANX1-3, which differ in tissue expression and physiological functions. PANX1, a plasma membrane ATP-release channel, is involved in numerous physiological processes associated with purinergic signaling. PANX2 participates in skin homeostasis, neuronal development, and ischemia induced brain injury. My lab has determined near-atomic resolution cryo-EM structures of the human PANX1 and PAXN2 channels. Our work reveals previously unknown architecture of pannexin channels and establishes a framework for understanding their unique physiological functions and channel properties. We have discovered that PANX2 displays a similar anion permeability sequence as volume-regulated anion channel (VRAC), and that PANX2 channel activity is inhibited by a commonly used VRAC inhibitor, DCPIB. Thus, the shared channel properties between PANX2 and VRAC may complicate dissection of their cellular functions through pharmacological manipulation. These results provide a framework for development of PANX2-specific reagents that are needed for better understanding of channel physiology and pathophysiology. Using an innovative fusion strategy, we have determined a cryo-EM structure of a small-sized chloride channel (TMEM206), which underlies ubiquitously expressed, proton-activated, outwardly rectifying anion currents. We revealed that

the core structure and assembly closely resemble those of the epithelial sodium channel/degenerin family of sodium channels that are unrelated in amino acid sequence and conduct cations instead of anions.

a. Deng Z, He Z, Maksaev G, Bitter RM, Rau M, Fitzpatrick JAJ, **Yuan P**. Cryo-EM structures of the ATP release channel pannexin 1. *Nature Structural & Molecular Biology* **27**:373-381 (2020). PMID: 32231289.
b. Deng Z, Zhao Y, Feng J, Zhang J, Zhao H, Rau MJ, Fitzpatrick JAJ, Hu H, **Yuan P**. Cryo-EM structure of a proton-activated chloride channel TMEM206. *Science Advances* **7**:eabe5983 (2021). PMCID: PMC7904269.
c. He Z, Zhao Y, Rau MJ, Fitzpatrick JAJ, Sah R, Hu H, **Yuan P**. Structural and functional analysis of human pannexin 2 channel. *Nature Communications* **14**:1712 (2023). PMCID: PMC10043284.

4. Molecular mechanisms of chaperone-usher pathway pilus biogenesis

Chaperone-usher pathway (CUP) pili are extracellular proteinaceous fibers ubiquitously found on Gram-negative bacteria, and mediate host-pathogen interactions and biofilm formation critical in pathogenesis in numerous human diseases. During pilus assembly, an outer membrane macromolecular machine called the usher catalyzes pilus biogenesis from the individual subunits that are delivered as chaperone-subunit complexes in the periplasm. Despite extensive studies, the mechanism by which the usher is activated to initiate pilus biogenesis is unknown. We determined the crystal structure of the full-length PapC usher from *Escherichia coli* in complex with its cognate PapDG chaperone-subunit complex in a pre-activation state, elucidating molecular details of how the usher is specifically engaged by allosteric interactions with its substrate preceding activation and how the usher facilitates the transfer of subunits during pilus assembly. Together with functional characterization, our work elucidates the intricate workings of a molecular machine that catalyzes CUP pilus assembly and opens the door for the development of potent inhibitors to block pilus biogenesis.

a. Omattage NS, Deng Z, Pinkner JS, Dodson KW, Almqvist F, **Yuan P**, Hultgren SJ. Structural basis for usher activation and intramolecular subunit transfer in P pilus biogenesis in Escherichia coli. *Nature Microbiology* **3**:1362-1368 (2018). PMCID: PMC6258349.

5. Molecular mechanisms of copper transport

Copper (Cu) is an essential trace element for growth and development, acting as a cofactor for enzymes involved in a wide spectrum of biochemical processes, including mitochondrial respiration, iron mobilization, superoxide detoxification, and hormone and neuropeptide biogenesis. Defective Cu acquisition underlies neurological, cardiac and innate immune disorders and iron-deficiency anemia, while tissue Cu overload is associated with Wilson's disease, cancer and neurodegeneration. Evolutionarily conserved from fungi to humans, the high-affinity Cu^+ transporter CTR1 is crucial for both dietary Cu uptake and peripheral distribution, yet the mechanisms for selective permeation of potentially toxic Cu^+ ions across cell membranes are unknown. Through innovative protein engineering, we have achieved X-ray crystal structures of CTR1 in both Cu^+-free and Cu^+-bound states, revealing a homo-trimeric Cu^+-selective ion channel-like architecture. These structures, together with CTR1 functional characterization, provide the first high-resolution picture to understand Cu^+ import across cellular membranes and suggest new therapeutic opportunities for intervention in diseases characterized by inappropriate Cu accumulation.

a. Ren F, Logeman BL, Zhang X, Liu Y, Thiele DJ, **Yuan P**. X-ray structures of the high-affinity copper transporter Ctr1. *Nature Communications* **10**:1386 (2019). PMCID: PMC6437178.
b. Bitter RM, Oh S, Deng Z, Rahman S, Hite RK, **Yuan P**. Structure of the Wilson disease copper transporter ATP7B. *Science Advances* **8**:eabl5508 (2022). PMCID: PMC8896786.

Complete List of Published Work in Pubmed:
https://www.ncbi.nlm.nih.gov/myncbi/1tWVIpcX59ckq/bibliography/public/

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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NAME: Jingying Zhang

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

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
Peking University	BS	07/2016	Pharmaceutical Sciences
Peking University	MS	05/2018	Pharmaceutical Sciences
Washington University in St. Louis	PHD	12/2023	Biochemistry, Biophysics & Structural biology
Icahn school of Medicine at Mount Sinai	Post Doc	In progress	Structural biology

A. Personal Statement

During my undergraduate and master's studies at Peking University spanning six years, I developed a targeting liposome with a combination of two drugs that demonstrated effectiveness in eliminating breast cancer stem cells and breast cancer cells, resulting in a promising drug delivery system described in my first-author publication in Molecular Therapy-Oncolytics. Throughout the journey, I am also involved in collaborations that resulting in co-author papers published in prestigious journals focusing on drug delivery process, such as Advanced Drug Delivery Reviews. However, I recognized the limitations of relying solely on macroscopic experiments to understand drug interactions at the cellular level. This realization prompted a shift in my focus towards structural biology, with a keen interest in unraveling protein and protein-drug complex structures. During my five-year doctoral journey in Dr. Peng Yuan's lab at Washington University in St. Louis, I honed my skills in protein structure determination using Cryo-EM. This cutting-edge technique offers unparalleled spatial resolution and experimental simplicity for imaging proteins in static environments. From construct design to protein purification, from Cryo-EM grids freezing to data processing including utilizing deep learning algorithms for EM map denoising, I navigated every step of the process. I leveraged my skills to investigate the gating mechanisms of mechanosensitive ion channels, including MSL1, MSL8, and MSL10. Furthermore, through collaborative efforts with other research groups, I contributed to the elucidation of drug binding sites for G-Protein Coupled Receptor (GPCR) proteins and captured a pentameric state of a Transient Receptor Potential Vanilloid (TRPV) channel. I believe that combining structural biology with functional studies can provide deeper insights into the gating mechanisms of mechanosensitive channels, thus facilitating future advancements in drug development.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2023 – present Icahn school of Medicine at Mount Sinai, Department of Pharmacological Sciences
2018 – 2023 Graduate Research Assistant, Washington University in St. Louis
2016 – 2018 Graduate Research Assistant, Peking University

Honors

2023 Jack P. Green Oral Presentation Award, Department of Pharmacological Sciences Research Retreat, Icahn school of medicine at Mount Sinai.

C. Contributions to Science

1. **Develop functional liposomes for treating breast cancer:** During both my bachelor's and master's degrees, I was part of Dr. Wanliang Lu's lab at Peking University, where I focused on the development of functional drug liposomes and investigating their efficacy in treating cancer stem cells. My work primarily involved utilizing the thin-film dispersion method to produce functional drug liposomes targeted at Mitochondria. I assessed their zeta potential and average particle size using the Zetasizer Nano and established optimal protocols for their preparation. Subsequently, I conducted experiments to identify effective combinations of drug liposomes, evaluating their efficacy through cell survival assays in cancer cell lines and in vivo models. Moreover, I delved into elucidating the signaling transduction pathways by identifying relevant biomarkers using techniques such as qPCR, western blotting, and flow cytometry. This allowed me to gain insights into the modulation mechanisms and treatment effects in cancer stem cells. Through this comprehensive project, I contributed to the development of a novel strategy for breast cancer treatment, targeting both cancer cells and cancer stem cells simultaneously. Additionally, I collaborated with fellow lab members on exploring alternative methods for cancer treatment.

   Relevant Publications:

   Zhang, J., Luo, Q., Xu, J., Bai, J., Mu, L., Yan, Y., Duan, J., Cui, Y., Su, Z., Xie, Y., & Lu, W. (2020). Regulating stem Cell-Related genes induces the plastic differentiation of cancer stem cells to treat breast cancer. Molecular Therapy - Oncolytics, 18, 396–408.

   Hu, Y., **Zhang, J.,** Luo, Q., Xu, J., Yan, Y., Mu, L., Bai, J., & Lu, W. (2018). Nanostructured dihydroartemisinin plus epirubicin liposomes enhance treatment efficacy of breast cancer by inducing autophagy and apoptosis. Nanomaterials, 8(10), 804.

   Zhang, J., Luo, Q., Xu, J., Bai, J., Liu, L., Mu, L., Yan, Y., & Lu, W. (2018). A derivatization method to improve the assay of salinomycin sodium and its application in the liposomal formulation. Journal of Chinese Pharmaceutical Sciences, 27(2), 75–81.

   Mu, L., Ju, R., Li, R., Bu, Y., **Zhang, J.,** Li, X., Zeng, F., & Lu, W. (2017). Dual-functional drug liposomes in treatment of resistant cancers. Advanced Drug Delivery Reviews, 115, 46–56.

2. **Gating mechanism of mechanosensitive channels of small conductance:** As a PhD student in Dr. Peng Yuan's lab, I conducted research on mechanosensitive ion channels, crucial components across various living organisms. These channels play pivotal roles in sensory perception, pain modulation, and blood pressure regulation in humans, while also serving essential functions in plants, aiding in prey capture and survival in fluctuating osmotic conditions. Despite their significance, the gating mechanisms of these channels are still not clear and highly debated. Mechanosensitive ion channels of small conductance (MscS) form a diverse superfamily found in archaea, bacteria, fungi, and plants, where they convert mechanical stimuli into electrochemical signals vital for survival and development. Among these, MscS homologs in plants, referred to as MscS-Like (MSL) channels, exhibit diverse functions and subcellular localization. In my doctoral thesis, I focused on elucidating the structural dynamics of MSL channels at various functional states. Our investigation of MSL1 revealed that the curved transmembrane region, upon channel opening, flattens and expands. Remarkably, a similar "flattening and expansion" gating mechanism was observed in the structurally distinct MS channel Piezo. Furthermore, our studies of MSL10 yielded the first open structure of a wild-type eukaryotic mechanosensitive ion channel. With the combination of electrophysiology, we unveiled unique features of MSL channels and provided insights into the underlying gating mechanisms. Additionally, leveraging my expertise in cryo-electron microscopy and protein biochemistry, I contributed to several other studies, including diverse targets such as TRPV, GPCR, MRS2, TMEM206, and ACAD.

Relevant Publications:

Zhang, J., Maksaev, G., & Yuan, P. (2023). Open structure and gating of the Arabidopsis mechanosensitive ion channel MSL10. Nature Communications, 14, 6284.

Lansky, S., Betancourt, J. M., **Zhang, J.,** Jiang, Y., Kim, E. D., Paknejad, N., Nimigean, C. M., Yuan, P., & Scheuring, S. (2023). A pentameric TRPV3 channel with a dilated pore. Nature, 621(7977), 206–214.

Han, J., **Zhang, J.,** Nazarova, A. L., Bernhard, S., Krumm, B. E., Zhao, L., Lam, J. H., Rangari, V. A., Majumdar, S., Nichols, D. E., Katritch, V., Yuan, P., Fay, J. F., & Che, T. (2023). Ligand and G-protein selectivity in the κ-opioid receptor. Nature, 617(7960), 417–425.

Deng, Z., Maksaev, G., Schlegel, A. M., **Zhang, J.,** Rau, M., Fitzpatrick, J. A., Haswell, E. S., & Yuan, P. (2020). Structural mechanism for gating of a eukaryotic mechanosensitive channel of small conductance. Nature Communications, 11, 3690.

BIOGRAPHICAL SKETCH

NAME: Mount, Jonathan

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

POSITION TITLE: PhD Candidate | Yuan Lab

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Washington, Seattle	Bachelor of Science	06/2015	Bioengineering
Washington University, St Louis	Doctor of Philosophy	*In progress, anticipated 2024*	Biochemistry, Biophysics and Structural Biology

A. Personal Statement

As a structural biologist, biophysicist and membrane protein biochemist, my primary research goal is to deepen our understanding of mechanosensation – a biological process deeply fundamental to all life on earth – and the critical protein complexes that enable it. I am conducting my PhD studies at Washington University in St Louis under the guidance of Dr. Peng Yuan, where I gained my background in membrane protein biochemistry and structural biology and became inspired to continue research in mechanobiology. My doctoral studies focus mainly on MscK and TRPV4, two unrelated ion channels that share the unique feature of dual regulation by mechanical forces and ligand binding. Excitingly, I have also recently determined the first cryo-EM structure of human ATP7A, a copper-transporting P-type ATPase, of which mutations cause devastating Menkes disease. Throughout the course of these studies, I discovered the first open and closed conformations of the bacterial MscK channel, as well as a variety of open conformations of mammalian TRPV channels. Additionally, I contribute to multiple projects in the lab and with collaborators who study the structure and function of KIR and HCN channels. Prior to beginning my PhD, my interest in ion channels developed when I worked as a laboratory research technician performing biochemical preparations and electrophysiological recordings of DNA translocation through mycobacterium smegmatis porin A (MSPA) nanopores reconstituted into painted bilayers. More specifically, I collected data which eventually proved that alternating voltage schemes could improve nanopore sequencing accuracy by providing information on enzyme stepping direction, a feature which is typically lost when measuring nanopore currents under constant voltage. Furthermore, I applied single-molecule-nanopore-tweezer (SPRNT) measurements of hel308 and PCRA helicase to understand how DNA-translocating enzymes are affected by opposing force and the sequence of the DNA that they are traversing. I am passionate about pushing the envelope at the interface of fundamental biology and emerging biotechnology. With my experience as a laboratory technician at the University of Washington and PhD candidate at Washington University in St Louis I have gained fundamental skill sets in protein biochemistry and structural biology and the necessary mindset to improve our understanding of protein complexes involved in mechanosensation. With an improved structural and functional understanding of these complexes, I anticipate that we can pave the way for the development of more selective antibiotics and therapies that target mechanosensitive protein complexes involved in disease.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2019 – Present PhD candidate, Department of Cell Biology and Physiology, Washington University, St Louis, MO

2016 – 2018 Laboratory Technician II, Gundlach Nanopore Laboratory, University of Washington, Seattle, WA

2013 – 2015 Undergraduate Researcher, Department of Bioengineering, Thomas Lab, University of Washington, Seattle, WA

Honors

2023 Boston Taiwanese Biotechnology Association Harvard Symposium – Best Poster Award
2022 Washington University in St Louis Biochemistry, Biophysics, and Structural Biology - Rising Star Award
2022 11th CIMED Annual Koster Memorial Lecture - Best Poster Award
2020 Biochemistry, Biophysics and Structural Biology Annual Retreat - Best Talk Award
2015 University of Washington Engineering Capstone Design Scholarship - Recipient
2013 Center for Sensorineural Engineering – Internship Award Recipient

C. Contributions to Science

1. *Improving Nanopore Sequencing Technology:* As a laboratory technician at the Gundlach nanopore laboratory, I performed extensive measurements of helicases, polymerases, and DNA translocases using a novel force spectroscopy technique—single molecule picometer resolution nanopore tweezers (SPRNT). The extremely-high spatiotemporal resolution of SPRNT enabled the lab to investigate previously inaccessible helicase and translocase behavior. I thrived in the collaborative environment working with multiple teams to design and execute experiments, manage and annotate large data sets, and train new laboratory members in data acquisition and laboratory practices. In the lab, I measured the DNA translocation activity of RNA polymerase, as well as the helicases RecQ, UVRD, hel308, and PCRA on a variety of DNA constructs, as well as performing much of the molecular biology to generate those constructs. Additionally, I pursued self-driven projects in the lab focused on generating template adapters that could be utilized to re-read one strand of DNA multiple times. My most impactful contribution to science at the nanopore lab stemmed from my collaboration with Dr. Matthew Noakes, where we proved that an alternating voltage scheme – when applied in nanopore sequencing – could be used to measure the stepping direction of a motor enzyme. This information, when integrated with standard nanopore sequencing processing techniques, provides a significant global boost to sequencing accuracy.

Relevant Publications:

Craig, Jonathan M., Mills, Maria., Kim, Hwanhee C., Huang, Jesse R., Abell, Sarah J., **Mount, Jonathan W.**, Gundlach, Jens H., Neumann, Keir C., Laszlo, Andrew H. (2022). “Nanopore tweezers measurements of RecQ conformational changes reveal the energy landscape of helicase motion.” Nucleic Acids Research 50(18): 10601-10613.

Laszlo, Andrew H., Craig, Jonathan M., Gavrilov, Momčilo, Tippana, Ramreddy, Nova, Ian C., Huang, Jesse R., Kim, Hwanhee C., Abell, Sarah J., deCampos-Stairiker, Mallory, **Mount, Jonathan W.**, Bowman, Jasmine L., Baker, Katherine S., Higinbotham, Hugh, Bobrovnikov, Dmitriy, Ha, Taekjip, Gundlach, Jens H. (2022). "Sequence-dependent mechanochemical coupling of helicase translocation and unwinding at single-nucleotide resolution." Proceedings of the National Academy of Sciences 119(36): e2202489119.

Craig, Jonathan M., Laszlo, Andrew H., Nova, Ian C., Brinkerhoff, Henry, Noakes, Matthew T., Baker, Katherine S., Bowman, Jasmine L., Higinbotham, Hugh R., **Mount, Jonathan W.**, Gundlach, Jens H.. (2019). "Determining the effects of DNA sequence on Hel308 helicase translocation along single-stranded DNA using nanopore tweezers." Nucleic acids research 47(5): 2506-2513.

Noakes, Matthew T., Brinkerhoff, Henry, Laszlo, Andrew H., Derrington, Ian M., Langford, Kyle W., **Mount, Jonathan W.**, Bowman, Jasmine L., Baker, Katherine S., Doering, Kenji M., Tickman, Benjamin I.. (2019). "Increasing the accuracy of nanopore DNA sequencing using a time-varying cross membrane voltage." Nature biotechnology 37(6): 651-656.

2. *Elucidating open and closed conformations of ion channels with a focus on MscK, the Largest Bacterial Mechanosensitive Ion Channel:* As a graduate research assistant in the Yuan lab at Washington University in St Louis, I study the structure and function of force-and-ligand dependent ion channels. The mechanism by which ion channels respond to force is intensely debated, and the advent of the Cryo-EM resolution revolution has enabled unprecedented insights into the macromolecular assemblies that enable mechanosensation. Mechanosensitive ion channels vary widely in their structural organization and have been identified in all kingdoms of life. Structures of MscS-like channels, PIEZO channels, NOMPC, OSCA, the MET-complex, and others have illuminated the fact that there are many structural folds that impart mechanosensitive behavior into an ion channel and suggest that different folds may serve to facilitate specific modes of mechanosensation. During the course of my PhD I engineered MscK constructs from a variety of organisms and screened them to optimize expression, stability, and study the effect of functional mutations on the structure of MscK. As a result of my efforts, I solved the first high resolution structure of an MscK channel in closed and open conformations, revealing the gating pathway and providing insights into the mechanism by which MscK responds to ions and mechanical force. I actively drove the project in collaboration with Dr. Grigory Maksaev, Professor Peng Yuan, Dr. Brock Summers, and Professor James Fitzpatrick, resulting in a manuscript detailing our findings. Additionally, I have applied the techniques I developed in the study of this channel to study a variety of unrelated ion channels including MRS2, HCN, and TRP channels and ion transporters such as ATP7A.

Relevant Publications*:*

In Review: He, Zhihui., Tu, Yung-Chi., Tsai, Chen-Wei., **Mount, Jonathan**., Zhang, Jingying., Tsai, Ming-Feng., Yuan, Peng. (2024). “Structure and function of the human mitochondrial MRS2 channel.” Nature Structural and Molecular Biology.

In Review: Burtscher, Verena.**, Mount, Jonathan W.**, Cowgill, John., Chang, Yongchang., Bickel, Katherine., Yuan, Peng., Chanda, Baron., (2024). “Structural Basis for Hyperpolarization-dependent Opening of the Human HCN1 Channel.” Nature Communications.

Mount, Jonathan W., Maksaev, Grigory., Summers, Brock., FitzPatrick, James. (2022). “Structural basis for mechanotransduction in a potassium-dependent mechanosensitive ion channel.” Nature Communications. 13(6904)

BIOGRAPHICAL SKETCH

NAME: Yuanyuan Li

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

POSITION TITLE: Postdoctoral Fellow

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Yunnan University	BS	06/2017	Pharmaceutical Engineering
Sichuan University	MS	06/2020	Pharmacy and Structural Biology
Sichuan University	PHD	09/2023	Cell Biology and Structural Biology
Ichan School of Medicine at Mount Sinai	Postdoctoral Fellow	Present	Structural Biology

A. Personal Statement

My academic training and research experience have provided me with an excellent background in multiple biological disciplines including molecular biology, microbiology, biochemistry, and structural biology. During my master's studies, I learned the technique of X-ray crystallography and related biochemical experiments under the supervision of Qiang Chen and studied the structure of human-derived tubulin and calcium transporter proteins. My doctoral research revealed the structure and mechanism of multiple anti-phage defense systems, including Thoeris, Septu, Kiwa, Retron, Hachiman, Gabija, and some toxin-antitoxin systems. I elucidated the activity of the proteins related to the anti-phage defense system by biochemical analysis, and obtained the structures of the target proteins by X-ray crystallography and cryo-EM technique, explaining the mechanism of the target system in resisting phage invasion. In addition, I build the first platform in our lab for cultivating bacteriophage and exploring interactions between bacteria and phage. I also contribute to multiple collaborative projects to expand the horizon in different fields. Recently, I joined Dr. Peng Yuan's lab as a postdoctoral associate to study ion channels and transporters using a combination of biochemical, biophysical and structural biology techniques including cryo-EM. These projects will provide me with new conceptual and technical training in structural biology. In addition, the postdoc training underlines a set of career development –such as grant writing, public speaking, lab management, and so on – designed to enhance my ability to become an independent investigator. My long-term research goal is to become an independent researcher developing a comprehensive understanding of key ion channel pathways and contributing to the treatment of human disease.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2024 – present Postdoctoral researcher, Icahn school of Medicine at Mount Sinai
2020 – 2023 PhD candidate, Sichuan University
2017 – 2020 Master candidate, Sichuan University

Honors

2022 Doctoral Innovation Scholarship, Sichuan University
2022 Yiqiao Shenzhou Scholarship, Sichuan University
2022 Title of Excellent Graduate Student, Sichuan University

C. Contributions to Science

1. **Master's Career:** My master's career contributions were focused on applying my knowledge in X-ray crystallography to phasing the structure of human tubulin and calcium transporter proteins. Microtubules are composed of $\alpha\beta$-tubulin heterodimers, and drugs that interfere with microtubule dynamics are used widely in cancer chemotherapy. Small synthetic molecules with an indole nucleus as a core structure have been identified as microtubule inhibitors and recognized as anticancer agents. My work has resulted in the crystal structures of tubulin in complex with two kinds of indole derivatives, it lays the foundation of tubulin-related biochemical therapy. Moreover, my thesis research work elucidated the structure and mechanism of S100G, a calcium transporter protein, by X-ray crystallography and biochemical analysis.

   Relevant Publications:

   a) **Li, Y.**, Yang, J., Niu, L., Hu, D., Li, H., Chen, L., Yu, Y., & Chen, Q. (2020). Structural insights into the design of indole derivatives as tubulin polymerization inhibitors. FEBS letters, 594(1), 199–204.

2. **PhD Studies:** During my PhD, I threw myself into the research of anti-phage defense systems in multiple bacteria. The perpetual arms race between bacteria and bacteriophages has driven bacteria to evolve intricate immune networks as a defense against phage attacks. Investigating these bacteria's immune systems has transformed biochemical research, such as restriction endonuclease coming from R-M system and ccdB gene coming from Toxin-Antitoxin system. My research was conducted to clarify the structure and mechanism of various bacteria immune systems, including Thoeris, Septu, Kiwa, Retron, Hachiman, Gabija, and some toxin-antitoxin systems. I contributed to demonstrating the activity of proteins related to anti-phage defense systems by biochemical analysis, combined with X-ray crystallography and cryo-EM technique, I uncovered the mechanism of the target system in resisting phage invasion. In addition, I collaborated with another lab on exploring the structure of triosephosphate isomerase 1 (TPI1), a metabolic crossroad interconnecting lipid and glucose metabolism.

   Relevant Publications:

   a) **Li, Y.**, Shen, Z., Zhang, M., Yang, X. Y., Cleary, S. P., Xie, J., Marathe, I. A., Kostelic, M., Greenwald, J., Rish, A. D., Wysocki, V. H., Chen, C., Chen, Q., Fu, T. M., & Yu, Y. (2024). PtuA and PtuB assemble into an inflammasome-like oligomer for anti-phage defense. Nature structural & molecular biology, 31(3), 413–423.
   b) Chunheng Mo, Hui Li, Mengli Yan, Shiyu Xu, Jinyan Wu, Jiachen Li, Chuan Wu, **Yuanyuan Li**, Jian Yang, Suping Xu, Jie Liu, Yuxin Zhang, Qiang Pu, Tinghong Ye, Zhongwei Cao, Bi-Sen Ding. Dopaminylated triosephosphate isomerase 1 (TPI1) in the vascular niche bypasses ferroptosis to promote lung regeneration over fibrosis. Science (Submitted).