BIOGRAPHICAL SKETCH

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NAME: Fan, Qing Rong

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

POSITION TITLE: Professor of Molecular Pharmacology and Therapeutics and Pathology and Cell Biology

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
Harvard-Radcliffe Colleges, Cambridge	B.A.	06/1994	Chemistry
Harvard University, Cambridge	M.A.	06/1996	Chemistry
Harvard University, Cambridge	Ph.D.	06/1999	Chemistry
Harvard University, Cambridge	Postdoctoral	06/2000	Structural Biology
Columbia University, New York	Postdoctoral	12/2006	Structural Biology

A. Personal Statement

I am interested in understanding the signaling mechanisms of cell surface receptors and how dysregulation of these receptors impact disease processes. I have been pursuing this goal through structural biology. The research in my laboratory has focused on the structure and function of a family of dimeric G-protein-coupled receptors (GPCRs), specifically human $GABA_B$ receptor and human calcium-sensing receptor (CaSR). My research goal is to understand how these dimeric GPCR assemblies transmit extracellular signals across the membrane. My laboratory determined the crystal structures of the $GABA_B$ receptor extracellular domain in multiple functional states, including apo, antagonist- and agonist-bound forms. Recently, we captured the inactive structure of a near full-length $GABA_B$ receptor by cryogenic electron microscopy (cryo-EM). This structure revealed an important heterodimeric interaction motif that controls receptor activation. We also discovered multiple endogenous ligands of $GABA_B$ receptor that include two phospholipids embedded in the transmembrane domains. We have determined the extracellular domain structures of human CaSR in both the resting and active conformations. Based on these structures, we found that amino acids and Ca^{2+} function as co-agonists of the CaSR. We also solved the structures of a near-full length CaSR in multiple functional states. We found that a critical development during receptor activation arises from a helix-breaking event that facilitates the formation of a novel transmembrane homodimer interface. Recently, we determined the structures of CaSR complexed with G proteins from three different subfamilies: G_q, G_i and G_s. These structures revealed the mechanism of G-protein activation and selectivity as well as the molecular basis of promiscuous G-protein coupling by CaSR. In all of our studies, we have collaborated with other scientists to examine the physiological relevance of our structural findings. In particular, we have been working with Dr. Jonathan A. Javitch, an expert on intracellular signaling, to examine the physiological relevance of our structural findings. With the support from our collaborators Dr. Joachim Frank and Dr. Oliver Clarke, my lab has also acquired proficiency in single particle cryo-EM reconstruction for our projects. Given our combined expertise, we are poised to make significant contributions to understanding the molecular mechanisms of dimeric GPCR activation and regulation.

Ongoing and recently completed projects that I would like to highlight include:
R35 GM141871

Fan (PI)
04/01/21-03/31/26
Molecular mechanism of dimeric G protein-coupled receptor signaling

R01 GM12580
Fan, Slesinger and Quick (PI)
09/01/18-07/31/22
Mechanism of activation and modulation in human GABA(B) receptor

Citations:

1. Geng, Y., Bush, M., Mosyak, L., Wang, F., and **Fan, Q. R.*** Structural mechanism of ligand activation in human $GABA_B$ receptor. *Nature* 504, 254-259 (2013). PMID: 24305054. PMC3865065. (*Corresponding author) Funding: R01GM088454 (NIGMS).
2. Park, J., Fu Z., Frangaj, A., Liu, J., Mosyak, L., Shen, T., Slavkovich, V.N., Ray, K.M., Taura, J., Cao, B., Geng, Y., Zuo, H., Kou, Y., Grassucci, R., Chen, S., Liu, Z., Lin, X., Williams, J.P., Rice, W.J., Eng, E.T., Huang, R.K., Soni, R.K., Kloss, B., Yu, Z., Javitch, J.A., Hendrickson, W.A., Slesinger, P.A., Quick, M., Graziano, J., Yu, H., Fiehn, O., Clarke, O.B.*, Frank, J.*, **Fan, Q.R.*** Structure of human $GABA_B$ receptor in an inactive state. *Nature* 584, 304-309 (2020). PMID: 32581365. PMC7725281. (*Corresponding authors) Funding: R01GM088454 (NIGMS), R01GM12580 (NIGMS), and R35GM141871 (NIGMS).
3. Park, J., Zuo, H., Frangaj, A., Fu, Z., Yen, L.Y., Zhang, Z., Mosyak, L., Slavkovich, V.N., Liu, J., Ray, K.M., Cao, B., Vallese, F., Geng, Y., Chen, S., Grassucci, R., Venkata, P.D., Tan, Y.Z., Eng, E., Lee, Y., Kloss, B., Liu, Z., Hendrickson, W.A.*, Potter, C.S., Carragher, B., Graziano, J., Conigrave, A.D.*, Frank, J.*, Clarke, O.B.*, and **Fan, Q.R.*** Symmetric activation and modulation of the calcium-sensing receptor. *Proc. Natl. Acad. Sci. USA* 118, e2115849118 (2021). PMID: 34916296. PMC8713963 (*Corresponding authors) Funding: R35GM141871 (NIGMS).
4. Zuo, H., Park, J., Frangaj, A., Ye, J., Lu, G., Manning, J.J., Asher, W.B., Lu, Z., Hu, G., Wang, L., Mendez, J., Eng, E., Zhang, Z., Lin, X., Grassucci, R., Hendrickson, W.A., Clarke, O.B., Javitch, J.A.*, Conigrave, A.D.*, and **Fan, Q.R.*** Promiscuous G-protein activation by the calcium-sensing receptor. *Nature* 629, 481-488 (2024). PMID: 38632411. PMC11844898. (*Corresponding authors) Funding: R35GM141871 (NIGMS).

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2024	NIH Scientific Peer Review Committee on Clinical Research Consortia (U54), reviewer Rare Diseases Clinical Research Consortia for the Rare Diseases Clinical Research Network
2023	NIH Special Emphasis Panels on Pilot Projects (R03), reviewer Investigating understudied proteins associated with rare diseases
2021	NIH Molecular and Integrative Signal Transduction Study Section, ad hoc reviewer
2020	NIH Special Emphasis Panel on Pilot Project (R03), reviewer Understudied G Protein-Coupled Receptors, Ion Channels, and Protein Kinases
2020-present	Member, Faculty Opinions Cell Signaling & Trafficking Structures Section
2019-2020	Member, F1000Prime Cell Signaling & Trafficking Structures Section
2018-2020	Consultant, PSY Therapeutics, INC, Consultant
2022-present	Professor of Pharmacology and Pathology and Cell Biology Department of Molecular Pharmacology & Therapeutics, Columbia University, New York, NY
2022-present	Professor of Pharmacology and Pathology and Cell Biology Department of Pathology & Cell Biology, Columbia University, New York, NY
2015-2022	Associate Professor of Pharmacology and Pathology and Cell Biology Department of Molecular Pharmacology & Therapeutics, Columbia University, New York, NY
2015-2022	Associate Professor of Pharmacology and Pathology and Cell Biology

Department of Pathology & Cell Biology, Columbia University, New York, NY
2007-2015 Assistant Professor of Pharmacology and Pathology and Cell Biology
Department of Pharmacology, Columbia University, New York, NY
2007-2015 Assistant Professor of Pharmacology and Pathology and Cell Biology
Department of Pathology & Cell Biology, Columbia University, New York, NY

Honors

2021-2026	NIH Maximizing Investigators' Research Award (MIRA)
2016	HHMI Faculty Scholars Competition Semifinalist
2013-2014	Schaefer Research Scholar
2011-2014	McKnight Scholar in Neuroscience
2009-2014	Pew Scholar Award in Biomedical Sciences
2009-2013	Irma T. Hirschl Career Scientist Award
2008-2009	Columbia University Fellowship for Minority and Women Junior Faculty
2001-2004	The Jane Coffin Childs Memorial Fund for Medical Research Postdoctoral Fellowship (Agouron Institute Fellow in Structural Biology)
1995-1998	National Science Foundation Predoctoral Fellowship
1994	Radcliffe Valedictorian, Harvard-Radcliffe Colleges

C. Contributions to Science

1. I have developed an independent research program to investigate the structure and function of human $GABA_B$ receptor, a class C GPCR important for inhibitory neurotransmission in the brain. $GABA_B$ receptor functions as an obligatory heterodimer of the $GABA_{B1}$ and $GABA_{B2}$ subunits. $GABA_{B1}$ is responsible for ligand binding, while $GABA_{B2}$ is involved in G-protein coupling.
   The first part of my work focuses on the molecular structures of various components of $GABA_B$ receptor. First, we solved the crystal structure of $GABA_{B2}$ extracellular domain, and demonstrated that $GABA_{B2}$ ectodomain directly interacts with $GABA_{B1}$ ectodomain to increase agonist affinity by selectively stabilizing the agonist-bound conformation of $GABA_{B1}$. Subsequently, we assembled a complex between the extracellular domains of the ligand-binding subunit ($GABA_{B1}$) and the modulatory subunit ($GABA_{B2}$). We determined crystal structures of the heterodimer in three states, in the apo form, bound to six different antagonists and bound to two different agonists. Structural comparison indicates a unique activation mechanism for the $GABA_B$ receptor that involves the formation of a novel heterodimer interface between its subunits. Our structures also revealed the molecular basis of ligand recognition by the $GABA_B$ receptor. In addition, we solved the crystal structure of an intracellular coiled-coil heterodimer of $GABA_B$ receptor. Our structure revealed the heterodimeric interaction that is responsible for concealing an endoplasmic reticulum retention signal in $GABA_{B1}$ and promoting the surface transport of the intact receptor. Recently, we solved the complex structure of the oligomerization domain of a intracellular KCTD protein bound to a $GABA_{B2}$-derived peptide. We found that KCTD forms a pentameric assembly and binds to $GABA_{B2}$ at a 5:1 molar ratio. The structure revealed the $GABA_{B2}$-KCTD interface and the residues that control the effect of KCTD on $GABA_B$ receptor activation and desensitization.

   a. Geng, Y., Xiong, D., Mosyak, L., Malito, D. L., Kniazeff, J., Chen, Y., Burmakina, S., Quick, M., Bush, M., Javitch, J. A., Pin, J.-P., and **Fan, Q. R.*** Structure and functional interaction of the extracellular domain of human $GABA_B$ receptor GBR2. *Nature Neuroscience* 15, 970-978 (2012). PMID: 22660477. PMC3374333. (*Corresponding author) Funding: R01GM088454 (NIGMS).
   b. Geng, Y., Bush, M., Mosyak, L., Wang, F., and **Fan, Q. R.*** Structural mechanism of ligand activation in human $GABA_B$ receptor. *Nature* 504, 254-259 (2013). PMID: 24305054. PMC3865065. (*Corresponding author) Funding: R01GM088454 (NIGMS).
   c. Burmakina, S., Geng, Y., Chen, Y., and **Fan, Q. R.*** Heterodimeric coiled-coil interactions of the human $GABA_B$ receptor. *Proc. Natl. Acad. Sci. USA*. 111, 6958-6963 (2014). PMID: 24778228. PMC4024898. (*Corresponding author) Funding: R01GM088454 (NIGMS).

d. Zuo, H., Glaaser, I., Zhao, Y., Kourinov, I., Mosyak, L., Wang, H., Liu, J., Park, J., Frangaj, A., Sturchler, E., Zhou, M., McDonald, P., Geng, Y., Slesinger, P.A. and **Fan, Q.R.*** Structural basis for auxiliary subunit KCTD16 regulation of the GABAB receptor. Proc. Natl. Acad. Sci. USA. 116, 8370-8379. PMID: 30971491. PMC6486783. (2019). (*Corresponding author) Funding: R01GM088454 (NIGMS) and R01GM12580 (NIGMS).

2. The second part of my work on $GABA_B$ receptor focuses on its transmembrane signaling mechanism. We recently captured the inactive-state structure of a near full-length human $GABA_B$ receptor by cryo-EM. Our structure revealed critical heterodimer interactions in the transmembrane region that control receptor activation. Specifically, the structure features a novel heterodimer interface between the transmembrane 3 (TM3) and 5 (TM5) helices of both $GABA_B$ subunits, which embodies the signature dimer arrangement of $GABA_B$ TM domains in the inactive conformation. Furthermore, we identified a unique ′intersubunit latch′ motif within this TM interface that maintains the inactive state of the receptor. We showed that disruption of the 'intersubunit latch' through single point mutations renders the receptor constitutively active. To our surprise, we discovered multiple endogenous ligands pre-associated with $GABA_B$ receptor, including two large phospholipids embedded within the transmembrane domains. These lipids are necessary structural components that maintain the receptor integrity.

    a. Park, J., Fu Z., Frangaj, A., Liu, J., Mosyak, L., Shen, T., Slavkovich, V.N., Ray, K.M., Taura, J., Cao, B., Geng, Y., Zuo, H., Kou, Y., Grassucci, R., Chen, S., Liu, Z., Lin, X., Williams, J.P., Rice, W.J., Eng, E.T., Huang, R.K., Soni, R.K., Kloss, B., Yu, Z., Javitch, J.A., Hendrickson, W.A., Slesinger, P.A., Quick, M., Graziano, J., Yu, H., Fiehn, O., Clarke, O.B.*, Frank, J.*, **Fan, Q.R.*** Structure of human $GABA_B$ receptor in an inactive state. *Nature* 584, 304-309 (2020). PMID: 32581365. PMC7725281. (*Corresponding authors) Funding: R01GM088454 (NIGMS) and R01GM12580 (NIGMS).

3. I have created an independent research program to study the structure and function of human calcium-sensing receptor (CaSR), a GPCR that maintains extracellular Ca^{2+} homeostasis through the regulation of parathyroid hormone secretion.
   We solved crystal structures of the extracellular domain of CaSR in the resting and active conformations. These structures provided direct evidence that L-amino acids and Ca^{2+} are co-agonists of the receptor. In the active structure, L-Trp occupies the orthosteric agonist-binding site at the interdomain cleft and is primarily responsible for inducing extracellular domain closure to initiate receptor activation. We also identified multiple binding sites for Ca^{2+} and PO_4^{3-}. Both ions are crucial for structural integrity of the receptor. While Ca^{2+} stabilizes the active state, PO_4^{3-} reinforces the inactive conformation. Binding of Ca^{2+} induces specific association of membrane-proximal domains to achieve full receptor activation.
   We also determined the cryo-EM structures of a near-full length CaSR in the presence and absence of allosteric modulators. We found that activation of CaSR requires a break in the transmembrane 6 (TM6) helix of each subunit, which facilitates the formation of a TM6-mediated homodimer interface. Allosteric modulators increase or decrease receptor activity by either reinforcing the disruption of TM6 helix or stabilizing its integrity.
   We recently solved the cryo-EM structures of CaSR complexed with four different G proteins from three subfamilies, G_q, G_i, and G_s. The restraint imposed by the receptor dimer and an intracellular loop (ICL2) of CaSR enables G-protein activation by facilitating conformational transition of Gα. We identified a single Gα residue that determines G_q and G_s vs G_i selectivity. Finally, the length and flexibility of ICL2 allows CaSR to bind all three Gα subtypes, thereby conferring capacity for promiscuous G-protein coupling.

    a. Geng, Y., Mosyak, L., Kurinov, I., Zuo, H., Sturchler, E. Cheng, T.C., Subramanyam, P., Brown, A.P., Brennan, S.C., Mun, H., Bush, M., Chen, Y., Nguyen, T.X., Cao, B., Chang, D.D., Quick, M., Conigrave, A.D., Colecraft, H.M., McDonald, P. and **Fan, Q.R.*** Structural mechanism of ligand activation in human calcium-sensing receptor. *eLife*. 5, e13662 (2016). PMID: 27434672. PMC4977154. (*Corresponding author) Funding: R01GM112973 (NIGMS).

b. Park, J., Zuo, H., Frangaj, A., Fu, Z., Yen, L.Y., Zhang, Z., Mosyak, L., Slavkovich, V.N., Liu, J., Ray, K.M., Cao, B., Vallese, F., Geng, Y., Chen, S., Grassucci, R., Venkata, P.D., Tan, Y.Z., Eng, E., Lee, Y., Kloss, B., Liu, Z., Hendrickson, W.A.*, Potter, C.S., Carragher, B., Graziano, J., Conigrave, A.D.*, Frank, J.*, Clarke, O.B.*, and **Fan, Q.R.*** Symmetric activation and modulation of the calcium-sensing receptor. *Proc. Natl. Acad. Sci. USA* 118, e2115849118 (2021). PMID: 34916296. PMC8713963. (*Corresponding authors) Funding: R35GM141871 (NIGMS).
c. Zuo, H., Park, J., Frangaj, A., Ye, J., Lu, G., Manning, J.J., Asher, W.B., Lu, Z., Hu, G., Wang, L., Mendez, J., Eng, E., Zhang, Z., Lin, X., Grassucci, R., Hendrickson, W.A., Clarke, O.B., Javitch, J.A.*, Conigrave, A.D.*, and **Fan, Q.R.*** Promiscuous G-protein activation by the calcium-sensing receptor. *Nature* 629, 481-488 (2024). PMID: 38632411. PMC11844898. (*Corresponding authors) Funding: R35GM141871 (NIGMS).

4. As a postdoctoral fellow in Professor Wayne Hendrickson's laboratory, I studied the structure of human follicle stimulating hormone (FSH) receptor. FSH is essential for the regulation of reproduction in mammals, as it induces the maturation of ovarian follicles in females and supports spermatogenesis in males. FSH belongs to the family of glycoprotein hormones, which act through specific GPCRs in the target cell membrane. I determined the crystal structure of human FSH bound to the extracellular hormone-binding domain of its receptor and described their binding mode. Our structure also provides an explanation for the specificity of recognition between glycoprotein hormones and their receptors.

    a. **Fan, Q. R.** and Hendrickson, W. A. Structure of human follicle-stimulating hormone in complex with its receptor. *Nature* 433:269-277 (2005). PMID: 15662415. PMC5514322
    b. **Fan, Q. R.** and Hendrickson, W. A. (2008). Comparative structural analysis of the binding domain of the follicle stimulating hormone receptor. *Proteins* 72, 393-401. PMID: 18214954. PMC3078555.

5. As a graduate student in late Professor Don Wiley's laboratory, I studied the structure and function of the human natural killer (NK) cell receptor KIR2D and its class I major histocompatibility complex (MHC) ligand HLA-Cw4. Natural killer cells are a class of lymphocytes that lyse transformed and virally infected cells deficient in class I MHC expression. Inhibitory receptors on NK cell surface down-regulate the cytotoxicity of NK cells upon recognition of specific MHC molecules on target cells. I determined the extracellular domain structure of the inhibitory receptor KIR2D, the class I MHC molecule HLA-Cw4, and their complex. These structures revealed the binding mode and specificity determinants of inhibitory NK receptors and their MHC ligands.

    a. **Fan, Q. R.**, Garboczi, D. N., Winter, C. C., Wagtmann, N., Long, E. O. and Wiley, D. C. Direct binding of a soluble natural killer cell inhibitory receptor to a soluble human leukocyte antigen-Cw4 class I major histocompatibility complex molecule. *Proc. Natl. Acad. Sci. USA* 93:7178-7183 (1996). PMID: 8692965. PMC38956
    b. **Fan, Q. R.**, Mosyak, L., Winter, C. C., Wagtmann, N., Long, E. O. and Wiley, D. C. Structure of the inhibitory receptor for human natural killer cells resembles haematopoietic receptors. *Nature* 389:96-100 (1997). PMID: 9288975.
    c. **Fan, Q. R.** and Wiley, D. C. Structure of human leukocyte antigen (HLA)-Cw4, a ligand for the KIR2D natural killer cell inhibitory receptor. *J. Exp. Med.* 190:113-123 (1999). PMID: 10429675. PMC2195553
    d. **Fan, Q. R.**, Long, E. O. and Wiley, D. C. Crystal structure of the human natural killer cell inhibitory receptor KIR2DL1 bound to its class I MHC ligand. *Nature Immunology* 2: 452-460. PMID: 11323700. This work was featured in a News and Views commentary in *Nature Immunology* 2, 379-380 (2001).

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/qing.fan.1/bibliography/40773268/public/?sort=date&direction=ascending

BIOGRAPHICAL SKETCH

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NAME: Ye, Jianxiang

eRA COMMONS USER NAME (credential, e.g., agency login): N/A

POSITION TITLE: PhD Candidate

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
Rensselaer Polytechnic Institute, Troy, NY	B.S.	5/2021	Biochemistry & Biophysics
Columbia University, New York, NY	M. A.	6/2023	Biology

A. Personal Statement

I am a Ph.D. candidate at Columbia University and an emerging scientist specializing in structural biology, with a focus on G protein-coupled receptors (GPCRs) studied through cryo-electron microscopy (cryo-EM). GPCRs are essential cell surface receptors involved in numerous physiological processes including sensory perception, immune regulation, and neural signaling, and are the target of over one-third of all prescription medications. My doctoral research investigates the molecular mechanisms of GPCR signaling, with an emphasis on structurally capturing dimeric receptor complexes to better understand their role in disease pathways such as cancer, cardiovascular conditions, and neurological disorders.

I bring a broad research background to this work, having trained in both bacterial and mammalian systems across multiple institutions. My research journey began as an undergraduate at the Wadsworth Center, New York State Department of Health, under the mentorship of Dr. Jon Paczkowski, where I studied bacterial quorum sensing and methods to disrupt pathogenic signaling. I then served as a research technician in Dr. Gang Lin's lab at Weill Cornell Medicine, contributing to the development of novel therapeutic agents targeting cancer and malaria. Since joining Columbia University in 2022, I have conducted my Ph.D. research under the mentorship of Professor Qing R. Fan in the Department of Cellular Physiology and Biophysics, where I apply high-resolution cryo-EM to uncover the structural basis of dimeric GPCR signaling.

Over the course of my academic career, I have published in high-impact journals such as Nature and Nature Communications. These publications reflect not only the scientific rigor of my work but also its relevance to the broader fields of pharmacology and structural biology. My research has been recognized internationally by scientists in the United States, China, Denmark, and other countries, underscoring the global relevance of my contributions.

In summary, I have demonstrated a consistent trajectory of impactful research and a deep commitment to advancing the understanding of GPCR-mediated signaling. With a strong foundation in structural biology, proven research productivity, and growing recognition in the field, I am well-positioned to successfully carry out the proposed research and contribute meaningfully to future therapeutic innovation.

Citations:

1. Hsu HC, Li D, Zhan W, **Ye J**, Liu YJ, Leung A, Qin J, Crespo B, Gamo FJ, Zhang H, Cui L, Roth A, Kirkman LA, Li H, Lin G. Structures revealing mechanisms of resistance and collateral sensitivity of Plasmodium falciparum to proteasome inhibitors. Nat Commun. 2023 Dec 14;14(1):8302. doi: 10.1038/s41467-023-44077-2. PMID: 38097652; PMCID: PMC10721928.

2. Zuo H, Park J, Frangaj A, **Ye J**, Lu G, Manning JJ, Asher WB, Lu Z, Hu GB, Wang L, Mendez J, Eng E, Zhang Z, Lin X, Grassucci R, Hendrickson WA, Clarke OB, Javitch JA, Conigrave AD, Fan QR. Promiscuous G-protein activation by the calcium-sensing receptor. Nature. 2024 May;629(8011):481-488. doi: 10.1038/s41586-024-07331-1. Epub 2024 Apr 17. PMID: 38632411

B. Positions, Scientific Appointments, and Honors

2022 – Present Ph.D. researcher thesis, Dept of Cellular Physiology, Columbia University, New York, NY
2021 – 2022 Research technician, Dept. of Immunology, Weill Cornell Medicine, New York, NY
2020 – 2021 Undergrad researcher, Wadsworth Center, New York State Dept of Health, Albany, NY

C. Contributions to Science

1. I played a key role in advancing our understanding of drug resistance mechanisms in malaria through structural studies of the Plasmodium falciparum proteasome (Pf20S). Working alongside a multidisciplinary team, I was responsible for the purification of high-quality Pf20S complexes, which enabled high-resolution cryo-EM studies. This structural work elucidated the binding interactions of Pf20S with the selective noncovalent inhibitor TDI-8304, and provided comparative insights through structures of the human constitutive proteasome with the same inhibitor, as well as a mutant Pf20Sβ6A117D with a β2-selective inhibitor, WLW-vs. These studies revealed key mechanisms of species selectivity, resistance, and collateral sensitivity. Importantly, the findings highlighted how resistance mutations can enhance susceptibility to alternative inhibitors, suggesting strategies for combination therapies that minimize resistance emergence. This work, published in Nature Communications (2023), contributes to the structure-guided development of next-generation Pf20S inhibitors to combat multidrug-resistant malaria.

A. Hsu HC, Li D, Zhan W, Ye J, Liu YJ, Leung A, Qin J, Crespo B, Gamo FJ, Zhang H, Cui L, Roth A, Kirkman LA, Li H, Lin G. Structures revealing mechanisms of resistance and collateral sensitivity of Plasmodium falciparum to proteasome inhibitors. Nat Commun. 2023 Dec 14;14(1):8302. doi: 10.1038/s41467-023-44077-2. PMID: 38097652; PMCID: PMC10721928.

2. In addition to the contributions described above, I serve as a key contributor in elucidating the structural and functional mechanisms of the human calcium-sensing receptor (CaSR) in complex with multiple G-protein subtypes. Working with a team of collaborators, I generated expression plasmids, conducted site-directed mutagenesis, and supported functional analysis to probe the receptor's signaling behavior. These efforts enabled the resolution of cryo-EM structures of CaSR in complex with Gq, Gi, and Gs proteins, revealing the unique coupling mechanism of this dimeric GPCR. This body of work demonstrated that CaSR can engage different G-protein subfamilies through a conserved interaction mode, in which a single G protein docks asymmetrically at the intracellular interface of the CaSR homodimer. These findings also identified a key residue in the Gα subunit responsible for determining subtype-specific coupling, highlighting molecular determinants that govern CaSR's signaling promiscuity. This work not only advances our understanding of CaSR biology but also provides a structural blueprint for targeting dimeric GPCRs and designing subtype-specific modulators. The findings have important implications for diseases associated with CaSR dysfunction, including both calcitropic and non-calcitropic disorders such as hypercalcemia, hypocalcemia, cardiovascular disease, and cancer.

A. Zuo H, Park J, Frangaj A, Ye J, Lu G, Manning JJ, Asher WB, Lu Z, Hu GB, Wang L, Mendez J, Eng E, Zhang Z, Lin X, Grassucci R, Hendrickson WA, Clarke OB, Javitch JA, Conigrave AD, Fan QR. Promiscuous G-protein activation by the calcium-sensing receptor. Nature. 2024 May;629(8011):481-488. doi: 10.1038/s41586-024-07331-1. Epub 2024 Apr 17. PMID: 38632411