BIOGRAPHICAL SKETCH

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NAME: Zhang, Cheng

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

POSITION TITLE: Associate Professor of Pharmacology and Chemical 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
University of Science and Technology of China, Hefei, An hui, China	BS	07/2003	Biology
University of Science and Technology of China, Hefei, An hui, China	PHD	07/2008	Biochemistry and Molecular Biology
Stanford University, Stanford, California, US	Postdoctoral	10/2013	GPCR structural biology and pharmacology

A. Personal Statement

I am a tenured Associate Professor of Pharmacology and Chemical Biology, and my research is focused on structure and pharmacology of integral membrane receptors including G protein-coupled receptors (GPCRs). My research group employs a broad range of research methods in structural biology including X-ray crystallography and cryo-electron microscopy (cryo-EM), cell biology and pharmacology to elucidate the molecular basis for the signal transduction of GPCRs and other integral membrane receptors involved in inflammation and immunity. We have determined the structures of important GPCRs including receptors for anaphylatoxins, prostaglandins, leukotrienes, cannabinoids, vasopressin and dopamine, which together with our results from ligand-binding assays and cell-based signaling assays provided novel insights into ligand action and receptor signaling. In addition, we develop functional membrane protein antibodies and small molecule GPCR ligands as potential therapeutics and research tools through multiple approaches. I serve as a PI or co-PI or co-Investigator on several NIH-funded grants. In summary, I have the expertise, leadership, training, expertise, and motivation necessary to successfully carry out the proposed research project.

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

R35 GM128641 (Zhang)
NIH/NIGMS
8/01/2018-7/31/2023
Structure, pharmacology and signaling of G protein-coupled receptors (GPCRs) in inflammation
Role: Principal Investigator

R03 TR003306
NIH/NCATS
Zhang (PI)
4/1/2021 - 3/31/2022

Structure and pharmacology of GPR32 in the resolution of inflammation
Role: Principal Investigator

R01 DA052329 (Xie and Zhang)
NIH/NIDA
7/1/2021 - 6/30/2026
Cannabinoid CB2 Receptor Structure and Allosteric Modulators
Role: Co-Principal Investigator

R01AI163011 (Yi, Duprex and Zhang)
NIH/ NIAID
4/1/2022 - 3/31/2027
Development of multivalent, ultrapotent nanobody cocktails for SARS-CoV-2 neutralization
Role: Co-Principal Investigator

R01 CA258778 (Feng)
NIH/NCI
4/1/2021 - 3/31/2026
Targeting tumor-associated macrophages for triple-negative breast cancer treatment
Role: Co-Investigator

Relevant publications for this project (membrane receptor cryo-EM structures, *Corresponding authors):

1. Qi X, Liu H, Thompson B, McDonald J, **Zhang C***, Li X*. Cryo-EM structure of oxysterol-bound human Smoothened coupled to a heterotrimeric Gi. Nature. 2019; 571:279-283. PMID: 31168089.
2. Zhuang Y, Liu H, Edward Zhou X, Kumar Verma R, de Waal PW, Jang W, Xu TH, Wang L, Meng X, Zhao G, Kang Y, Melcher K, Fan H, Lambert NA, Eric Xu H*, **Zhang C***. Structure of formylpeptide receptor 2-G_i complex reveals insights into ligand recognition and signaling. Nature Communications. 2020 Feb 14;11(1):885. PMID: 32060286. PMCID: PMC7021761.
3. Zhuang Y, Xu P, Mao C, Wang L, Krumm B, Zhou XE, Huang S, Liu H, Cheng X, Huang XP, Shen DD, Xu T, Liu YF, Wang Y, Guo J, Jiang Y, Jiang H, Melcher K, Roth BL*, Zhang Y*, **Zhang C***, Xu HE*. Structural insights into the human D1 and D2 dopamine receptor signaling complexes. Cell. 2021 Feb 18;184(4):931-942.e18. PMID: 33571431.
4. Zhuang Y, Wang L, Guo J, Sun D, Wang Y, Liu W, Xu HE*, **Zhang C***. Molecular recognition of formylpeptides and diverse agonists by the formylpeptide receptors FPR1 and FPR2. *Nature Communications*. 2022 Feb 25;13(1):1054. PMID: 35217703. PMCID: PMC8881469.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021 - 2022	NIH Peer Review Committee, Special Emphasis Panel, Emergency Awards: Antiviral Drug Discovery (AViDD) Centers for Pathogens of Pandemic Concern (U grants).
2021 - current	Consultant, Biogen, Boston, MA.
2021 - current	Associate Professor of Pharmacology and Chemical Biology, University of Pittsburgh, School of Medicine, Pittsburgh, PA.
2021 - current	Member, American Society for Pharmacology and Experimental Therapeutics (ASPET).
2020 - current	Member, American Society for Biochemistry and Molecular Biology (ASBMB).
2020	NIH Peer Review Committee, Special Emphasis Panel, Neuropharmacology.
2014 - 2021	Assistant Professor of Pharmacology and Chemical Biology, University of Pittsburgh, School of Medicine, Pittsburgh, PA

2013 - 2014 Basic Life Science Research Associate, Stanford University, Stanford, CA

Honors

2022 Division for Molecular Pharmacology Early Career Award, ASPET, USA.

2021 ASBMB 2021 Early Career Faculty Annual Meeting Award, ASBMB, USA.

2018 Maximizing Investigators' Research Award, NIH, USA.

2017 Competitive Medical Research Fund (CMRF), University of Pittsburgh, USA.

2006 David Blow Visiting Scholarship, CCP4 community, UK.

C. Contributions to Science

1. Structural basis for the signaling and regulation of chemotactic GPCRs. My lab at the University of Pittsburgh studies a group of non-chemokine chemoattractant GPCRs that mediate chemotaxis of innate immune cells by anaphylatoxins, prostaglandin D_2, formylpeptides and leukotrienes. We have solved multiple crystal structures of two receptors, the C5a receptor (C5aR) and the prostaglandin D_2 receptor CRTH2, bound to orthosteric and allosteric ligands, and cryo-EM structures of the formylpeptide receptor 2 (FPR2)-Gi signaling complex with peptide and non-peptide agonists. The structures provided unprecedented insights into how this family of GPCRs recognize chemically diverse inflammatory molecules to induce cellular signaling events. Based on the structures, we proposed novel strategies for developing ligands of those GPCRs as potential therapeutics with improved pharmacological properties. We also collaborated with other groups to use atomic-force microscopy (AFM) and computational simulation and docking methods to study ligand binding on these receptors.

a. Liu H, Kim HR, Deepak RNV, Wang L, Chung KY, Fan H, Wei Z, Zhang C. Orthosteric and allosteric action of the C5a receptor antagonists. Nature Structural & Molecular Biology. 2018;25(6):472-81. PMID: 29867214.

b. Wang L, Yao D, Deepak RNV, Liu H, Xiao Q, Fan H, Gong W, Wei Z, Zhang C. Structures of the human PGD_2 receptor CRTH2 reveal novel mechanisms for ligand recognition. Molecular Cell. 2018. 72, 1–12. PMID: 30220562.

c. Zhuang Y, Liu H, Edward Zhou X, Kumar Verma R, de Waal PW, Jang W, Xu TH, Wang L, Meng X, Zhao G, Kang Y, Melcher K, Fan H, Lambert NA, Eric Xu H, Zhang C. Structure of formylpeptide receptor 2-G_i complex reveals insights into ligand recognition and signaling. Nature Communications. 2020 Feb 14;11(1):885. PMID: 32060286.

d. Liu H, Deepak RNVK, Shiriaeva A, Gati C, Batyuk A, Hu H, Weierstall U, Liu W, Wang L, Cherezov V, Fan H, Zhang C. Molecular basis for lipid recognition by the prostaglandin D_2 receptor CRTH2. Proc Natl Acad Sci U S A. 2021 Aug 10;118(32). PubMed PMID: 34341104. PMCID: PMC8364189.

2. Structural basis for the signaling of dopamine receptors. Dopamine acts on five GPCRs, dopamine D1 to D5 receptors (D1-5Rs), in the central nervous system (CNS). D1R and D2R are the most abundant receptors in the CNS, representing the primary excitatory and inhibitory dopamine receptor, respectively, in all dopaminergic pathways. In collaboration with Dr. Bryan Roth and other research groups, we have determined cryo-EM structures of several D1R-G_s complexes with orthosteric and allosteric ligands and a cryo-EM structure of the D2R-G_i complex. Collectively, these structures revealed the molecular basis for ligand binding, receptor activation and G protein coupling of D1R and D2R. We are currently working on other dopamine receptors, aiming to gain a comprehensive molecular understanding of dopamine signaling through the entire dopamine receptor family.

a. Zhuang Y, Xu P, Mao C, Wang L, Krumm B, Zhou XE, Huang S, Liu H, Cheng X, Huang XP, Shen DD, Xu T, Liu YF, Wang Y, Guo J, Jiang Y, Jiang H, Melcher K, Roth BL*, Zhang Y*, Zhang C*, Xu

HE*. Structural insights into the human D1 and D2 dopamine receptor signaling complexes. Cell. 2021 Feb 18;184(4):931-942.e18. PMID: 33571431. (*Corresponding authors)

b. Zhuang Y, Krumm B, Zhang H, Zhou XE, Wang Y, Huang XP, Liu Y, Cheng X, Jiang Y, Jiang H, Zhang C, Yi W, Roth BL, Zhang Y, Xu HE. Mechanism of dopamine binding and allosteric modulation of the human D1 dopamine receptor. Cell Res. 2021 May;31(5):593-596. PMID: 33750903.

3. Molecular mechanisms underlying signaling of neuropeptide GPCRs. GPCRs for peptide hormones regulate diverse behaviors and physiological functions including appetite, energy homeostasis and motivation. We have determined cryo-EM structures of two neuropeptide GPCRs, the vasopressin V2 receptor (V2R) and the ghrelin receptor GHSR, bound to endogenous and synthetic agonists. Together with data from functional assays, our structures revealed unique binding mechanisms for the cyclic arginine vasopressin peptide and the lipidated ghrelin peptide. They also provided important molecular insights into how synthetic agonists of these two GPCRs mimic endogenous peptide agonists to activate their receptors. Our results are expected to facilitate development of novel agonist drugs for these two receptors.

a. Wang L, Xu J, Cao S, Sun D, Liu H, Lu Q, Liu Z, Du Y, Zhang C. Cryo-EM structure of the AVP-vasopressin receptor 2-G_s signaling complex. Cell Res. 2021 Mar 4. PMID: 33664408.

b. Liu H, Sun D, Myasnikov A, Damiaan M, Baneres JL, Sun J, Zhang C. Structural basis of human ghrelin receptor signaling by ghrelin and the synthetic agonist ibutamoren. Nature Communications. 2021 Nov 4, 12: 6410.

4. Structural and pharmacological characterization of cannabinoid receptors. In collaboration with Dr. Xiang-qun Xie's group and other research groups, we have determined a cryo-EM structure of human cannabinoid receptor CB2 and Gi signaling complex. Structural analysis together with computational studies suggested the structural determinants for distinguishing CB2 agonists and antagonists and revealed significant differences between the two cannabinoid receptors, CB1 and CB2, in receptor activation, ligand recognition and G protein coupling. The results paved the road for our future studies to design novel CB2 ligands including allosteric modulators, which hold promise for treating numerous inflammatory diseases and pain.

a. Xing C, Zhuang Y, Xu T, McDonald J, Feng Z, Zhou E, Chen M, Wang L, Meng X, Xue Y, Wang J, Liu H, McGuire T, Zhao G, Melcher K, Zhang C*, Xu E*, Xie X*. Cryo-EM Structure of Human Cannabinoid Receptor CB2-Gi Signaling Complex. Cell. 2020 Feb 20;180(4):645-654.e13. PMID: 32004460. (*Corresponding authors)

5. Structural characterization of a Smoothened signaling complex. Smoothened (SMO) is an oncoprotein that transduces the Hedgehog signal from the tumor repressor Patched-1 to the glioma-associated oncogene transcription factors GLI. It belongs to the Class-F GPCRs, which also include Frizzled receptors. In collaboration with Dr. Xiaochun Li at the UT Southwestern Medical Center, we solved the structure of SMO and Gi signaling complex with a sterol agonist by cryo-EM. This is the first structure of a Class-F GPCR signaling complex. The structure revealed a new sterol ligand binding site in the 7-transmembrane domain, a novel receptor activation mechanism and a new binding mode of Gi protein that is different from Class-A GPCRs. Our work provides innovative insights into Hedgehog signaling and the activation of Class-F GPCRs.

a. Qi X, Liu H, Thompson B, McDonald J, Zhang C*, Li X*. Cryo-EM structure of oxysterol-bound human Smoothened coupled to a heterotrimeric Gi. Nature. 2019; 571:279-283. PMID: 31168089. (*Corresponding authors).

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