BIOGRAPHICAL SKETCH

NAME: Gouaux, James Eric

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

POSITION TITLE: Senior Scientist

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Harvard College, Cambridge MA	AB	1984	Chemistry
Harvard University, Cambridge MA	PhD	1989	Physical chemistry
Harvard University, Cambridge MA	Postdoc	1989-90	Crystallography
Massachusetts Institute of Technology, Cambridge MA	Postdoc	1990-92	Membrane proteins

A. Personal Statement

My research focuses on the molecular mechanisms and receptor organization at chemical synapses. To do this, I have previously employed x-ray crystallographic methods to elucidate atomic resolution structures of crucial neurotransmitter receptors and transporters, yet I have also enthusiastically engaged and learned complimentary biochemical and biophysical methods with the ultimate aim of using all possible approaches to elaborate structure-based mechanisms. Thus, I have extensive experience in the expression, characterization and structure determination of complex neurotransmitter receptors and transporters, as well as in electrophysiology and total internal reflection microscopy (TIRF; SimPull). In addition, I have now established single particle cryo-electron microscopy (cryo-EM), high pressure freezing, cryo-confocal microscopy and FIB/SEM milling together with cryo-electron tomography (cryo-ET) in my laboratory as central methods by which to elucidate neurotransmitter receptor and transporter structures and to elaborate the organization of receptors in synapses. I have also become proficient, and internationally recognized, in the production of high quality monoclonal antibodies, and their respective domains, for use in labeling receptors and transporters. In this lab, these antibody reagents have allowed us to lead the field in isolation and structure determination of native neurotransmitter receptor complexes. More recently, I have pioneered the use of Fab conjugates with small gold nanoparticles (AuNPs) for studies of receptors at synapses and have established the first use of AuNP multimers, thus expanding the palette of AuNPs. As evidence of my progress in this area, I have published multiple papers in which we have used single particle cryo-EM as the primary tool to elucidate molecular structure and, together with biochemical, electrophysiological and computational approaches have gone on to define structure-based mechanisms for important receptors and transporters. Importantly, I have also established methods to isolate synaptosomes and brain tissue for tomography studies, to harness fluorescence microscopy to target regions for cryo-ET, and to lead efforts to obtain lamella from specific brain regions. The use of *C. elegans* as a model organism for isolation of native complexes has also been pioneered in this lab and I have used this approach to elucidate the first structure of long-sought after TMC-1 and TMC-2 complexes. I also was the founding PI for the PNCC, an NIH-funded, national cryo-EM center, and continue to serve on the PI team.

Projects to highlight include:

NIH 5 R01 MH070039-22
Gouaux, James Eric (PI)
07/01/2004-05/31/2029
Structure and Function of Neurotransmitter Transporters

HHMI (no number)
Gouaux, James Eric (PI)
09/01/2010-08/31/2027
Elucidation of the molecular structures and mechanisms underpinning hair cell mechanosensory transduction

NIH 1 R21 GM154202
Gouaux, James Eric (Co-PI)
06/01/2024-05/31/2026
Graphene Covalent Grids for Single-Particle Cryo-EM

CZI 2024-351065
Gouaux, James Eric (PI)
12/01/2024-11/30/2025
Cryo-ET Investigation of Excitatory Synapses from Mouse Brain

NIH 2 R01 NS038631-27
Gouaux, James Eric (PI)
03/19/1999-02/28/2025, Renewal pending
3D Structure and Function of Ligand-Gated Ion Channels

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2015-Present	Jennifer and Bernard Lacroute Term Chair in Neuroscience Research, Portland OR
2005-Present	Senior Scientist, Vollum Institute, Oregon Health and Science Univ., Portland OR
2000-Present	Investigator, Howard Hughes Medical Institute
2001-2005	Professor, Dept. Biochem. Mol. Biophys., Columbia Univ., New York NY
2000-2001	Associate Professor, Dept. Biochem. Mol. Biophys., Columbia Univ., New York NY
1996-2000	Assistant Professor, Dept. Biochem. Mol. Biophys., Columbia Univ., New York NY
1993-1996	Assistant Professor, Dept. Biochem. Mol. Biol., Univ. Chicago, Chicago IL

Honors

2025	Biophysical Society Lecturer
2020	National Academy of Medicine Member
2016	Anatrace Membrane Protein Award, Biophysical Society
2014	Honorary Doctorate, University of Copenhagen
2014	W. Alden Spencer Award, Columbia University
2014	Alexander M. Cruickshank Lecture, Gordon Research Conferences
2013	Physiological Society Annual Review Prize Lecture
2010	Distinguished Faculty Awards Winner for Outstanding Research
2010	National Academy of Sciences Member
2009	Medical Research Foundation Discovery Award, Oregon Health & Science University
2009	NIHMH MERIT Award
2008	NINDS Javits Investigator Award
2007	American Association for the Advancement of Science Fellow
2003	P&S Dean's Distinguished Award in the Basic Sciences, Columbia University
2000	P&S Doctor Harold & Golden Lamport Award for Excellence in Basic Science Research, Columbia University
1998	Klingenstein Research Fellow
1997	Alfred P. Sloan Research Fellow
1995	National Science Foundation Young Investigator
1994	Searle Scholar

C. Contributions to Science

My major contributions have been to provide a molecular basis for understanding the function of neurotransmitter receptor and transporters, fundamental molecular machines that mediate signal transduction at the chemical synapses of the central nervous system. We have focused on ionotropic glutamate receptors, acid sensing ion channels, ATP-gated P2X receptors and pentameric Cys-loop receptors, as well as on the transporters for glutamate and the biogenic amines, and the complexes essential to force transduction in the hair cells. More recently, we have established methods to image glutamate receptors at synapses. My work has not only provided insights into the three-dimensional structures of these crucial receptors and transporters, but because all of our results are deposited in the publicly accessible Protein Data Bank, the results of my work are available to everyone throughout the world. Thus, our studies will not only inform society on the fundamental building blocks of the brain, but they will also provide a foundation for those who are devoted to developing new therapeutic agents.

1. Our studies on the ionotropic glutamate receptors have provided deep insight into their mechanism of action, showing how antagonists, agonists and allosteric modulators act on these fundamental receptors, and the architecture and subunit organization of native complexes.

a. Yu J, Rao P, Clark S, Mitra J, Ha T, Gouaux E. (2021). Hippocampal AMPA receptor assemblies and mechanism of allosteric inhibition. Nature, 594(7863), 448-453. PMID: 33981040; PMCID: PMC8270219.

b. Zhao Y, Chen S, Swensen AC, Qian WJ, Gouaux E. (2019). Architecture and subunit arrangement of native AMPA receptors elucidated by cryo-EM. Science, 364(6438), 355-362. PMID: 30975770; PMCID: PMC6701862.

c. Jalali-Yazdi F, Chowdhury S, Yoshioka C, Gouaux E. (2018). Mechanisms for Zinc and Proton Inhibition of the GluN1/GluN2A NMDA Receptor. Cell, 175(6), 1520-1532. PMID: 30500536; PMCID: PMC6333211.

2. We have also elaborated the molecular structure of the two major classes of neurotransmitter transporters, showing how these remarkably machines carry neurotransmitter from one side of the membrane to the other and determining methods for isolation and resulting structures of native transporters from brain tissue.

a. Srivastava DK, Navratna V, Tosh DK, Chinn A, Sk MF, Tajkhorshid E, Jacobson KA, Gouaux E. (2024). Structure of the human dopamine transporter and mechanisms of inhibition. Nature, 632(8025), 672-677. PMID: 39112705; PMCID: PMC11324517.

b. Yang D, Zhao Z, Tajkhorshid E, Gouaux E. (2023). Structures and membrane interactions of native serotonin transporter in complexes with psychostimulants. Proc Natl Acad Sci U S A, 120(29), e2304602120. PMID: 37436958; PMCID: PMC10629533.

c. Yang D, Gouaux E. Illumination of serotonin transporter mechanism and role of the allosteric site. (2021). Sci Adv., 7(49), eabl3857. PMID: 34851672; PMCID: PMC8635421.

3. We have elaborated the structures of other neurotransmitter receptors and ligand gated ion channels from recombinant or endogenous sources, shedding new light on native receptor structure, mechanism and assembly.

a. Sun C, Zhu H, Clark S, Gouaux E. (2023). Cryo-EM structures reveal native $GABA_A$ receptor assemblies and pharmacology. Nature, 622(7981), 195-201. PMID: 37730991; PMCID: PMC10550821.

b. Zhu H, Gouaux E. (2021). Architecture and assembly mechanism of native glycine receptors. Nature, 599(7885), 513-517. PMID: 34555840; PMCID: PMC8647860.

c. Yu J, Zhu H, Lape R, Greiner T, Du J, Lü W, Sivilotti L, Gouaux E. (2021). Mechanism of gating and partial agonist action in the glycine receptor. Cell, 184(4), 957-968.e21. PMID: 33567265; PMCID: PMC8115384.

4. We have pioneered the use of C. elegans as model organism for the isolation of native membrane protein complexes and have used this approach, together with recombinant methods and other biophysical approaches, to define the structures for the transduction machinery of cochlea and vestibular hair cells.

a. Clark S, Jeong H, Posert R, Goehring A, Gouaux E. (2024). The structure of the *Caenorhabditis elegans* TMC-2 complex suggests roles of lipid-mediated subunit contacts in mechanosensory transduction. Proc Natl Acad Sci U S A, 121(8), e2314096121. PMID: 38354260; PMCID: PMC10895266.

b. Clark S, Jeong H, Goehring A, Kang Y, Gouaux E. (2023). Large-scale growth of C. elegans and isolation of membrane protein complexes. Nat Protoc., 18(9), 2699-2716. PMID: 37495753.

c. Jeong H, Clark S, Goehring A, Dehghani-Ghahnaviyeh S, Rasouli A, Tajkhorshid E, Gouaux E. (2022). Structures of the TMC-1 complex illuminate mechanosensory transduction. Nature, 610(7933), 796-803. PMID: 36224384; PMCID: PMC9605866.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/james.gouaux.1/bibliography/40629156/public/?sort=date&direction=ascending

BIOGRAPHICAL SKETCH

NAME: Weng, Gaoqi

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

POSITION TITLE: Postdoc

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Zhejiang University, China	BS	06/2018	Pharmaceutical Science
Zhejiang University, China	PhD	06/2023	Medicinal Chemistry
Oregon Health & Science University, Portland OR	Postdoc	11/2023-Ongoing	Structural Biology

A. Personal Statement

My postdoc research focuses on the molecular underpinnings of the function of the mechanosensory transduction complex in hair cells. To do this, I employ single-particle cryo-EM and cryo-electron tomography with complementary computational, biochemical, fluorescence, and biophysical approaches. We have solved many technical challenges associated with the preparation of lamella containing the stereocilia tips and now have a preparation that is ready for structural studies of the cochlea tip link. During my graduate studies, I specialized in computational methodologies for studying protein-protein interactions (PPIs) and PROTACs. I developed several widely used computational tools, including HawkDock, a web server for predicting and analyzing PPIs; PROTAC-Model, an integrative protocol for modeling PROTAC-mediated ternary complexes; and PROTAC-DB, a database that compiles structural and experimental data on PROTACs. With my combined expertise in computational modeling and experimental techniques, I am well-positioned to successfully execute the proposed research project, bridging structural biology and computational analysis to advance our understanding of mechanosensory transduction.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments
2024 – Present, Member, Biophysical Society

Honors
2023 Outstanding PhD Graduate of Zhejiang Province, Zhejiang Province, China

C. Contributions to Science

During my PhD study, I focused on the computational methodologies for studying protein-protein interactions (PPIs) and PROTACs. The most cited work was HawkDock, a web server for predicting and analyzing PPIs. I seamlessly integrated the ATTRACT docking algorithm, the HawkRank scoring function, and the MM/GBSA free energy decomposition analysis into a multi-functional platform. Over the past years, it has processed over 230,000 user tasks and has been cited over 500 times. Leveraging my expertise in protein-protein docking, I also designed PROTAC-Model, an integrative protocol for accurately modeling PROTAC-mediated ternary complexes from unbound structures. In addition, I constructed the web-accessible database of PROTACs, PROTAC-DB, which integrates structural information and experimental data of PROTACs, and is very popular in the targeted protein degradation field.

a. **Weng, G.**; Wang, E.; Wang, Z.; Liu, H.; Zhu, F.; Li, D.; Hou, T. HawkDock: a web server to predict and analyze the protein-protein complex based on computational docking and MM/GBSA. Nucleic Acids Res 2019, 47, W322-W330.
b. **Weng, G.**; Li, D.; Kang, Y.; Hou, T. Integrative Modeling of PROTAC-Mediated Ternary Complexes. J Med Chem 2021, 64, 16271-16281.
c. **Weng, G.**; Shen, C.; Cao, D.; Gao, J.; Dong, X.; He, Q.; Yang, B.; Li, D.; Wu, J.; Hou, T. PROTAC-DB: an online database of PROTACs. Nucleic Acids Res 2021, 49, D1381-D1387.
d. **Weng, G.**; Cai, X.; Cao, D.; Du, H.; Shen, C.; Deng, Y.; He, Q.; Yang, B.; Li, D.; Hou, T. PROTAC-DB 2.0: an updated database of PROTACs. Nucleic Acids Res 2023, 51, D1367-D1372.

Complete List of Published Work in My Google Scholar:
https://scholar.google.com/citations?user=Cj0oKoEAAAAJ