BIOGRAPHICAL SKETCH

Applicant Name: Dongxue Yang, Ph.D.

Position Title: Postdoctoral Fellow

Education/Training

Institution & Location	Dates Attended	Degree	Conferred	Field of Study
University of Science and Technology of China	09/2007	B.S	07/2011	Life Science
Institute of Biophysics, Chinese Academy of Sciences	09/2011	Ph.D.	07/2016	Biochemistry and molecular biology
Oregon Health and Science University, Portland OR	09/2016	Postdoc		Structural Biology

1. Personal Statement

I have a strong background in protein biochemistry with additional experience in molecular biology and x-ray crystallography of proteins. I mainly focused on obtaining x-ray crystal structures of nucleosome related complexes during my Ph.D study. I got much experience in protein crystallography and macromolecular assembly from my prior experimental work. I am very interested in structural biology and membrane transport. I have joined Gouaux lab as a postdoctoral fellow and focus on serotonin transporter. Gouaux lab provides all aspects of equipment and reagents for structural and functional study of membrane proteins. My mentor has much experience in purification and analysis of membrane proteins and he will instruct me to prepare well for purifying, characterizing membrane proteins.

My goal is to investigate the mechanism and structural basis of membrane transport. I believe the excellent research environment of Gouaux lab will allow me to accomplish my aim. My research is directly implicated in human disease and disorders and is of importance and relevance to the mental health and physical well-being of millions of Americans. I am pretty sure to determine high-resolution structure of SERTin complex with serotonin with cryo-EM. I believe that the scope time from NCCAT is crucial to the success of my project.

2. Positions/Employment, Memberships and Honors

2016-Present	Postdoctoral Fellow, Vollum Institute, Oregon Health and Science University
2011-2016	Graduate Student, Department of National Laboratory Of Biomacromolecules, Institute of Biophysics, Chinese Academy of Sciences
2007-2011	Undergraduate Student, School of life Sciences, University of Science and Technology of China
2016	Pivot of Merit Student

2015	National Scholarship
2014	President prize of Chinese Academy of Sciences
2014	Broken Hill Proprietary Billiton (BHPB) Scholarship
2013	First prize of Director Scholarship of Institute of Biophysics
2010	National Scholarship
	Outstanding Student Scholarship (Grade 1)
2009	Outstanding Student Scholarship (Grade 2)
2008	Outstanding Student Scholarship (Grade 2)
2007	Special Freshman Scholarship

3. Contribution to Science

1) Silencing of the mating-type (*HM*) and telomeric loci in yeast requires the set of *trans*-acting silent information regulators Sir1, Sir2, Sir3 and Sir4. Sir3 has an N-terminal BAH domain, which is essential for Sir3's silencing function. The silencing function of Sir3 or its BAH domain depends on the acetylation of the terminal α-amino group. But how Nα acetylation of the Sir3 BAH domain affects NCP binding was not known. I solved the crystal structure of acSir3-NCP complex and found Ala2 acetylation strengthens the interaction between Sir3BAH and NCP by stabilizing loop 3 of Sir3BAH in a productive conformation, which provided insights into the structure and function of the vast eukaryotic N-terminal acetylome.

2) Mecp2 belongs to methyl-CpG binding protein family. There are 5 sites in MBD domain possessing high frequency of mutations, which always result in the serious RETT syndrome. MeCP2 mediates chromatin array compaction but the mechanism is not clear. In order to investigate the mechanism of chromatin compaction mediated by MeCP2, I successfully reconstituted tetra-nucleosome array in vitro and assembled complex with MeCP2. I found that MeCP2 can compact tetra-NCP and got crystal of the complex, which is still under optimization.

3) The serotonin transporter (SERT) terminates signaling through the sodium-and chloride-dependent reuptake of neurotransmitter into presynaptic neurons. Neurotransmitter transporters utilize an alternating access mechanism in which conformational changes expose a central substrate binding site to each side of the membrane. Crystal structures of human SERT in complex with selective serotonin reuptake inhibitors (SSRIs) have advanced our mechanistic understanding of SSRI inhibition and indicate that these drugs, in general, bind to the central binding pocket, thus providing a structural understanding for their competitive mechanism of inhibition. The mechanism of neurotransmitter transport, however, remains elusive. Unlike SSRI inhibitors, ibogaine is a hallucinogenic alkaloid that non-competitively inhibits transport, yet exhibits competitive binding toward SSRIs. Taken together, the structural mechanism by which ibogaine acts on SERT is unclear. We have captured ibogaine bound to SERT in complexes with antibody fragment(s) in three distinct conformational states– outward-open, occluded, and inward open using single particle cryo-EM. Detailed analysis of the cryo-EM structures show how ibogaine is accommodated within the central site of the transporter in these three distinct conformational states and illuminate the structural basis of ibogaine inhibition. These structures also show how closure of the extracellular gate largely involves movements of TMs 1b and 6a and the opening of the intracellular gate is accompanied by a hinge-like movement of TM1a and partial unwinding of TM5. Our studies thus define the structural rearrangements which occur from the outward to the inward states and provide insight into the mechanism of neurotransmitter transport.

4. Peer Reviewed Publications

Yang, D.*, Fang, Q.*, Wang, M.*, Ren, R., Wang, H., He, M., Sun, Y., Yang, N., Xu, R.M. (2013) (*Equal contribution.).Nα-acetylated Sir3 stabilizes the conformation of a nucleosome-binding loop in the BAH domain. Nat Struct Mol Biol 20, 1116-8.

Campbell, N.G., Shekar, A., Aguilar, J.I., Peng, D., Navratna, V., **Yang, D**., Morley, A.N., Duran, A.M., Galli, G., O'Grady, B., et al. (2019). Structural, functional, and behavioral insights of dopamine dysfunction revealed by a deletion in SLC6A3. Proc Natl Acad Sci U S A 116, 3853-3862.

Coleman, J.*, **Yang, D.***, Zhao, Z., Wen, P., Yoshioka, C., Tajkhorshid, E., Gouaux, E. (2018) (*Equal contribution.). Serotonin transporter–ibogaine complexes illuminate mechanisms of inhibition and transport. (Accepted in Nature)

5. Research Support

NONE

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Gouaux, James Eric

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

POSITION TITLE: Senior Scientist

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 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 underpinning signal transduction at chemical synapses. To do this, I have primarily 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 crystallization of complex neurotransmitter receptors and transporters, as well as in x-ray crystallography and electrophysiology. I have gained hands-on experience in single particle cryo electron microscopy (cryo EM) by working in the laboratory of Yifan Cheng at UCSF and by intensive interactions with Tom Walz (Harvard), Niko Grigorieff (Janelia) and Craig Yoshioka (OHSU). Thus, I have now established single particle cryo EM in my laboratory as an exciting and highly promising method by which to elucidate neurotransmitter receptor structures. As evidence of my progress in this area, I have published 3 papers in which we have used single particle cryo-EM as the primary tool to elucidate molecular structure.

B. Positions and Honors

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

1994	Searle Scholar
1995	National Science Foundation Young Investigator
1997	Alfred P. Sloan Research Fellow
1998	Klingenstein Research Fellow
2000	P&S Doctor Harold & Golden Lamport Award for Excellence in Basic Science Research, Columbia University

2003	P&S Dean's Distinguished Award in the Basic Sciences, Columbia University
2007	American Association for the Advancement of Science Fellow
2008	NINDS Javits Investigator Award
2009	NIHMH MERIT Award
2009	Medical Research Foundation Discovery Award, Oregon Health & Science University
2010	National Academy of Sciences Member
2010	Distinguished Faculty Awards Winner for Outstanding Research
2013	Physiological Society Annual Review Prize Lecture
2014	Alexander M. Cruickshank Lecture, Gordon Research Conferences
2014	W. Alden Spencer Award, Columbia University
2014	Honorary Doctorate, University of Copenhagen
2016	Anatrace Membrane Protein Award, Biophysical Society

C. Contribution 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. 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 publically 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.

a. Zhu S. Stein RA, Yoshioka C, Lee CH, Goehring A, Mchaourab HS, Gouaux E. Mechanism of NMDA receptor inhibition and activation. *Cell* 165: 704-14 (2016). PMCID: PMC4914038
b. Dürr KL, Chen L, Stein RA, De Zorzi R, Folea IM, Walz T, Mchaourab HS, Gouaux E. Structure and dynamics of AMPA receptor GluA2 in resting, pre-open, and desensitized states. *Cell* 158:778-92 (2014). PMCID: PMC4263325
c. Chen L, Dürr KL, Gouaux E. X-ray structures of AMPA receptor–cone snail toxin complexes illuminate activation mechanism. *Science* 345:1021-6 (2014). PMCID: PMC25103405

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.

a. Coleman JA, Green EM, Gouaux E. X-ray structures and mechanism of the human serotonin transporter. *Nature* 532: 334-39 (2016). PMCID: PMC4898786
b. Wang KH, Penmatsa A, Gouaux E. Neurotransmitter and psychostimulant recognition by the dopamine transporter. *Nature* 521:322-27 (2015). PMCID: PMC4469479.
c. Penmatsa A, Wang K, Gouaux E. X-ray structure of the dopamine transporter illuminates mechanism of antidepressant action. *Nature* 503:85-90 (2013). PMCID: PMC3904663

3. In addition, we have elaborated the structures of other neurotransmitter receptors and ligand gated ion channels of the brain, from acid sensing ion channels and ATP-gated P2X receptors to pentameric Cys-loop receptors, thus providing the neuroscience field with molecular blueprints upon which to ground studies of mechanism and drug development.

a. Du J, Lü W, Wu S, Cheng Y, Gouaux E. Glycine receptor mechanism illuminated by electron cryo-microscopy. *Nature* 526:224-29 (2015). PMCID: PMC4659708
b. Hattori M, Gouaux E. Molecular mechanism of ATP binding and ion channel activation in P2X receptors. *Nature* 485:207-212. (2012). PMCID: PMC3391165

c. Mansoor SE, Lü W, Oosterheert W, Shekhar M, Tajkhorshid E, Gouaux E. X-ray structures define human P2X3 receptor gating cycle and antagonist action. Nature doi: 10.1038/nature19367 (epub ahead of print). NIHMSID: NIHMS821331.

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

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D. Research Support

NIH 2 R01 NS038631-19 Gouaux, James Eric (PI) 03/19/1999-02/28/2020
3D Structure and Function of Ligand-Gated Ion Channels
The focus of this work is on determining the atomic structure of ligand-gated ion channels activated glutamate (AMPA receptors) or protons (ASICs) using x-ray diffraction techniques, on developing mechanisms for the activity of these channels, and on testing the mechanisms by a variety of techniques that include electrophysiology and other biochemical and biophysical methods. I am involved in all aspects of these studies, from experimental design to manuscript preparation.
Role: PI

NIH 4 R37 MH070039-14 Gouaux, James Eric (PI) 07/01/2004-02/28/2019
Structure and Function of Neurotransmitter Transporters
The research supported by this grant is concentrated on determining structures of bacterial homologs of human neurotransmitter transporters by x-ray crystallography and on studying the mechanism of these bacterial proteins using a combination of site-directed mutagenesis, flux assays and other biochemical and biophysical studies, with the aim being to understand the architecture of this important family of proteins and how that architecture relates the function of both prokaryotic and eukaryotic transporters. I am involved in all aspects of these studies, from experimental design to manuscript preparation.
Role: PI

HHMI (no number) Gouaux, James Eric (PI) 09/01/2010-08/31/2020
Molecular Studies of Synapses
The research supported by these funds is focused on developing new methods for the purification of native membrane proteins from their endogenous context - on a nanogram scale - using novel fluorescently labeled affinity tags, in the development of new methods for EM grid preparation and in the isolation and structural study of complexes involved in mechanotransduction. I am involved in all aspects of these studies, from experimental design to manuscript preparation.
Role: PI

RECENT
NIH 5 R01 GM100400-04 Gouaux, James Eric (PI) 02/01/2012-01/31/2016
NIH/NIGMS
Structural biology of neurotransmitter ion channels
The aim of this work is to solve high resolution x-ray crystal structures of P2X and Cys-loop receptors bound to their cognate neurotransmitter and to competitive antagonists, to test the veracity of the mapped sites by site-directed mutagenesis and ligand-binding assays, and to develop molecular mechanisms for the action of agonists and antagonists in these receptors. I am involved in all aspects of these studies, from experimental design to manuscript preparation.
Role: PI

NIH 5 P50 DA018165-08 Janowsky, Aaron (PI) 07/01/2014-06/30/2015
NIH/NIDA
Structural and biochemical dissection of the mechanism of inhibition by methamphetamine at the dopamine transporter
The goal of this research is to solve the X-ray crystal structure of a methamphetamine-dDAT complex. To complement the structure, we will also dissect the biochemical nature of the inhibition mechanism using in vitro flux assays and radioligand binding experiments. I am involved in all aspects of these studies, from experimental design to manuscript preparation.
Role: Co-PI