BIOGRAPHICAL SKETCH

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NAME: Xi-Ping Huang

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POSITION TITLE: Research Assistant Professor, Pharmacology; Assistant Scientific Director, NIMH PDSP

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	Completion Date	FIELD OF STUDY
Nanjing University, Nanjing, PR China	BS	07/1986	Biochemistry
Institute of Microbiology, Chinese Academy of Science, Beijing, PR China	MS	12/1989	Microbiology
University of Toledo, Toledo, OH	PhD	05/2000	Medicinal & Biological Chemistry
SUNY at Stony Brook, Stony Brook, NY	Postdoctoral	07/2002	$G_{\alpha s}$ function in vivo
Hershey Medical Center, PSU, Hershey, PA	Postdoctoral	01/2007	GPCR allosteric modulation

A. Personal Statement

I have over 20 years of experience in molecular pharmacology of G-protein coupled receptors (GPCRs). Since 2007, I have been working with the NIMH-PDSP (National Institute of Mental Health Psychoactive Active Drug Screening Program, directed by Bryan Roth, MD, PhD) in the Department of Pharmacology, UNC at Chapel Hill. The NIMH PDSP provides screening service at human GPCRs to academic investigators at no cost. At the NIMH-PDSP, I started as a Research Associate responsible for assay development and functional assays, mainly with GPCRs. Since 2013, I have been serving as Assistant Scientific Director of PDSP, assisting Dr. Roth running the NIMH PDSP. My roles include assay design and development, functional assays, trouble shooting, quality control, supervising staff scientists and technicians, communicating with and providing technical assistance to the investigators who requesting screening services from PDSP. Over the years, I have been involved in many collaboration projects, from high throughput screening campaigns to characterization of lead compounds and structure-activity relationship (SAR) studies; from GPCR structure projects to functional selectivity (bias), probe design and optimization. In the same time, I have been developing my own research projects focusing on H^+-sensing GPCRs, also funded by NIMH. I reported the first small molecule positive allosteric modulator (PAM) ogerin, selective for GPR68 and now commercially available from several vendors as a tool compound. With ogerin as a template, I developed a much better PAM MS48107 for GPR68. Initial results indicate that MS48107 is in vivo active in the pancreas (where GPR68 is highly expressed) and enhances glucose-depended insulin secretion in wild-type but not in GPR68 KO mice (unpublished and a patent is pending). I have also initiated a project to design and develop PAM-antagonists for GPR68 (R21, ongoing). Most recently, I reported that divalent metal ions (Cd^{2+}, Co^{2+}, Fe^{2+}, Mn^{2+}, Ni^{2+}, and Zn^{2+}) all act as PAMs for GPR68 at pathophysiologically relevant concentrations. Their allosteric actions are dependent on certain extracellular Histidine residues which are also critical for H^+-sensing. The current proposal builds on my recent findings on metal ion modulation of GPR68 and focuses on identifying NAMs to inhibit metal ion activated GPR68 as potential therapeutic agents.

Key representative publications:

A. **Huang XP***, Karpiak J*, Kroeze WK*, Zhu H, Chen X, Moy SS, Saddoris KA, Nikolova VD, Farrell MS, Wang S, Mangano TJ, Deshpande DA, Jiang A, Penn RB, Jin J, Koller BH, Kenakin T, Shoichet BK, Roth BL. Allosteric ligands for the pharmacologically dark receptors GPR68 and GPR65. **Nature**. 2015

Nov 26;527(7579):477-83. Doi: 10.1038/nature15699. PMID: 26550826. PMCID: PMC4796946. (* equal authorship).

B. Yu XF, **Huang XP***, Kenakin TP, Slocum ST, Chen X, Martini ML, Liu J*, and Jin J*. Design, synthesis, and characterization of ogerin-based positive allosteric modulators for G protein-coupled receptor 68 (GPR68). **J Med Chem** 2019 Aug 22; 62(16):7557-7574. Doi: 10.1021/acs.jmedchem.9b00869. PMID: 31298539. PMCID: PMC6923801. (*corresponding authors)

C. **Huang XP***, Kenakin TP, Gu S, Shoichet BK, and Roth BL. Differential roles of extracellular Histidine residues of GPR68 for proton-sensing and allosteric modulation by divalent metal ions. **Biochemistry** 2020 Sep 29; 59(38):3594-3614. Doi: 10.1021/acs.biochem.0c00576. PMID:32865988. (*corresponding author)

D. Foster SR, Hauser AS, Vedel L, Strachan RT, **Huang XP**, […] David E. Gloriam. Discovery of human signaling systems: Pairing peptides to G protein-coupled receptors. **Cell** 2019 Oct 31;179(4):895-908.e21. Doi: 10.1016/j.cell.2019.10.010. PMID: 31675498, PMCID: PMC6838683.

B. Positions and Honors

2007-2012: Research Associate, NIMH Psychoactive Drug Screening Program (NIMH PDSP), Department of Pharmacology, UNC at Chapel Hill.
2010-2011: Review committee and Chair of the Special Emphasis Panel on NIEHS Small Business Innovation Research (SBIR) Phase I Contract Proposal (PHS 2011-1) Topic 114, November 2010-January 2011.
2013 – Current: Assistant Scientific Director, NIMH PDSP; Research Assistant Professor, Department of Pharmacology, UNC at Chapel Hill.
2013-Current: F1000Prime Associate Faculty Member, Pharmacology and Drug Discovery, f1000.com
2014-2015: Guest Editor, Current Protocols in Pharmacology (Wiley.com)

C. Contributions to Science

1. Designing and developing PRESTO-Tango GPCRome high throughput screening platform and applications. Human genome contains about 350 nonolfacotry GPCRs. Among them, about 100 are orphan receptors with yet to be identified endogenous agonists. A universal platform is urgently needed to screen for agonist activity at all human GPCRs. We reported a such screening platform in 2015 to measure potential agonist activity at 320 human nonolfactory GPCRs. I was involved in the initial assay design, development, and optimization of the screening assays, and am a co-first author of the PRESTO-Tango paper. The PRESTO-Tango assay platform has been widely used in NIMH PDSP as indicated by selected high impact papers below. I am responsible for further optimizations and supervising routine screening assays.

A. Kroeze WK*, Sassano MF*, Huang XP*, […] Roth BL. PRESTO-Tango as an open-source resource for interrogation of the druggable human GPCRome. Nat Struct Mol Biol. 2015 May;22(5):362-9. Doi: 10.1038/nsmb.3014. PMID: 25895059; PMCID: PMC4424118. (* equal authorship).

B. Lansu K, Karpiak J, Liu J, Huang XP, […] Roth BL. In silico design of novel probes for the atypical opioid receptor MRGPRX2. Nat Chem Bio. 2017 May; 13(5):529-536. Doi:10.1038/nchembio.2334. PMID: 28288109. PMCID: PMC5391270.

C. Wang S, Wacker D, Levit A, Che T, […] Roth BL. D_4 dopamine receptor high resolution structures template the discovery of selective agonists. Science 2017 Oct 20; 358(6361): 381-386. Doi: 10.1126/science.aan5468. PMID:29051383. PMCID: PMC5856174.

D. Stein RM, Kang HJ, McCorvy JD, […] Dubocovich ML. Virtual discovery of melatonin receptor ligands to modulate circadian rhythms. Nature 2020 Mar; 579(7800):609-614. Doi: 10.1038/s41586-020-2027-0. PMID: 32040955. PMCID: PMC7134359.

2. Designing and developing high throughput counter screening for risk-targets and their applications. Counter-screenings at risk-targets (such as hERG channels and 5-HT2B receptors) are popular requests among PIs who request screening assays at NIMH PDSP, to identify compounds with potential liability issues in early stages of drug design and development, I developed screening assays. These assays are conducted regularly in the NIMH PDSP. For example, during the COVID 19 shut-down months in early

2020, I participated in a large collaboration project, tested several compounds at hERG channels as well as other targets, contributed to the large campaign to identify potential targets for SARS-CoV 2.

A. Huang XP, Mangano T, Hufeisen S, Setola V, Roth BL. Identification of human Ether-à-go-go related gene modulators by three screening platforms in an academic drug-discovery setting. Assay Drug Dev Technol. 2010 Dec;8(6):727-42. Doi: 10.1089/adt.2010.0331. PMID: 21158687; PMCID:3002179.

B. Huang XP, Setola V, Yadav PN, Allen JA, Rogan SC, Hanson BJ, Revankar C, Robers M, Doucette C, Roth BL. Parallel functional activity profiling reveals valvulopathogens are potent 5-hydroxytryptamine(2B) receptor agonists: implications for drug safety assessment. Mol Pharmacol. 2009 Oct;76(4):710-22. Doi: 10.1124/mol.109.058057. PMID: 19570945; PMCID: PMC2769050.

C. Gordon DE, Jang GM, […] Krogan NJ. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature 2020 Jul; 583(7816):459-468. Doi: 10.1038/s41586-020-2286-9. PMID: 32353859. PMCID: PMC7430030.

3. Collaborations to design, develop, and optimize novel ligands as chemical probes and potential therapeutics at GPCRs. In these collaborations and selected papers, I am responsible for designing and carrying out binding and or functional assays to profile the leads, analyze results for publications.

A. Allen JA, Yost JM, Setola V, Chen X, Sassano MF, Chen M, Peterson S, Yadav PN, Huang XP, […] Jin J. Discovery of β-arrestin-biased dopamine D_2 ligands for probing signal transduction pathways essential for antipsychotic efficacy. Proc Natl Acad Sci U S A. 2011 Nov 8;108(45):18488-93. doi: 10.1073/pnas.1104807108. PMID: 22025698; PMCID: PMC3215024.

B. Manglik A, Lin H, Aryal DK, McCorvy JD, Dengler D, Corder G, Levit A, Kling RC, Bernat V, Hubner H, Huang XP, […] Shoichet BK. Structure-based discovery of opioid analgesics with reduced side effects. Nature 2016 537(7619):185-190, doi:10.1038/nature19112. PMID:27533032.

C. Che T, Majumdar S, Zaidi SA, Ondachi P, Mccorvy JD, Wang S, Mosier PD, Uprety R, Vardy E, Krumm BE, […] Roth BL. Structure of the Nanobody-stabilized active state of the Kappa opioid receptor. Cell. 2018 jan 11:172(1-2):55-67. E15. PMID: 29307491, PMCID:5802374.

D. Nagai Y, Miyakawa N, […] Minamimoto T. Deschloroclozapine, a potent and selective chemogenetic actuator enables rapid neuronal and behavioral modulations in mice and monkeys. Nat Neurosci 2020 Sep; 23(9):1157-1167. Doi:10.1038/s41593-020-0661-3. PMID: 32632286.

4. Collaborations to understand GPCR structure, function, and molecular and structural basis for functional selectivity. In these collaborations and selected papers, I am responsible for creating mutant receptors, designing and carrying out binding and functional assays, analyze results for publications.

A. Stauch B, Johansson LC, […] Vadim Cherezov. Structural basis of ligand recognition at the human MT1 melatonin receptor. Nature 2019 May; 569(7755):284-288. Doi: 10.1038/s41586-019-1141-3. PMID: 31019306. PMCID: PMC66966938.

B. Johansson LC, Stauch B, […] Vadim Cherezov. XFEL structures of the human MT2 melatonin receptor reveal the basis of subtype selectivity. Nature 2019 May; 569(7755): 289-292. Doi: 10.1038/s41586-019-1144-0. PMID: 31019305. PMCID: PMC6589158.

C. Xu P, Huang S, Mao C, Krumm B, Zhou XE, Tan X, Huang XP, […], Xu HE. Structures of the human dopamine D3 receptor-Gi complexes. Mol Cell. 2021 Jan 27; S1097-2765(21)00003-4. Doi: 10.1016/j.molcel.2021.01.003. PMID: 33548201.

D. Zhuang Y, Xu P, Mao C, Wang L, Krumm B, Zhou XE, Huang S, Liu H, Cheng X, Huang XP, […], Xu HE. Structural insights into the human D1 and D2 dopamine receptor signaling complexes. Cell 2021 Feb 5; S0092-8674(21)00070-2. Doi: 10.1016/j.cell/2121.01.027. PMID: 33571431.

Complete list of published papers is available in My NCBI > My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/xp.huang.1/bibliography/public/

D. Additional Information: Research Support and/or Scholastic Performance

1. R56 MH111769-01 Xi-Ping Huang (PI) and Terry Kenakin 2017-2018

NIMH, Designing and Developing Functional Selective Allosteric Modulators for GPR68

For this completed project, I was the corresponding PI. The main goal is to design better positive allosteric modulators (PAMs) for GPR68. With the first GPR68 PAM ogerin as the starting template, we carried out extensive structure-activity relationship (SAR) studies and cell-based pharmacological assays, which led to a group of new PAMs with improved allosteric activity. One best compound MS48107 showed 30x higher allosteric activity than ogerin, active at both human and mouse GPR68, selective for GPR68 over GPR4 and GPR65, low binding activity at common drug targets, and good PK profile. These findings have been published (Yu et al., JMC 2019, PMID 31298539).

2. R21 MH120422 Xi-Ping Huang (PI) and Terry Kenakin 2019-2021
NIMH, Designing and Developing PAM-antagonists for GPR68

For this ongoing project, I am the corresponding PI. The main goal is to design PAM-antagonists for GPR68 based on a newly discovered small molecule lead. PAM-antagonist is a unique type of allosteric modulators which has increased binding affinity in the presence of orthosteric agonist (protons in this case) and in the same time inhibits orthosteric agonist efficacy. This type of modulators would seek and selectively block GPR68 only when extracellular pH is reducing (more protons). We are conducting both SAR and mutational studies to examine molecular mechanisms and design novel PAM-antagonists for GPR68. One most recent finding is that divalent metal ions (such as Cd^{2+}, Co^{2+}, Fe^{2+}, Mn^{2+}, Ni^{2+}, and Zn^{2+}) are actual PAMs for GPR68 and they greatly potentiate proton activity at GPR68, but not GPR4 or GPR65, at pathophysiologically relevant concentrations. GPR68 activation by protons and allosteric potentiation by divalent metal ions are two inseparable processes in vivo. To inhibit GPR68 activity, a comprehensive molecular intervention is needed. This finding has been published recently (Huang et al., 2020, Biochemistry, PMID32865988). The new finding established a supporting rationale for this current application – to find and optimize mechanism-based negative allosteric modulators (NAMs) to selectively block GPR68 activity that is potentiated by divalent metal ions under acidic conditions (such as neuroinflammatory conditions).