BIOGRAPHICAL SKETCH

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NAME: Zhang, Qisheng

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

POSITION TITLE: Associate Professor

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
Tsinghua University, Beijing	B.S.	06/1995	Chemical Engineering
Shanghai Institute of Organic Chemistry	M.S.	06/1998	Organic Chemistry
University of Pittsburgh, Pittsburgh, PA	Ph.D.	04/2003	Organic Chemistry
The Scripps Research Institute, La Jolla, CA	Post-doc	12/2006	Chemical Biology

A. Personal Statement

My research interest is focused on understanding how lipid metabolism organizes membrane structure and signaling, and developing new chemical tools targeting lipid signaling pathways for potential diagnostic and therapeutic applications. Lipids play essential roles in all living organisms. Other than being major membrane constituents in cells, many lipids function as signaling molecules. Consequently, abnormal levels of lipids and aberrant regulation of their metabolizing enzymes have been associated with onset and progression of various diseases. However, how lipid signaling pathways regulate normal development and diseases is still poorly understood, largely due to their dynamic metabolism in the cells and the lack of available reagents and assays for lipids and their metabolic enzymes. I am interested in three different approaches to profile and understand lipid metabolism: 1) Develop small molecule sensors and modulators for different lipid metabolizing enzymes; 2) Develop efficient methods and technologies to profile lipids and use the resulting data for precision medicine and identification of new signaling molecules; and 3) Investigate cellular functions of known and unknown phospholipids, particularly their synergistic actions with small GTPases ADP-ribosylation factors in regulating protein trafficking in signaling transduction. More recently, we have also extended our efforts to drug discovery towards diseases (particularly cancer and neurodegenerative diseases) where lipid metabolizing enzymes are dysregulated. Toward this end, we are constructing library of small molecules with unique structures and functions.

I am committed to mentoring the next generation of scientists and have completed the mentorship trainings by the Office of Graduate Education. As the Director of Graduate Studies in the Division of Chemical Biology and Medicinal Chemistry, I oversee a graduate program with approximately 40 graduate students. As a member of the Graduate Education Committee in the Eshelman School of Pharmacy, I am actively involved in establishing and implementing policies related to training of graduate students. UNC recently was rewarded an NIH T32 pre-doctoral training grant at the Chemistry-Biology Interface. I have been serving on the steering committee to select trainees. I also serve as the Division Director of the RASP (Research and Scholarship in Pharmacy) program that enables PharmD students to have research experience. In the past 10 years, I have mentored eight postdoctoral fellows, two graduate students and seven PharmD students. Two students have been awarded fellowship from the American Foundation for Pharmaceutical Education (AFPE) and one postdoctoral fellow has been selected as a trainee for the NIH training program in Cancer Nanotechnology.

On-going projects that I would like to highlight:

R01CA258993-01 (Zhang/Pearce/Sondek) NIH 05/01/2021-04/30/2025
A high-throughput platform to identify selective allosteric inhibitors of the PLC-gamma isozymes
Role: Principal Investigator

The goal of this grant is to develop an innovative high-throughput platform to identify selective allosteric inhibitors of the PLC-gamma isozymes that are ready for further development.

R01CA177993-01A1 (Allbritton/Armistead/Gomez/Zhang) NIH 05/07/2019-04/30/2024
Microfabricated instrumentation to measure sphingolipid signaling in human acute myeloid leukemia
Role: Multiple Principal Investigator

The goal of this grant is to develop an innovative platform to measure the activity of the sphingolipid pathway in single cells from primary, human, acute myeloid leukemia.

Not numbered (Zhang) Eshelman Institute for Innovation 07/01/2021-06/30/2024
Targeting LRRK2 for novel therapeutics for Parkinson's disease
Role: Principal Investigator

The goal of this grant is to further develop a small molecule that regulates LRRK2's GTPase activity through inhibition of ArfGAP1 as a lead for novel therapeutic to treat Parkinson's disease.

R56AG083424-01 (Zhang/Pearce/Sondek) NIH 09/01/2023-08/31/2025
Discovery of allosteric activators of PLC-γ2 as novel therapeutics to treat Alzheimer's disease
Role: Principal Investigator

The goal of this grant is to discover PLC-γ2 activators as novel therapeutics for Alzheimer's disease.

R01CA282339-01 (La-Beck/Zhang) NIH 09/19/2023-08/31/2028
Cholesterol metabolism in the pharmacology of liposomal therapeutics
Role: Multiple Principal Investigator

The goals of this grant are to understand how liposomes interact with the immune system to control tumor growth and to develop novel cholesterol analogs for liposomal delivery.

Citations:

1. Gallion, L. A.; Wang, Y.; Massaro, A.; Petersen, B. V.; Huang, W.; Zhang, Q.; Carr, A.; Zhang, Q.; Allbritton, N. L. "Fix and click" for assay of sphingolipid signaling in single primary human intestinal epithelial cells. *Anal. Chem.* **2022**, 94, 1594-1600.
2. Huang, W.; Carr, A. J.; Hajicek, N.; Sokolovski, M.; Siraliev-Perez, E.; Hardy, P. B.; Pearce, K. H.; Sondek, J.; Zhang, Q. A High-throughput Assay to Identify Allosteric Inhibitors of the PLC-γ Isozymes Operating at Membranes. *Biochemistry* **2020**, 59, 4029-4038.
3. Hajicek, N.; Keith, N. C.; Siraliev-Perez, E.; Temple, B. R. S.; Huang, W.; Zhang, Q.; Harden, T. K.; Sondek J. Structural Basis for the Activation of PLC-γ Isozymes by Phosphorylation and Cancer-associated Mutations. *Elife* **2019**, 8:e51700.
4. Huang, W.; Wang, X.; Endo-Streeter, S.; Barrett, M.; Waybright, J.; Wohlfeld, C.; Hajcek, N.; Harden, T. K.; Sondek, J.; Zhang, Q. A Membrane-associated, Fluorogenic Reporter for Mammalian Phospholipase C Isozymes. *J. Biol. Chem*. **2018**, 293, 1728-1735. PMCID: PMC5798302.

B. Positions, Scientific Appointments, and Honors

Professional Positions

3/2018- present	Director of Graduate Studies, Chemical Biology and Medicinal Chemistry, UNC
9/2014 - present	Associate Professor of Pharmacology, UNC-Chapel Hill
1/2013 - present	Associate Professor of Chemical Biology and Medicinal Chemistry, UNC-Chapel Hill
9/2011- present	Member, UNC Lineberger Comprehensive Cancer Center
1/2007 - 1/2013	Assistant Professor of Chemical Biology and Medicinal Chemistry, UNC-Chapel Hill

Selected Professional Services

2021	NIH study section, High Throughput Screening panel
2021	NIH study section, ZAI1 NPEV panel
11/2019-08/2020	Consultant, Eisai Inc., Boston, MA

Honors

2015	PY2 Instructor of the Year, UNC Eshelman School of Pharmacy
2007	Junior Faculty R. J. Reynolds Fund Award

C. Contribution to Science

For a complete list of peer-reviewed publications (47) please consult:
http://www.ncbi.nlm.nih.gov/pubmed/?term=qisheng+zhang

Chemical tools to monitor and regulate activity of the phospholipase C isozymes

Extracellular stimuli including hormones, growth factors, and neurotransmitters promote activation of phospholipase C (PLC) isozymes and cleavage of the membrane lipid phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P_2) into the classical second messengers, diacylglycerol and inositol 1,4,5-trisphosphate (IP_3). These second messengers coordinately control numerous signaling cascades through the mobilization of intracellular Ca^{2+} stores and the activation of protein kinase C. Aberrant regulation of PLCs contribute to diverse human diseases including cancer, cardiovascular diseases, neuropathic pain, and Alzheimer's disease. We have invented a series of small molecule reporters for PLCs including WH-15 and XY-69 to monitor their activity. These reporters are then utilized to develop high-throughput assays to identify small molecule modulators of PLCs, both as chemical probes to study PLC biology and starting points for drug discovery.

1. Siraliev-Perez, E.; Hoffmann, R.; Stariha, J.; Temple, B. R.; Zhang, Q.; Hajicek, N.; Burke, J. E.; Sondek, J. Dynamics of allosteric regulation of the phospholipase C-γ isozymes upon recruitment to membranes. *eLife* **2022**, 11:e77809.
2. Huang, W.; Carr, A. J.; Hajicek, N.; Sokolovski, M.; Siraliev-Perez, E.; Hardy, P. B.; Pearce, K. H.; Sondek, J.; Zhang, Q. A High-throughput Assay to Identify Allosteric Inhibitors of the PLC-γ Isozymes Operating at Membranes. *Biochemistry* **2020**, 59, 4029-4038.
3. Huang, W.; Wang, X.; Endo-Streeter, S.; Barrett, M.; Waybright, J.; Wohlfeld, C.; Hajcek, N.; Harden, T. K.; Sondek, J.; Zhang, Q. A Membrane-associated, Fluorogenic Reporter for Mammalian Phospholipase C Isozymes. *J. Biol. Chem*. **2018**, 293, 1728-1735. PMCID: PMC5798302.
4. Huang, W.; Hicks, S. N.; Sondek, J.; Zhang, Q. A Fluorogenic, Small Molecule Reporter for Mammalian Phospholipase C Isozymes. *ACS Chem. Biol.* **2011**, 6, 223-228. PMCID: PMC3312000.

Targeted and untargeted profiling of lipid signaling pathways

Abnormal levels of phospholipids and aberrant regulation of their metabolizing enzymes have been associated with onset and progression of various diseases. However, direct analysis of lipid profiles and measurement activity of their metabolizing enzymes have been challenging. In addition, traditional genetic and biochemical methods usually study lipids and their metabolizing enzymes individually. We have developed novel fluorescent and clickable derivatives of phosphatidylinositides and sphingolipids to measure enzymatic activity, both in bulk cells and single cells. These efforts have recently been extended to analogs of ether lipids and cholesterol derivatives. We are also developing novel lipidomics methods to profile lipids including low abundant signaling lipids.

1. Gallion, L. A.; Wang, Y.; Massaro, A.; Petersen, B. V.; Huang, W.; Zhang, Q.; Carr, A.; Zhang, Q.; Allbritton, N. L. "Fix and click" for assay of sphingolipid signaling in single primary human intestinal epithelial cells. *Anal. Chem.* **2022**, 94, 1594-1600.
2. Waybright, J.; Huang, W.; Proctor, A.; Wang, X.; Allbritton, N. L.; Zhang, Q. Required Hydrophobicity of Fluorescent Reporters for Phosphatidylinositol Family of Lipid Enzymes. *Anal. Bioanal. Chem*. **2017**, 409, 6781-6789. PMCID: PMC5671358.
3. Huang, W.; Proctor, A.; Sims, C. E.; Allbritton, N. L.; Zhang, Q. Fluorous Enzymatic Synthesis of Phosphatidylinositides. *Chem. Commun*. **2014**, 50, 2928-2931. PMCID: PMC3993006.
4. Huang, W.; Jiang, D.; Wang, X.; Sims, C. E.; Allbritton, N. L.; Zhang, Q.* Kinetic analysis of PI3K reactions with fluorescent PIP_2 derivatives. *Anal. Bioanal. Chem*. **2011**, 401, 1881-1888.

Regulation of small GTPases ADP-ribosylation factors (ARFs)

While working as a postdoctoral fellow in Dr. Peter Schultz's lab at Scripps, I have established chemical and genetic screens to identify novel modulators of the canonical Wnt/β-catenin signaling pathway. One small molecule, QS11 synergistically activates the Wnt/β-catenin pathway through interacting with ARFGAP1 and thereby activating small GTPase ARFs. Several groups have since followed up our initial discovery to illustrate how ARFs crosstalk with the Wnt/β-catenin signaling. Realizing that synergy between ARFs and PIs is one of the major mechanisms to regulate membrane trafficking, I continue to study ARFs by illustrating how QS11 interacts with ARFGAP1/ARF1. I have also developed the first high-throughput screen assay of ARFGAP enzymatic activity. In collaboration with the NIH screening center at Scripps Florida, we have completed a screen

of over 370,000 compounds and are working on 3 promising chemical series to develop potent and selective ARFGAP inhibitors. These compounds represent the first set of ARFGAP inhibitors. We have also developed a chemical biology approach to selectively modify and regulate ARFs.

1. Gao, H.; Sun, W.; Song, Z.; Yu, Y.; Wang, L.; Chen, X.; Zhang, Q. A Method to Generate and Analyze Modified Myristoylated Proteins. *Chembiochem* **2017**, 18, 324-330. PMCID: PMC5285324.
2. Sun, W.; Vanhooke, J.; Sondek, J.; Zhang, Q. High Throughput Fluorescence Polarization Assay for the Enzymatic Activity of GTPase-activating Protein of ADP-ribosylation Factor (ARFGAP). *J. Biomol. Screen.* **2011**, 16, 717-723.
3. Jones, C. A.; Nishiya, N.; London, N. R.; Zhu, W.; Sorensen, L. K.; Chan, A.; Lim, C. J.; Chen, H.; Zhang, Q.; Schultz, P. G.; Hayallah, A. M.; Thomas, K. R.; Famulok, M.; Zhang, K.; Ginsberg, M. H.; Li, D. Y. Slit2-Robo4 Signaling Promotes Vascular Stability by Blocking Arf6 Activity. *Nature Cell Biol*. **2009**, 11, 1325-1331. PMCID: PMC2854659.
4. Zhang, Q.; Major, B.; Takanashi, S.; Camp, N. D.; Nishiya, N.; Peters, E. C.; Ginsberg, M.; Schultz, P. G.; Moon, R. T.; Ding, S. A Small Molecule Synergist of the Wnt/β-catenin Signaling Pathway. *Proc. Natl. Acad. Sci. U. S. A.* **2007**, 104, 7444–7448. PMCID: PMC1863490.

Fluorous chemistry in biological applications

I was trained as a synthetic organic chemist in graduate school under Dr. Dennis Curran's guidance at the University of Pittsburgh. As the major contributor to the technique "fluorous quasiracemic synthesis", I developed the strategy to synthesize multiple natural products simultaneously by tagging different starting materials with distinct fluorous tags and subsequently separating products based on tags. The power of using fluorous tags to separate products from complex reaction mixtures prompted me to further develop fluorous techniques in my independent research, but in biological applications rather than chemical synthesis. We have introduced "fluorous enzymatic profiling" and "fluorous enzymatic synthesis" techniques to identify new targets of small molecule drugs and to generate endogenous, complex signaling molecules such as PIs.

1. Huang, W.; Proctor, A.; Sims, C. E.; Allbritton, N. L.; Zhang, Q. Fluorous Enzymatic Synthesis of Phosphatidylinositides. *Chem. Commun*. **2014**, 50, 2928-2931. PMCID: PMC3993006.
2. Song, Z.; Huang, W.; Zhang, Q. Isotope-coded, Fluorous Photoaffinity Labeling Reagents. *Chem. Commun*. **2012**, 48, 3339-3341.
3. Zhang, Q.; Lu, H.; Richard, C. R.; Curran, D. P. Synthesis of Sixteen Stereoisomers of Murisolin, Murisolin A and 16,19-cis-Murisolin by Fluorous Mixture Synthesis. *J. Am. Chem. Soc.* **2004**, 126, 36–37.
4. Luo, Z.; Zhang, Q.; Oderaotoshi, Y.; Curran, D. P. Fluorous Mixture Synthesis: A Fluorous-Tagging Strategy for the Synthesis and Separation of Mixtures of Organic Compounds. *Science* **2001**, 291, 1766–1769.

Drug discovery through targeting trafficking processes

Phospholipids and small GTPases are major regulators of trafficking events. Many diseases, particularly infectious diseases, have close association with aberrant trafficking processes. We used both target-based and phenotype-based approaches to identify small molecules that inhibit growth of virus, pathogenic bacteria, and malaria.

1. Clements, R. L.; Streva, V.; Dumoulin, P.; Huang, W.; Owens, E.; Raj, D. K.; Burleigh, B.; Llinas, M.; Winzeler, E. A.; Zhang, Q.; Dvorin, J. D. A Novel Antiparasitic Compound Kills Ring-stage Plasmodium Falciparum and Retains Activity Against Artemisinin-resistant Parasites. *J. Infect. Dis.* **2020**, 221, 956-962.
2. Tan, L.; Zhou, T.; Cederquist, G.; Mukherjee, S.; Kristen, B.; Zhang, Q.; Schwartz, R.; Evans, T. R.; Chen, S. High Content Screening in hESC-Neural Progenitors Identifies Drug Candidates that Inhibit Zika Virus Infection in Fetal-like Organoids and Adult Brain. *Cell Stem Cell* **2017**, 21, 274-283. PMCID: PMC5553280.
3. Singh, M. H.; Gao, H.; Sun, W.; Song, Z.; Schmalzigaug, R.; Premont, R. T.; Zhang, Q. Structure-activity Relationship Studies of QS11, a Small Molecule Wnt Synergistic Agonist. *Bioorg. Med. Chem*. *Lett.* **2015**, 25, 4838-4842. PMCID: PMC4607626.
4. Huang, W.; Barrett, M.; Hajicek, N.; Hicks, S.; Harden, T. K.; Sondek, J.; Zhang, Q. Small Molecule Inhibitors of Phospholipase C from a Novel High-throughput Screen. *J. Biol. Chem*. **2013**, 288, 5840-5848. PMCID: PMC3581404.