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	2003-2006	Chemical Biology

A. Personal Statement

My research interest is focused on understanding the roles of endogenous small molecules, particularly the phosphatidylinositides (PIs), in cell signaling events that are responsible for both normal development and diseases. PIs are one of the most versatile signaling molecules, yet are difficult to study due to their dynamic metabolism in the cells and the lack of available reagents and assays for PIs and their metabolic enzymes. Consequently, how PI signaling pathways regulate normal development and diseases is still poorly understood. I am interested in three different approaches to address this question: 1) develop efficient methods and technologies to synthesize PIs and identify their interacting proteins; 2) develop small molecule sensors and inhibitors for different PI metabolic enzymes; and 3) investigate the cellular functions of known and unknown PIs, particularly their synergistic actions with small GTPases ADP-ribosylation factors in regulating protein trafficking in signaling transduction.

B. Positions and Honors

Professional Positions

1/2007 - 1/2013 Assistant Professor of Chemical Biology and Medicinal Chemistry, UNC-Chapel Hill
1/2013 - present Associate Professor of Chemical Biology and Medicinal Chemistry, UNC-Chapel Hill
9/2014 - present Associate Professor of Pharmacology, UNC-Chapel Hill

Honors

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

C. Contribution to Science

For a complete list of peer-reviewed publications (31) please consult:
http://www.ncbi.nlm.nih.gov/pubmed/?term=qisheng+zhang

Chemical probes for phosphatidylinositide signaling pathway

Phosphatidylinositides (PIs) play diverse roles in various cellular processes. Every enzyme that is involved in PI metabolism, when mutated, deleted, or abnormally amplified, is linked to at least one type of human diseases. However, the roles of PIs in disease development are poorly understood due to their dynamic metabolism in the cells, complex chemical structures and cellular localizations, and the lack of available reagents and assays for PIs and their metabolic enzymes. We have developed a novel fluorogenic reporter, WH-15 that enables the development of the first high-throughput screen to identify small molecule inhibitors for

mammalian phospholipase C isozymes. We have also developed fluorescent PtdIns(4,5)P_2 derivatives, when coupled with capillary electrophoresis that enables simultaneously measuring activity of multiple PI metabolic enzymes.

1. 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.
2. 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. [PMC journal- in process].
3. Wang, X.; Barrett, M.; Sondek, J.; Harden, T. K.; Zhang, Q. Fluorescent Phosphatidylinositol 4,5-Bisphosphate Derivatives with Modified 6-Hydroxy Group as Novel Substrates for Phospholipase C. *Biochemistry* **2012**, 51, 5300-5306. [PMC journal- in process].
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. [PMC journal- in process].

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. 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.
2. 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.
3. 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. [PMC journal- in process].
4. 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**, in press. doi: 10.1016/j.bmcl.2015.06.062. [PMC journal- in process].

Fluorous chemistry in biological applications

I was trained as a synthetic organic chemist in graduate school in Dr. Dennis Curran's lab 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. Song, Z. and Zhang, Q. Fluorous Aryl Diazirine Photoaffinity Labeling Reagents. *Org. Lett.* **2009**, 11, 4883-4885. [PMC journal- in process].
2. Song, Z.; Zhang, Q. "Design, Synthesis, and Incorporation of Fluorous 5-Methylcytosines into Oligonucleotides". *J. Org. Chem*. **2011**, 76, 10263-10268. [PMC journal- in process].

3. Song, Z.; Huang, W.; Zhang, Q. Isotope-coded, Fluorous Photoaffinity Labeling Reagents. *Chem. Commun*. **2012**, 48, 3339-3341. [PMC journal- in process].
4. Huang, W.; Proctor, A.; Sims, C. E.; Allbritton, N. L.; Zhang, Q. Fluorous Enzymatic Synthesis of Phosphatidylinositides. *Chem. Commun*. **2014**, 50, 2928-2931. [PMC journal- in process].

D. Research Support

On-going research support

R01GM086558-01A1 (Zhang) NIH 09/01/2011-08/31/2016
Developing Small Molecule ARFGAP Regulators to Dissect Cell Signaling
Role: Principal Investigator
The goal of this grant is to develop small molecule ARFGAP regulators to probe cell signaling, particularly the role of ARFGAP-regulated processes for the Wnt/β-catenin signaling pathway.

R01GM098894-01 (MPI: Sondek/Zhang) NIH 09/26/2011/-08/31/2015
High-throughput Screens to Identify Modulators of Phospholipase C Isozymes
Role: Principal Investigator
The goal of this grant is to develop integrated screening strategies for the identification of modulators of PLCs.

R01CA177993-01A1 (Allbritton) NIH 08/15/2014-07/31/2019
Single-cell Measurement of Lipid Signaling in Colorectal Cancer
Role: Co-investigator
The goal of this application is to develop a technology platform to readily measure lipid signaling in single cells of colorectal cancer cell lines or patient samples. My lab is responsible for design, synthesis, and characterization of various lipid probes.

Pending research support

R33CA202833-01 (MPI: Allbritton/Zhang) NIH 12/01/2015-11/30/2018
Profiling Phosphoinositide Signaling to Improve Diagnosis of Thyroid Cancer
Role: Principal Investigator
The goal of this grant is to develop a fluorous mixture synthesis approach in live cells to profile phosphoinoside signaling for diagnosis uses.

R21EB022116-01 (Zhang) NIH 04/01/2016-03/31/2018
Small Molecule Biosensors for Mammalian Phospholipase C Isozymes
Role: Principal Investigator
The goal of this grant is to develop small molecule biosensors to monitor cellular activity of mammalian phospholipase C isozymes with spatial and temporal resolution.

Overlap

None.

Completed research support

1R21NS073041-01 (Zhang) NIH 09/01/2010-08/31/2013
High Throughput Assay Development for ARFGAP Modulators
Role: Principal Investigator
The goal of this grant is to develop a fluorescence polarization-based assay that is amenable to high through screen of ARFGAP modulators.

3R21NS073041-01S1 (Zhang) NIH 09/01/2010-08/31/2013
High Throughput Assay Development for ARFGAP Modulators
Role: Principal Investigator
The goal of this grant is to apply the fluorescence polarization-based assay to high through screen at NIH Florida screening center to identify ARFGAP modulators.

R01HL094463-01 (Liu) NIH 02/01/2009-01/31/2014
In Vitro Synthesis of Recombinant Heparan Sulfate
Role: Co-investigator

The goals of this grant are: 1) develop a fluorous tag-based enzymatic synthesis strategy to synthesize structurally-defined oligosaccharides; 2) determine the substrate specificities of a variety of heparan sulfate biosynthetic enzymes; and 3) utilize the newly developed method to investigate novel anticoagulant HS structures.

R01ES013611-01S1 (Jaspers) NIH 08/01/2013-06/30/2015
Diesel-induced Alterations of Influenza Infectivity
Role: Co-investigator

The overall goal of this grant is to develop novel technologies and complementary experimental approaches to investigate how exposures to diesel exhaust modify innate immune responses in humans.