

BIOGRAPHICAL SKETCH

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NAME: Zijian Xie

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

POSITION TITLE: Investigator and Director, Marshall Institute for Interdisciplinary Research

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
Nanjing College of Pharmacy, PRC	B.S.	1982	Pharmacy
Chinese Academy of Md. Sci., PRC	M.S.	1984	Toxicology
Medical College of Ohio, Toledo, OH	Ph.D.	1990	Pharmacology
Medical College of Ohio, Toledo, OH	Post-doc.	1990-91	Pharmacol./Pathology
Washington University, St. Louis, MO	Visiting Asst. Prof.	1997	Cell Biology and Physiology

Please refer to the Biographical Sketch sample in order to complete sections A, B, C, and D of the Biographical Sketch.

A. PERSONAL STATEMENT

For the past 25 years, I have been interested in the cell biology of Na/K-ATPase in epithelial and cardiac cells. Specifically, I have been focused on revealing the non-pumping functions of this plasma membrane protein. Much of this investigation has been funded by grants from NIH. My lab has demonstrated that the Na/K-ATPase has an ion-pumping independent signaling function. Moreover, we have shown the relevance of the signaling function of Na/K-ATPase to the pathophysiology of renal and cardiovascular diseases. Recently, we have developed a novel peptide (pNaKtide) antagonist of receptor Na/K-ATPase and shown that pNaKtide blocks ouabain-induced signal transduction in cultured cardiac myocytes. We have further demonstrated the effectiveness of pNaKtide in intact animals. In the current project, Dr. Jiang Tian proposes to study the role of Na/K-ATPase and its signaling function in regulating cardiac fibrosis through miR-29b related mechanism using an animal model with chronic kidney disease. Dr. Tian's lab has found that pNaKtide can attenuate ouabain-induced decrease in miR-29b expression, which is a novel finding and will potentially advance the understanding the role of Na/K-ATPase on regulation of cardiac fibrosis in CKD models. I will collaborate with Dr. Tian and provide him with my expertise and established tools for the proposed studies.

1. Tian, J., Cai, T., Yuan, Z., Wang, H., Liu, L., Haas, M., Maksimova, E., Huang, X-Y., and Xie, Z. (2006) Binding of Src to Na⁺/K⁺-ATPase forms a functional signaling complex. *Mol. Biol. Cell* 17, 317-326. PMID: PMC1345669.
2. Liang, M., Cai, T., Tian, J., Qu, W., and Xie, Z.J. (2006) Functional characterization of Src-interacting Na/K-ATPase using RNA interference assay. *J. Biol. Chem.*, 281, 19709-19719. PMID: 16698801.
3. Li, Z., Cai, T., Tian, J., Xie, J.X., Zhao, X., Liu, L., Shapiro, J.I., and Xie, Z. (2009) NaKtide, a Na/K-ATPase-derived peptide Src inhibitor, antagonizes ouabain-activated signal transduction in cultured cells. *J. Biol. Chem.* 284: 21066-21076. PMID: PMC2742871.
4. Li, Z., Zhang, Z., Xie, J.X., Li, X., Tian, J., Cai, T., Cui, H., Ding, H., Shapiro, J.I., and Xie, Z. (2011) Na/K-ATPase mimetic pNaKtide inhibits the growth of human cancer cells. *J Biol. Chem.* 286: 32394-32403. PMID: PMC3173162.

B. Positions and Honors

Positions AND Employment

1984-1986	Assoc. Res. Inst. Of Food Safety Control and Inspection, Chinese Acad. of Prev. Med.
1990-1992	Postdoc. Fellow, Depart. of Pharmacology and Pathology, Med. Coll. of Ohio, Toledo, OH
1991-1992	Instructor, Department of Pharmacology, Medical College of Ohio, Toledo, OH
1992-1996	Res. Asst. Professor, Department of Pharmacology, Medical College of Ohio, Toledo, OH
1996-2000	Assistant Professor, Department of Pharmacology, Medical College of Ohio, Toledo, OH
2000-2005	Associate Professor, Department of Pharmacology, Medical College of Ohio, Toledo, OH
2001-2005	Associate Professor, Department of Medicine, Medical College of Ohio, Toledo, OH
2005-2006	Professor, Departments of Physiology, Pharmacology, Metabolism, and Cardiovascular Sciences, and Professor, Department of Medicine, Medical University of Ohio, Toledo, OH
2006-2013	Professor, Departments of Physiology and Pharmacology, and Professor, Department of Medicine, Health Science Campus, The University of Toledo, Toledo, OH
2013-present	Investigator and Director, Marshall Institute for Interdisciplinary Research, Marshall University, Huntington, WV

Other Experience and Professional memberships

2005-2009	CMBK Study Section (NIH), Regular Member
2009-2011	MIST Study Section (NIH), Ad Hoc Member
2011	Special Panel, ZRG1 DKUS-D, Member
2012-2018	MIST Study Section (NIH), Regular Member
2010	Scientific Advisor, International Workshop on "Interactions of Cardiac Steroids and the Na ⁺ , K ⁺ -ATPase: Molecular, Physiological and Pharmacological Implications", Jerusalem, Israel.
2010-2011	Member, organizing committee "13 th International Conference "Na,K-ATPase and Related P-ATPases: Structure, Biology and Medicine"
2011	Chair, Round Table Discussion, International Workshop on "Interactions of Cardiac Steroids and the Na ⁺ , K ⁺ -ATPase: Molecular, Physiological and Pharmacological Implications", Jerusalem, Israel.

C. Contributions to Science

1. My laboratory has identified for the first time the important receptor-like function of Na/K-ATPase that allows endogenous cardiotonic steroids to provoke protein and lipid kinases. This receptor-like function of $\alpha 1$ Na/K-ATPase depends on its intrinsic ability to interact directly with and regulate the functionality of non-receptor protein kinase Src. While the Na/K-ATPase provides the binding site for its ligands, the associated Src acts as a signal transducer, converting and amplifying the ligand-induced conformational change in the Na/K-ATPase to activation and assembly of down-stream signaling processes.
 1. Tian, J., Cai, T., Yuan, Z., Wang, H., Liu, L., Haas, M., Maksimova, E., Huang, X-Y., and Xie, Z. (2006) Binding of Src to Na⁺/K⁺-ATPase forms a functional signaling complex. *Mol. Biol. Cell* 17, 317-326. PMID: PMC1345669.
 2. Liang, M., Cai, T., Tian, J., Qu, W., and Xie, Z.J. (2006) Functional characterization of Src-interacting Na/K-ATPase using RNA interference assay. *J. Biol. Chem.*, 281, 19709-19719. PMID: 16698801.
 3. Liang, M., Tian, J., Liu, L., Pierre, S., Shapiro J., and Xie, Z-J. (2007) Identification of a pool of non-pumping Na/K-ATPase. *J. Biol. Chem.* 282, 10585-10593. PMID: 17296611.
 4. Ye, Q., Li, Z., Tian, J., Xie, J., Liu, L., and Xie, Z. (2011) Identification of a potential receptor that couples ion transport to protein kinase activity. *J. Biol. Chem.* 286, 6225-6232. PMID: PMC3057788.
2. Our investigation has also revealed the important scaffolding function of $\alpha 1$ Na/K-ATPase in the formation of efficient signaling microdomains and membrane structures such as caveolae.

1. Wang, H., M. Haas, M. Liang, T. Cai, J. Tian, S. Li and Z. Xie (2004). Ouabain assembles signaling cascades through the caveolar Na⁺/K⁺-ATPase. *J. Biol. Chem.* 279(17): 17250-17259.
2. Cai, T., Wang, H., Chen, Y., Quintas, L.E.M., Liu, L., Gunning, W.T., and Xie, Z.-J. (2008) Regulation of caveolin-1 membrane traffic by the Na/K-ATPase. *J. Cell. Biol.* 182, 1153-1169. PMID: PMC2542476.
3. Chen, Y., Cai, T., Wang, H., Li, Z., Loreaux, E., Lingrel, J.B., and Xie, Z. (2009) Regulation of intracellular cholesterol distribution by the Na/K-ATPase. *J. Biol. Chem.* 284: 14881-14890. PMID: PMC2685670.

3. We have been able to show the relevance of these newly discovered functions of Na/K-ATPase to the pathophysiology of renal and cardiovascular diseases, and recently to cancer biology. Naturally, these new discoveries have prompted us to develop and test new receptor Na/K-ATPase agonists and antagonists as therapeutics for human diseases. Together, these previous findings demonstrate my record of successful research projects, my ability to direct a successful research program, and my willingness to establish a productive collaboration with experts in other research fields to translate the basic research of Na/K-ATPase biology to physiology and pathology.

1. Li, Z., Cai, T., Tian, J., Xie, J.X., Zhao, X., Liu, L., Shapiro, J.I., and Xie, Z. (2009) NaKtide, a Na/K-ATPase-derived peptide Src inhibitor, antagonizes ouabain-activated signal transduction in cultured cells. *J. Biol. Chem.* 284: 21066-21076. PMID: PMC2742871.
2. Liu, J., Yan, Y., Liu, L., Xie, Z., Malhotra, D., Joe, B., Shapiro, J.I. (2011) Impairment of Na/K-ATPase signaling in renal proximal tubule contributes to Dahl salt-sensitive hypertension. *J. Biol. Chem.* 286, 22806-22813. PMID: PMC3123048.
3. Li, Z., Zhang, Z., Xie, J.X., Li, X., Tian, J., Cai, T., Cui, H., Ding, H., Shapiro, J.I., and Xie, Z. (2011) Na/K-ATPase mimetic pNaKtide inhibits the growth of human cancer cells. *J Biol. Chem.* 286: 32394-32403. PMID: PMC3173162.
4. Lai F, Madan N, Ye Q, Duan Q, Li Z, Wang S, Si S, Xie Z. (2013). Identification of a mutant $\alpha 1$ Na/K-ATPase that pumps but is defective in signal transduction. *J Biol Chem.* 2013 May 10;288(19):13295-304. doi: 10.1074/jbc.M113.467381.

Complete List of Published Work:

<http://www.ncbi.nlm.nih.gov/pubmed/?term=Xie+Z%5Bauthor%5D+AND+Na%2FK-ATPase>

D. Research Support

Ongoing Research Support

HL109015-01 Xie (PI) 07/01/11-06/30/15
 Receptor Na/K-ATPase antagonists as novel therapeutics for renal/cardiac diseases
 This application is aimed to develop and assess the antagonists of Na/K-ATPase in reduction of renal and cardiac fibrosis.
 Role: PI

HL 105649-01A1 Tian (PI) 12/15/11-11/30/16
 Na/K-ATPase reduction in renal disease-related cardiac dysfunction
 This application assesses the increase in endogenous cardiotonic steroids in renal artery stenosis patients and its role in the development of cardiac cell death.
 Role: Co-Investigator

Completed

1R01GM078565-01A1 Xie (PI) 07/01/07-06/30/11
 NIGMS
 Na,K-ATPase as an Integrator of the Calcium-signaling Machinery
 The major goals of this grant are to define the molecular mechanism by which the Na/K-ATPase integrates Src, PLC- γ /PKC and IP3R into a functional Ca²⁺ signaling module; to reveal the significance of protein/protein interactions in the targeting of IP3 receptors and in the ouabain-induced Ca²⁺ signaling, and to identify the plasma membrane channel(s) that interacts with the Na/K-ATPase and is responsible for ouabain-induced Ca²⁺ influx.
 Role: PI

P01 HL36573-20 Askari (Program Director) 03/01/03-02/28/09

NHLBI

Interactions of Na/K-ATPase with its Signaling Partners

This is one of the components of HL36573-19 (Project Leader)

The major goals of this grant are to search for new partners of the signaling Na/K-ATPase using proteomic approaches and to delineate the structural basis of the interaction between the Na/K-ATPase and Src.

Role: Project Leader

R01 HL67963-01 Xie (PI) 07/01/02-06/30/08

NHLBI

The Role of ROS and Na/K-ATPase in Uremic Cardiomyopathy

The major goal of this grant are to test whether the signaling function of Na/K-ATPase plays a role in uremic cardiomyopathy.

Role: PI