BIOGRAPHICAL SKETCH
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NAME: Cao, Erhu

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

POSITION TITLE: Assistant 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
Huazhong Agricultural University, China	B.S.	07/1996	Plant Biology
Albert Einstein College of Medicine, USA	Ph.D.	03/2007	Biomedical Science
University of California, San Francisco, USA	Postdoctoral	08/2015	Molecular Pharmacology

A. Personal Statement

As a Ph.D. student with Steven Almo and Stanley Nathenson at the Albert Einstein College of Medicine, I trained as biochemist and structural biologist, and determined X-ray crystal structures of multiple proteins/complexes of receptors that contribute to cellular immunity. As a postdoc in the Julius' laboratory at UCSF, I pursued biochemical, biophysical and structural analyses of transient receptor potential (TRP) ion channels, which are key players in sensory signaling and in the detection of noxious stimuli. Consequently, I have extensive experience in molecular biology, protein biochemistry, ion channel reconstitution, ion channel electrophysiology, single particle electron cryo-microscopy (cryo-EM), and protein crystallography. As an independent faculty member at the University of Utah, my goal is to elucidate the structure, pharmacology, function, and pathophysiology of ion channels and receptors that play pivotal roles in renal physiology and are implicated in kidney diseases in human. My current research program focuses on the PKD1 receptor and PKD2 channel, which are sites of mutations that cause the prevalent human genetic disorder autosomal dominant polycystic kidney disease (ADPKD). PKD2 shows distant sequence similarity with the TRPV1 channel whose properties I characterized and structure I determined as a postdoctoral fellow. We recently determined a 3.0Å cryo-EM structure of closed PKD2 channel that reveals unanticipated mechanistic insights. We are determining additional structures of PKD2 in other functional states and structures of PKD1 and the PKD1/PKD2 complex by single particle cryo-EM, as well as developing molecular pharmacology for PKD proteins. In the current research proposal, we plan to apply the cutting edge single-particle cryo-EM method and in vitro nanobody selection to determine structures of the cation chloride cotransporters.

Peter S. Shen[#], Xiaoyong Yang[#], Paul G. Decaen, Xiaowen Liu, David Bulkley, David E. Clapham*, and **Erhu Cao***. The structure of the polycystic kidney disease 2 channel in lipid nanodiscs. *Cell* (2016) 167: 763-773.
[#] Co-first authors * Corresponding authors

Wang Zheng[#], Xiaoyong Yang[#], Ruikun Hu, Ruiqi Cai, Laura Hofmann, Zhifei Wang, Qiaolin Hu, Xiong Liu, David Bulkey, Yong Yu, Jingfeng Tang*, Veit Flockerzi, Ying Cao, **Erhu Cao**[*], and Xing-Zhen Chen[*].

Hydrophobic pore gates regulate ion permeation in polycystic kidney disease 2 and 2L1 channels. *Nature Communication*. # Co-first authors * Corresponding authors

B. Positions and Honors

Position/Employment

1999 – 2001	Research assistant, Youxin Jin lab, Shanghai Institute of Biochemistry, Shanghai, China.
2001 – 2007	Graduate student, Steven Almo and Stanley Nathenson laboratories, Albert Einstein College of Medicine.
2007 – 2015	Postdoctoral fellow, David Julius Laboratory, Department of Physiology, UCSF.
2015 – present	Assistant professor, Department of Biochemistry, University of Utah School of Medicine.

Honors

2007	Julius Marmur Research Award (Albert Einstein College of Medicine Highest Award to the Best Graduate Students)
2008 – 2010	Damon Runyon Cancer Research Foundation Postdoctoral Fellowship
2017 – 2021	Pew Scholar Award

Professional Membership

Biophysical Society, since 2010
American Heart Association, since 2014

C. Contributions to Science

1. **Ph.D. graduate studies - structural mechanisms of regulation of cellular immunity by NTB-A, TIM-3 and PD-1 receptors.**

NTB-A, TIM-3, and PD-1 all belong to the immunoglobulin (Ig) superfamily of receptors that are capable of stimulating or inhibiting a variety of immune cells (e.g. T cells, B cells, and natural killer cells) upon engaging their cognate ligands via extracellular Ig domains. Notably, tumor cells often exploit the immunosuppressive interactions between PD-1 and its ligands (PD-L1 and PD-L2) to evade immune surveillance. Indeed, antibodies that block the inhibitory PD-1/PD-L1 pathway can boost immune responses against malignant cells in patients, and are currently in clinical trial for treating various cancers. In my graduate work, I have determined crystal structures of NTB-A, TIM-3, and PD-1 in complex with PD-L2, and performed associated biochemical analyses. Together, these findings provide structural blueprints for understanding ligand recognition by these receptors and suggest sites or hot spots that can be targeted for the development of novel immunotherapies to treat cancer and other immune related diseases.

a. Xuewu Zhang, Jean-Claude D. Schwartz, Xiaoling Guo, Sumeena Bhatia, **Erhu Cao**, Michael Lorenz, Michael Cammer, Lieping Chen, Zhong-Yin Zhang, Michael A. Edidin, Stanley G. Nathenson, and Steven C. Almo. Structural and functional analysis of the costimulatory receptor programmed death-1. *Immunity* (2004) 20: 337-47.

b. **Erhu Cao**, Udupi A. Ramagopal, Alexander Fedorov, Elena Fedorov, Qingrong Yan, Jeffrey W. Lary, James L. Cole, Stanley G. Nathenson, and Steven C. Almo. NTB-A Receptor Crystal Structure: Insights into Homophilic Interactions in the Signaling Lymphocytic Activation Molecule Receptor Family. *Immunity* (2006) 25: 559-70

c. **Erhu Cao**, Xingxing Zang, Udupi A. Ramagopal, Arunika Mukhopadhaya, Alexander Fedorov, Elena Fedorov, Wendy D. Zencheck, Jeffrey W. Lary, James L. Cole, Haiteng Deng, Teresa P. DiLorenzo, James P. Allison, Stanley G. Nathenson, and Steven C. Almo. T Cell Immunoglobulin Mucin-3 Crystal Structure Reveals a Galectin-9- independent Ligand-Binding Surface. *Immunity* (2007) 26: 311-321

d. *Eszter Lázár-Molnár, *Qingrong Yan, ***Erhu Cao**, Udupi Ramagopal, Stanley G. Nathenson and Steven C. Almo. Crystal structure of the complex between programmed death-1 (PD-1) and its ligand PD-L2. *Proc Natl Acad Sci U S A.* (2008) 105: 10483-8. PMCID: PMC2492495 * Equally contributing authors

2. **Postdoctoral studies – structural and functional insights into the mechanisms of TRPV1 activation and drug action.**

My postdoctoral work in the Julius lab at UCSF focused on the structure and physiology of sensory TRP channels, in particular, the TRPV1 channel. TRPV1 is a major player in the pain pathway, which is capable of detecting and integrating a wide range of pain-producing physiological and environmental stimuli. These include noxious heat, proton, pro-inflammatory agents, as well as natural products (e.g. capsaicin found in chili pepper and peptide toxins present in spider venoms) that are evolved as defense mechanisms to discourage herbivory or to deter predators.

In one research direction, I reconstituted purified TRPV1 into giant liposomes that allow for characterization of its intrinsic properties by patch clamp recording. By taking this reductionist's approach, I showed that TRPV1 is directly activated by heat without the requirement for any other cellular factors. Moreover, I demonstrated that TRPV1 is directly inhibited by PIP_2, thereby providing a mechanistic explanation for how TRPV1 is sensitized by numerous pro-inflammatory agents that lead to activation of phospholipase C (PLC) and consequent PIP_2 degradation. This approach will be extremely powerful in deciphering the functions of polycystin proteins, which are the focus of this proposal, because they exhibit predominant endoplasmic reticulum localization and hence are not amenable to conventional patch clamp recording at the plasma membrane.

In addition, I collaborated with Maofu Liao in Yifan Cheng' lab at UCSF, and together we determined structures of the TRPV1 channel locked in three distinct functional states (i.e. closed, partially activated, and fully activated) by single particle cryo-EM. These structures revealed a unique two-gate mechanism of channel activation, which includes an unusually dynamic outer pore region, and indicated the relevance of this mechanism to channel sensitization by tissue acidosis and other pro-inflammatory agents. We also resolved binding sites for pain-producing spider toxins and pungent natural products, and determined how these sites relate to mechanisms of channel activation.

This work represents a seminal achievement in the field because it provided a landmark blueprint for future biophysical and pharmacological studies of TRP channels. Delineation of TRPV1 structure to near atomic resolution without the need to obtain protein crystals also represented a technical breakthrough in single particle cryo-EM. I believe that our success has enormous ramifications for the future of membrane protein structure determination because it opens the way to determining receptor and ion channel structures in the many cases where material is limiting or conformationally heterogeneous.

a. **Erhu Cao**, Julio F. Cordero-Morales, Beiying Liu, Feng Qin, and David Julius. TRPV1 channels are intrinsically heat sensitive and negatively regulated by phosphoinositide lipids. *Neuron* (2013) February; 77:667-679. PMCID: PMC3583019.

b. ***Erhu Cao**, *Maofu Liao, Yifan Cheng, and David Julius. TRPV1 structures indistinct conformations reveal activation mechanisms. *Nature (Article with News and Views written by Richard Henderson)* (2013) 504:113-118. PMCID: PMC4023639. * Equally contributing authors

c. *Maofu Liao, ***Erhu Cao**, David Julius, and Yifan Cheng. Structure of the TRPV1 channel determined by electron cryo-microscopy. *Nature (Article with News and Views written by Richard Henderson)* (2013) 504:107-112. PMCID: PMC4078027. *Equally contributing authors

d. Yuan Gao, **Erhu Cao**, David Julius, and Yifan Cheng. TRPV1 structures in nanodiscs reveal mechanisms of ligand and lipid action. *Nature* (2016) 534:347-351. PMCID: PMC4911334.

Complete List of Published Work in MyBibliography

http://www.ncbi.nlm.nih.gov/sites/myncbi/erhu.cao.1/bibliography/48756658/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

R01 DK110575 Cao (PI) 09/01/2016 – 07/01/2021 3.60 calendar months
National Institutes of Health $225,000 per year
Structures and Mechanisms of Polycystic Kidney Disease Proteins

The goal of this proposal is to elucidate the structural principles and fundamental biophysical properties of polycystic kidney disease proteins, which are the sites of mutations that cause autosomal dominant polycystic kidney disease. Treatment options for this prevalent genetic disorder are currently limited, in large part because the molecular mechanisms of the relevant proteins are only poorly understood. Successful outcome will provide structural and biochemical insights that will inform the development of novel therapeutic strategies.

Pew Scholar Award Cao (PI) 08/01/2017 – 08/01/2021
The Pew Charity Trust $75,000 per year

DoD Discovery Grant Cao (PI) 08/01/2016 – 01/31/2019 1.20 calendar months
Department of Defense $200,000 per year
Pharmacology of Polycystic Kidney Disease Proteins

The major aim of this project is to develop pharmacological tools (e.g., small chemical compounds, peptide toxins from venomous animals, and conformation-sensitive, functional antibodies) for dissecting structures and physiology of polycystic kidney disease proteins. Such pharmacological studies of PKD proteins will also help to establish therapeutic principles for treating autosomal dominant polycystic kidney disease.

Completed Research Support

Seed Grant Cao (PI) 07/01/2016 – 06/30/2017 1.20 calendar months
University of Utah Research Foundation $20,000
Pharmacology of Polycystic Kidney Disease Proteins
Role: PI