BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Shi, Huanan

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

POSITION TITLE: Graduate Student

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
Renmin University of China	BS	07/2016	Physics
University of California, Berkeley	N/A	08/2014	N/A
Baylor College of Medicine	PhD		Molecular Physiology and Biophysics

A. Personal Statement

My long-term research interests involve understanding the mechanisms underlying obstructive sleep apnea related hypertension and to develop potential therapeutics for vasculature dysfunction. My career goal is to conduct independent translational research in academic setting.

I started my first molecular biology lab training in January 2015 at Beijing Jiaotong University, in which we have focused on ABOPEC proteins related oncogenesis. I joined Dr. David Clapham's Lab at Boston Children's Hospital as student intern in my senior year of college. After two months training and working on ion channels and surface receptors of mammalian sperm both *in vivo* and *in vitro*, I had the opportunity to help my supervisor Dr. Jean-Ju Chung to start her new lab at Yale University as she moved from Harvard and continue the same project. I have been trained in mouse work, biochemistry, molecular biology, and immunofluorescence imaging, including super-resolution microscopy during my time as a visiting student in research at Yale School of medicine. I then moved to Houston to pursue my PhD at Baylor College of Medicine. I rotated with Dr. Joel Neilson to study RNA regulation in breast cancer and with Dr. Robia Pautler to study Alzheimer's Disease in mouse model using MRI. I later spent two years working with Dr. Russell Ray to study brainstem respiratory control and were trained in mouse behavior assays, stereotaxic virus injection, plethysmography and pneumotachography, and immunohistochemistry.

My current dissertation work in Dr. David Durgan's and Dr. Robert Bryan Jr.'s labs is to understand the mechanisms how changes of gut microbiota contribute to gut wall pathology, inflammation, and hypertension in various animal models. The studies focus on microbiome-host interactions, GI-derived hormone and metabolites signaling, and GI-based therapeutics. The training under Dr. David Durgan will provide me an excellent foundation, from which I can build my career to conduct basic and translational research.

B. Positions and Honors

Positions and Employment

02/2015 – 06/2015 Undergraduate Research Assistant, Beijing Jiaotong University
07/2015 – 11/2015 Trainee, Boston Children's Hospital
09/2015 – 06/2016 Visiting Student in Research, Yale University School of Medicine

Other Experience and Professional Memberships

2016 - Student Member, American Physiological Society
2017 - Associate Member, Sigma Xi
2019 - Member, American Heart Association

Honors

2014	Second Prize in Beijing of China Undergraduate Mathematical Contest in Modeling, China Society for Industrial and Applied Mathematics
2015	Honorable Mention of Mathematical Contest in Modeling, Consortium for Mathematics and Its Applications
2020	Second Place Award for Outstanding Poster Presentation, 11th Frontiers in Digestive Diseases Symposium, Texas Medical Center Digestive Diseases Center

C. Contributions to Science

1. My early contributions to science addressed control of sperm motility and male fertility by sperm specific Ca^{2+} channels, CatSpers. CatSper is critical for sperm hyperactivation, an asymmetric flagellar motion of the sperm tail that provides spermatozoa the force to penetrate the *zona pellucida* of the egg. As the channel is not reconstituted in heterologous systems, molecular organization of the CatSper channel and its signal transduction in mammalian fertilization had not been clear. I helped characterize novel CatSper auxiliary subunits ζ and ε and studied their function in mouse models. I demonstrated that targeted disruption of CatSperζ reduces efficiency of sperm rheotactic and fertilization *in vivo* in mice, resulting in severe male subfertility. Normally distributed in linear quadrilateral nanodomains along the flagellum, the complex lacking CatSperζ is disrupted at ~0.8 mm intervals along the flagellum. This disruption renders the proximal flagellum inflexible and alters the 3D flagellar envelope, thus preventing sperm from reorienting against fluid flow *in vitro* and efficiently migrating *in vivo*. I showed that ejaculated CatSperζ-null sperm cells retrieved from the mated female uterus partially rescue in vitro fertilization that failed with epididymal spermatozoa alone. These data suggested that the newly identified CatSperζ subunit is a late evolutionary adaptation to maximize fertilization inside the mammalian female reproductive tract.
   a. Chung JJ, Miki K, Kim D, Shim SH, **Shi HF**, Hwang JY, Cai X, Iseri Y, Zhuang X, Clapham DE. CatSperζ regulates the structural continuity of sperm Ca^{2+} signaling domains and is required for normal fertility. *eLife*. 2017 Feb 23;6 PubMed PMID: 28226241; PubMed Central PMCID: PMC5362262.
2. My early work in graduate school is to characterize brainstem respiratory control in respiratory pathophysiologies, such as Alzheimer's Disease (AD). Alzheimer's disease is a chronic neurodegenerative disease. Early presentation starts with short-term memory loss that progresses to disorientation and dementia until key bodily functions fail leading to death. It has become clear that a strong association exists between the onset and progression of AD and disturbed respiratory control, such as sleep apnea and aspiration pneumonia, which are related to upper airway function. Additionally, studies in rodent AD and tauopathy models show perturbations to respiratory homeostasis. However, it remains unclear how AD pathophysiology and disordered breathing may interact to exacerbate disease progression. Thus, a better understanding of the relationship between AD progression and respiratory homeostasis is needed. I characterized respiratory function in forebrain amyloid precursor protein (APP) pathology model generated by Dr. Joanna Jankowsky at Baylor College of Medicine. Although forebrain perturbations and injuries, including seizures and strokes, can result in acute and chronic breathing irregularities, I was able to show that disordered breathing associated with AD progression may stem from direct effects on brainstem or peripheral circuits. To further understand neural mechanisms that underlie upper airway control, swallowing coordination, and cough reflex throughout life, I identified GABAergic neurons as a potential key player. Though GABAergic signaling is critical to modulate breathing, the functional organization of widespread GABAergic neurons throughout the brainstem remains unclear. I demonstrated in preliminary studies that GABAergic neurons are essential to maintain basal respiratory function and stability, are involved in adult chemosensory reflexes, and may also modulate upper airway function and cough reflexes.
   a. **Shi H**, Saldana Morales FB, Martinez VK, Jankowsky JL, and Ray RS. Forebrain Alzheimer's Disease pathology does not result in disordered breathing in mice. *FASEB J.* 2019; 33(1_suppement):lb583.
   b. **Shi H** and Ray RS. Mapping neural circuits critical to upper airway function and breathing-swallowing coordination *FASEB J.* 2019; 33(1_suppement):lb584.
3. My current dissertation work is to understand the roles of gut microbe-host interaction in the regulation of blood pressure. Previous studies have shown disruption in composition of gut microbiome or gut dysbiosis in various hypertensive models and patients, suggesting a key role of gut microbiome in pathophysiologies of hypertension. However, how gut microbiome regulate blood pressure is still unclear. Current researches suggest the important role of microbial metabolites, such as short-chain fatty acids, in the development of

hypertension. My study will help determine how gut microbiota and microbial metabolites regulate blood pressure. Bioinformatic tools, including machine learning approaches, and traditional biochemistry, molecular biology and cardiovascular physiological experiments are performed to address these questions.