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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: Hong S. Lu

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

POSITION TITLE: Associate Professor, Saha Cardiovascular Research Center and Department of Physiology

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
Zhejiang University School of Medicine, China	M.D.	06/1993	Medicine
Zhejiang University Sir Run Run Shaw Hospital, China	Residency	07/1996	Internal Medicine
Zhejiang University Sir Run Run Shaw Hospital, China	Clinical Fellow	05/1998	Cardiology
Kanazawa University Graduate School of Medical Sciences, Japan	Ph.D.	03/2003	Molecular Genetics in Medical Sciences
University of Kentucky, Lexington, KY	Postdoctoral Fellow	09/2007	Atherosclerosis and Aortic Aneurysms

A. Personal Statement

My professional career was first developed with the benefit of expert training in Clinical Medicine as an Internal Medicine physician including Cardiology, Nephrology, Hematology, and Neurology. My research career was instilled with graduate research training in human molecular genetics of hypercholesterolemia and coronary atherosclerotic disease at Kanazawa University in Japan. I had extensive training focusing on atherosclerosis and aortic aneurysms as a postdoctoral fellow in Dr. Alan Daugherty's laboratory at the University of Kentucky. My research expertise includes atherosclerosis, aortic aneurysms, and renin-angiotensin regulation.

Rigor, Reproducibility, and Transparency have been the most important parts of my research career. I have been a Technical Editor of ATVB (Arteriosclerosis, Thrombosis and Vascular Biology), an AHA (American Heart Association) journal, since July 2017. My role is to oversee whether original research manuscripts follow the NIH principles and guidelines for rigor, reproducibility, and transparency in reporting preclinical research.

Ongoing or recently completed projects that I would like to highlight:
R01HL139748 Lu and Daugherty (MPI) 05/01/2018 - 03/31/2023 (NCE)
NIH/NHLBI
Atherosclerosis Mechanisms: Angiotensin II production and action
This grant aims to determine molecular mechanisms by which the renin-angiotensin system contributes atherosclerosis using multiple mouse models.
Role: Contact PI

R35HL155649 Daugherty (PI) 06/01/2021 - 05/31/2028
NIH/NHLBI
Novel Mechanisms of Thoracic Aortic Aneurysm and Dissection
The R35 program will determine complex mechanisms of aortic aneurysms and dissection related to heterogeneity of different aortic regions.
Role: Co-I

18SFRN33900001 Daugherty (Center Director) 04/01/2018 - 03/31/2023 (NCE)
American Heart Association
University of Kentucky-Baylor College of Medicine Aortopathy Center - Strategically Focused Research Network (SFRN) Program
Role: Training Director (01/01/2022-03/31/2023)

KYNETIC - NIH's Research Evaluation and Commercialization Hub (REACH) Program
NIH Sheppard, Lu, and Daugherty (MPI) 07/01/2021 - 12/31/2021
Use of antisense oligonucleotides targeted against angiotensinogen (GalNAc AGT ASO) in Marfan syndrome
This NIH funded project aims to determine whether inhibition of AGT protects against aortic aneurysms in a Marfan mouse model
Role: MPI

B. Positions, Scientific Appointments, and Honors

Positions

07/2022-Present: Associate Professor (Regular Title Series with Tenure), Saha Cardiovascular Research Center and Department of Physiology, University of Kentucky, Lexington, KY
03/2020-06/2022: Assistant Professor (Regular Title Series), Saha Cardiovascular Research Center and Department of Physiology, University of Kentucky, Lexington, KY
2015-2020: Associate Professor (Research Title Series), Saha Cardiovascular Research Center and Department of Physiology, University of Kentucky, Lexington, KY
2012-2015: Assistant Professor (Research Title Series), Saha Cardiovascular Research Center, University of Kentucky, Lexington, KY
2010-2011: Assistant Professor (Research Title Series), Department of Cell Biology and Anatomy, University of South Carolina School of Medicine, Columbia, SC
2008-2009: Assistant Professor (Research Title Series), Saha Cardiovascular Research Center, University of Kentucky, Lexington, KY
2007-2008: Scientist III, Saha Cardiovascular Research Center, University of Kentucky, Lexington, KY
1999-2000: Researcher, the Second Department of Internal Medicine, Kanazawa University, Kanazawa, Japan
1998-1999: Exchange scholar, the First Department of Internal Medicine, Fukui Medical University, Fukui, Japan

Scientific Appointments

Review Panels:

2021-2022: Co-Chair of Fellowships Vascular Biology 1 Committee of American Heart Association
2019-2022: Chair or Co-Chair of Institutional Undergraduate Student Fellowship Committee of American Heart Association
2013-Present: Vascular Biology Committee and Undergraduate Student Fellowship Committee of American Heart Association

Journal Editors:

2021-Present: Guest Theme Editor of Frontiers in Cardiovascular Medicine (Women in Cardiovascular Therapeutics)
2021-Present: Guest Theme Editor of Frontiers in Cardiovascular Medicine (Novel Epigenetic Medicine and Cardiovascular Diseases)
2021-Present: Associate Editor of Frontiers in Cardiovascular Medicine (Cardiovascular Therapeutics)
2021-Present: Guest Editor of Biomolecules (Aortic Aneurysms: Heterogeneity and Molecular Mechanisms)
2020-Present: Associate Editor of BMC Cardiovascular Disorders
2020-2022: Guest Theme Editor of Frontiers in Cardiovascular Medicine (Cardiovascular Fibrosis and Related Diseases)

Other Roles:

2022: Editorial Board, Reviews in Cardiovascular Medicine
2020: GBD (Global Burden of Disease)-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group (Aortic Aneurysm section)
2019-Present: Editorial Board, Journal of Thoracic Disease

2017-Present: Technical Editor of ATVB (oversee rigor and reproducibility of the journal)
2013-Present: Editorial Board, ATVB

Honors

2016-2022: Top reviewer award of an AHA (American Heart Association) journal, ATVB (Arteriosclerosis, Thrombosis, and Vascular Biology)
2014: Top reviewer award of an AHA journal, ATVB
2006: New Investigator Travel Award, ATVB Council of the AHA
2005: Finalist, Junior Women's Award, ATVB Council of the AHA
2004: New Investigator Travel Award, ATVB Council of the American Heart Association

C. Contributions to Science

Complete List of Published Work in My NCBI: 130 publications (Updated on July 1, 2022)
https://www.ncbi.nlm.nih.gov/myncbi/143PDNDsrP6/bibliography/public/

Ascending Aortopathies

Ascending aortopathies (AAs) represent a spectrum of pathological changes in the ascending aorta including luminal dilations, medial dissections, transmural rupture, and pathological remodeling of the aortic wall. My research work aims to (1) understand embryonic origin-related cellular and molecular mechanisms, (2) determine the contributions of the renin-angiotensin components to pathogenesis, and (3) explore potential therapeutic targets and strategies.

a. Chen JZ, Sawada H, Ye D, Katsumata Y, Kukida M, Ohno-Urabe S, Moorleghen JJ, Franklin MK, Howatt DA, Sheppard MB, Mullick AE, **Lu HS**, Daugherty A. Deletion of AT1a receptor or inhibition of angiotensinogen synthesis attenuates thoracic aortic pathology in fibrillin-1$^{C1041G/+}$ mice. *Arterioscler Thromb Vasc Biol*. 2021; 41:2538-2550. (PMID: 34407634; PMCID: PMC8458261)
b. Sawada H, Katsumata Y, Higashi H, Zhang C, Li Y, Morgan S, Lee LH, Singh SA, Chen JZ, Franklin MK, Moorleghen JJ, Howatt DA, Rateri DL, Shen YH, LeMaire SA, Aikawa M, Majesky MW, **Lu HS**, Daugherty A. Second heart field-derived cells contribute to angiotensin II-mediated ascending aortopathies. *Circulation*. 2022; 145:987-1001. (PMID: 35143327; PMCID: PMC9008740)
c. Ito S, **Lu HS**, Daugherty A, Sawada H. Imaging techniques for aortic aneurysms and dissections in mice: Comparisons of ex vivo, in situ, and ultrasound approaches. *Biomolecules* 2022; 12:339. (PMID: 35204838; PMCID: PMC8869425)
d. Sawada H, Beckner ZA, Ito S, Daugherty A, **Lu HS**. β-aminopropionitrile induced aortic aneurysm and dissection in mice. *JVS Vasc Sci* 2022; 3:64-72. (PMID: 35141570; PMCID: PMC8814647)

Abdominal Aortic Aneurysms (AAAs)

My research work on AAAs has been focusing on (1) determining mechanisms by which hypercholesterolemia contributes to AngII-induced aortic aneurysmal development, (2) understanding the complex pathogenesis and molecular mechanisms, and (3) exploring potential therapeutic strategies.

a. **Lu H**, Howatt DA, Balakrishnan A, Moorleghen JJ, Rateri DL, Cassis LA, Daugherty A. Subcutaneous angiotensin II infusion using osmotic pumps induces aortic aneurysms in mice. *J Vis Exp*. 2015; 103. (PMID 26436287; PMCID: PMC4692630)
b. **Lu H**, Howatt DA, Balakrishnan A, Graham MJ, Mullick AE, Daugherty A. Hypercholesterolemia induced by a PCSK9 gain-of-function mutation augments angiotensin II-induced abdominal aortic aneurysms in C57BL/6 mice. *Arterioscler Thromb Vasc Biol*. 2016; 36:1753-1757. (PMID 27470509; PMCID: PMC5001883)
c. Howatt DA, Dajee M, Xie X, Moorleghen J, Rateri DL, Balakrishnan A, Da Cunha V, Johns DG, Gutstein DE, Daugherty A, **Lu H**. Relaxin and matrix metalloproteinase-9 in angiotensin II-induced abdominal aortic aneurysms. *Circ J*. 2017; 81:888-890. (PMID 28420827; PMCID: PMC5964022)
d. Ye D, Wu C-Q, Chen H, Liang CL, Howatt DA, Franklin MK, Moorleghen JJ, Tyagi SC, Uijl E, Danser AHJ, Sawada H, Daugherty A, **Lu HS**. Fludrocortisone induces aortic pathologies in mice. *Biomolecules* 2022; 12:825. (PMID: 35740952)

The Renin-Angiotensin System and Atherosclerosis
The renin-angiotensin system has been recognized as an increasingly complex system in the past 20 years. My research work has determined (1) whether different components of the renin-angiotensin system have differential effects on hypercholesterolemia-induced atherosclerosis, and (2) molecular mechanisms by which these renin-angiotensin components contribute to atherosclerosis. Our recent studies have also provided new insights into that (1) angiotensinogen (AGT), the substrate of the renin-angiotensin system, is regulated by megalin, which is attributed to megalin recognizing potentially functional sequences of AGT; and (2) AngII and AT1aR promote atherosclerosis independent of their action on the vascular wall.

a. **Lu H**, Balakrishnan A, Howatt DA, Wu C, Charnigo R, Liau G, Cassis LA, Daugherty A. Comparative effects of different modes of renin angiotensin system inhibition on hypercholesterolemia-induced atherosclerosis. *Br J Pharmacol.* 2012; 165:2000-2008. (PMID: 22014125; PMCID: PMC3372847)
b. **Lu H**, Wu C, Howatt DA, Balakrishnan A, Moorleghen JJ, Chen X, Zhao M, Graham MJ, Mullick AE, Crooke RM, Feldman DL, Cassis LA, Vander Kooi CW, Daugherty A. Angiotensinogen exerts effects independent of angiotensin II. *Arterioscler Thromb Vasc Biol.* 2016; 36:256-265. (PMID: 26681751; PMCID: PMC4732917)
c. Ye F, Wang Y, Wu C, Howatt DA, Wu CH, Balakrishnan A, Mullick AE, Graham MJ, Danser AHJ, Wang J, Daugherty A, **Lu HS**. Angiotensinogen and megalin interactions contribute to atherosclerosis. *Arterioscler Thromb Vasc Biol.* 2019; 39:150-155. (PMID: 30567480; PMCID: PMC6344256)
d. Wu CQ, Ye D, Mullick AE, Li Z, Danser AHJ, Daugherty A, **Lu HS**. Effects of renin-angiotensin inhibition on ACE2 (angiotensin-converting enzyme 2) and TMPRSS2 (Transmembrane protease serine 2) expression: Insights into COVID-19. *Hypertension.* 2020; 76:e29-e30. (PMID: 32673509; PMCID: PMC7375182)

The Renin-Angiotensin Regulation in Nonhuman Primates
There are many differences in the renin-angiotensin regulations between mice and humans. To enhance the human relevance of our research work on the renin-angiotensin system contributions to cardiovascular disease, we are studying the renin-angiotensin regulation in a nonhuman primate (NHP) model to expand our current knowledge.

a. Kukida M, Cai L, Ye D, Sawada H, Katsumata Y, Franklin MK, Hecker PI, Kampbell KS, Danser AHJ, Mullick AE, Daugherty A, Temel RE, **Lu HS**. Renal angiotensinogen is predominantly liver derived in nonhuman primates. *Arterioscler Thromb Vasc Biol*. 2021; 41:2851-2853. (PMID: 34496634; PMC8551028)

Molecular Genetic Analysis of Hypercholesterolemia in Patients with Familial Hypercholesterolemia
My graduate training at Kanazawa University Graduate Program of Medicine (Japan) focused on molecular genetic analysis in patients with familial hypercholesterolemia. One major project was to identify potentially functional single nucleotide polymorphisms (SNP) of the estrogen receptor α gene in hypercholesterolemia-associated coronary artery disease. In addition, I have also completed a project that determined associations between cholesteryl ester transfer protein (CETP) and LDL receptor SNPs and hypercholesterolemia.

a. **Lu H**, Higashikata T, Inazu A, Nohara A, Yu W, Shimizu M, Mabuchi H. Association of estrogen receptor-alpha gene polymorphisms with coronary artery disease in patients with familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol*. 2002; 22:817-823. (PMID: 12006396)
b. **Lu H**, Inazu A, Moriyama Y, Higashikata T, Kawashiri MA, Yu W, Okamura T, Mabuchi H. Haplotype analyses of cholesteryl ester transfer protein gene promoter: a clue to an unsolved mystery of TaqIB polymorphism. *J Mol Med* 2003; 81:246-255. (PMID: 12700892)
c. Yu W, Nohara A, Higashikata T, **Lu H**, Inazu A, Mabuchi H. Molecular genetic analysis of familial hypercholesterolemia: spectrum and regional difference of LDL receptor gene mutations in Japanese population. *Atherosclerosis*. 2002; 165:335-342. (PMID: 12417285)
d. Mabuchi H, Higashikata T, Nohara A, **Lu H**, Yu W, Nozue T, Noji Y, Katsuda S, Kawashiri MA, Inazu A, Kobayashi J, Koizumi J. Cutoff point separating affected and unaffected familial hypercholesterolemic patients validated by LDL receptor gene mutants. *J Arterioscler Thromb*. 2005; 12:35-40. (PMID: 15725694)

Mechanisms of Volume Overload-induced Cardiac Dysfunction

During my short-term (2010-2011) relocation to the University of South Carolina School of Medicine, I studied mechanisms of cardiac dysfunction associated with sex difference and mast cell biology using rat models.

a. **Lu H**, Meléndez GC, Levick SP, Janicki JS. Volume overload has differential effects on the initial phase of cardiac remodeling in female rats with and without ovariectomy. *Am J Physiol Heart Circ Physiol* 2012; 302:H811-817. (PMID: 22160000; PMCID: PMC3353795)
b. Li J, **Lu H***, Plante E, Melendez GC, Levick SP, Janicki JS. Stem cell factor is responsible for the rapid response in mature mast cell density in the acutely stresses heart. *J Mol Cell Cardiol* 2012; 53:469-474. (PMID: 22850284; PMCID: PMC3438908) *Co-first author.