OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 01/31/2026)

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: Song, Kunhua

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

POSITION TITLE: Associate Professor of Internal Medicine

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) | Start DateMM/YYYY | Completion DateMM/YYYY | FIELD OF STUDY |
| --- | --- | --- | --- | --- |
| Fudan University, China | B.S | 09/1991 | 07/1996 | Biology |
| Zhejiang University, China | M.A | 09/1996 | 07/1999 | Virology and Immunology |
| University of Arkansas-Fayetteville  | M.S | 08/2000 | 05/2002 | Cell & Molecular Biology |
| University of Texas Southwestern Medical Center | Ph.D | 08/2002 | 05/2007 | Genetics & Development |
| University of Texas Southwestern Medical Center | Postdoctoral Fellow | 06/2007 | 05/2013 | Cardiac biology |

**A. Personal Statement**

I had been trained in cardiac biology and stem cell biology, with specific training and expertise in research areas including molecular mechanisms of cardiac development, heart physiological and pathological growth, cardiac cellular reprogramming, and heart disease modeling using induced human pluripotent stem cells (iPSCs) and rodent models. In graduate school, my research focused on understanding mechanisms by which a calcium-activated transcription activator regulates cardiac hypertrophy using transgenic and knockout mouse models (Song et al., 2006, PMID: 16678093). Later, we discovered that a cardiac transcriptional network was able to reprogram cardiac fibroblasts into induced cardiomyocytes *in vitro* and *in vivo* (Song et al., 2012, PMID: 22660318). Research in my laboratory focuses on understanding molecular mechanisms and signaling pathways that govern cardiac cell fate commitment and congenital heart defects (Zhao et al., 2015, PMID: 26354680; Riching et al., 2021, PMID: 33359755; Waugh et al., 2023, PMID: 37277650; Chi et al., 2023, PMID: 37360690) and cardiomyopathy/heart failure (Chi et al., 2019, PMID: 30584088; Knight et al., 2021, PMID: 33636116; Zhao et al., 2022, PMID:35862102).

**Ongoing projects that I would like to highlight include:**

R01HL133230 Song (PI, 25% effort) 08/01/2016 - 08/31/2027

Mechanisms for cell signaling in the control of cardiomyogenesis

R01HL159086 Song (PI, 25% effort), Vondriska (Co-PI) 09/01/2022 – 08/31/2026

Regulation of gene transcription and alternative splicing by a long non-coding RNA

Department of Defense PRMRP Nakano (PI), Song (Co-I, 10% effort) 03/15/2023 – 03/14/2027

Cardiomyocyte Autonomous Contractility Defects in Hypoplastic Left Heart Sndrome (HLHS)

R01HL168686 Zheng (PI), Song (Subcontract PI, 15% effort) 02/01/2024 – 01/31/2028

Mechanistic studies of human transporter Sialin

* 1. Zhao Y, Londono P, Cao Y, Sharpe EJ, Proenza C, O'Rourke R, Jones KL, Jeong MY, Walker LA, Buttrick PM, McKinsey TA, **Song K**. High-efficiency reprogramming of fibroblasts into cardiomyocytes requires suppression of pro-fibrotic signalling. ***Nat Commun.***2015 Sep 10;6:8243. PMID: 26354680; PMCID: PMC4579788.
1. Chi C, Leonard A, Knight WE, Beussman KM, Zhao Y, Cao Y, Londono P, Aune E, Trembley MA, Small EM, Jeong MY, Walker LA, Xu H, Sniadecki NJ, Taylor MR, Buttrick PM, **Song K**. LAMP-2B regulates human cardiomyocyte function by mediating autophagosome-lysosome fusion. ***Proc Natl Acad Sci U S A****.* 2019 Jan 8;116(2):556-565. PMID: 30584088; PMCID: PMC6329949.
2. Zhao Y, Riching AS, Knight WE, Chi C, Broadwell LJ, Du Y, Abdel-Hafiz M, Ambardekar AV, Irwin DC, Proenza C, Xu H, Leinwand LA, Walker LA, Woulfe KC, Bristow MR, Buttrick PM, **Song K**. Cardiomyocyte-Specific Long Noncoding RNA Regulates Alternative Splicing of the Triadin Gene in the Heart. ***Circulation****.* 2022 Aug 30;146(9):699-714. PMID: 35862102.
3. Waugh KA, Minter R, Baxter J, Chi C, Galbraith MD, Tuttle KD, Eduthan NP, Kinning KT, Andrysik Z, Araya P, Dougherty H, Dunn LN, Ludwig M, Schade KA, Tracy D, Smith KP, Granrath RE, Busquet N, Khanal S, Anderson RD, Cox LL, Estrada BE, Rachubinski AL, Lyford HR, Britton EC, Fantauzzo KA, Orlicky DJ, Matsuda JL, **Song K**, Cox TC, Sullivan KD, Espinosa JM. Triplication of the interferon receptor locus contributes to hallmarks of Down syndrome in a mouse model. ***Nat Genet****.* 2023 Jun;55(6):1034-1047. PMID: 37277650.

**B. Positions, Scientific Appointments and Honors**

**Positions**

08/2023 - Associate Professor of Internal Medicine with tenure, Heart Institute, Department of Internal Medicine, University of South Florida Health, Tampa, FL

07/2020 – 08/2023 Associate Professor, Division of Cardiology, Charles C. Gates Center for Regenerative Medicine and Stem Cell Biology, Linda Crnic Institute for Down Syndrome, University of Colorado School of Medicine, Aurora, CO

06/2013 – 07/2020 Assistant Professor, Division of Cardiology, Department of Medicine, Charles C. Gates Center for Regenerative Medicine and Stem Cell Biology, University of Colorado School of Medicine, Aurora, CO

**Peer Reviewer for Funding Agencies**

02/2024 AHA Second Century Early Faculty Independence Award Review Committee

06/2023 AHA Second Century Early Faculty Independence Award Review Committee

05/2023 Grant Reviewer for European Research Council (ERC)

02/2023 Ad-hoc reviewer for NIH Therapeutic Development and Preclinical Studies Study Section (TDPS)

01/2023 Ad-hoc reviewer for NIH study sections MCST Special emphasis panel **ZRG1 IMST-M (03)**

05/2022 Ad-hoc reviewer for NIH study sections MCST Special emphasis panel **ZRG1 IMST-J (02)**

02/2022 University of California Office of the President TRDRP General Biology Review Committee

05/2022 - 04/2023 AHA Transformational Project Award (TPA) Basic Science Committee.

02/2018 – 04/2021 AHA Peer Review Committee: Career Development Award Basic Science

09/2018 – 09/2019 AHA Fellowship Peer Review Committee: Signaling and cell transport 2.

10/2018 Peer Review panel: Medical Research Program Focused Program - Heart Diseases (FP-HD) for the Department of Defense Congressionally Directed Medical Research Programs (CDMRP).

11/2017 Ad-hoc reviewer for NIH study sections (MTI, special emphasis panel ZRG1 IMST-J)

07/2015 Review panel for Wellcome Trust, UK

10/2013-10/2016 AHA Peer Review Committee: MSignal BSc2

**Peer Reviewer for Journals**

Journal of Genetics and Genomics, Stem Cell Research, Journal of Cardiac Failure, International Journal of Biological Sciences, Scientific Report, PLOS One, Cell Research, Stem Cells, JOVE, Journal of Molecular and Cellular Cardiology (JMCC), JAHA, Journal of Cellular Physiology, Circulation Research, BBA-Molecular Basis of Disease, Proceeding of the National Academy of Sciences (PNAS), Cells, Developmental Cell, Scientific Data, Journal of Affective Disorders, Cell Stem Cell, PLOS Biology, iScience, Development, Science Advances, Nature Communications, Immunity, Nature Cardiovascular Research, Cell Reports, JCI,

**Honors and Services**

2021 - Selection Committee for ISHR-NAS annual Eric N Olson Mentorship Award

2023 - Associate Editor, Frontiers in Cardiovascular Medicine

2022 JMCC’s “Papers of the Year” of 2021.

2020 - 2021 Guest Associate Editor, Frontiers in Cardiovascular Medicine

2019 2019 International Society for Heart Research (ISHR) Early-Career Investigator Travel Award.

2018 Gates Grubstake Award, Gates Frontiers Fund & University of Colorado, Aurora, CO.

2017 Outstanding Early Career Scholar, University of Colorado Department of Medicine

2015 Outstanding Early Career Investigator Award Finalist, American Heart Association-Council on Basic Cardiovascular Sciences (AHA-BCVS)

2014 Early-career Investigator Biomedical Research Award, Boettcher Foundation, CO

2012 Top 10 advances in heart disease and stroke research selected by American Heart Association/American Stroke Association

2011 Meritorious Research Award in Biomedical Sciences, UT Southwestern Medical Center

 **C. Contributions to Science**

1. **Signaling and Transcriptional regulation in cardiac hypertrophy (P.h.D. studies)**. My early publications addressed molecular mechanisms underlying cardiac hypertrophy. Post-natal cardiac myocytes respond to diverse signals by hypertrophic growth and activation of a fetal gene program. I discovered that a family of transcriptional coactivators, CAMTAs, promotes cardiomyocyte hypertrophy by coordinating with class II histone deacetylases (HDACs), negative regulators of cardiac growth. Accordingly, mice homozygous for a loss-of-function mutation in a CAMTA gene are defective in stress-dependent cardiac growth and gene expression, whereas mice lacking HDAC5, a class II HDAC, are hypersensitive to the pro-hypertrophic actions of CAMTA. Collaborating with Dr. Backs, I also found that HDAC4 plays a central role in calcium/calmodulin-dependent kinase II (CaMKII) signaling pathways in various cell types. Phosphorylation of HDAC4 by calcium-activated CaMKII promotes nuclear export of HDAC4, with consequent derepression of HDAC target genes and hypertrophic growth. These publications document signaling networks governing cardiac hypertrophy in the heart. These studies facilitate screening efforts to identify drug-like molecules that specifically interrupt the interaction between HDACs and their binding factors or substrates. I served as the primary investigator or co-investigator.

* 1. **Song K**, Backs J, McAnally J, Qi X, Gerard RD, Richardson JA, Hill JA, Bassel-Duby R, Olson EN. The transcriptional coactivator CAMTA2 stimulates cardiac growth by opposing class II histone deacetylases. *Cell*. 2006 May 5;125(3):453-66. PMID: 16678093.
	2. Long C\*, Grueter CE\*, **Song K\***, Qin S, Qi X, Kong YM, Shelton JM, Richardson JA, Zhang CL, Bassel-Duby R, Olson EN. Ataxia and Purkinje cell degeneration in mice lacking the CAMTA1 transcription factor. *Proc Natl Acad Sci U S A.* 2014 Aug 5;111(31):11521-6. PMID: 25049392; PMCID: PMC4128133. (\*These authors equally contributed)
	3. Bagchi RA, Ferguson BS, Stratton MS, Hu T, Cavasin MA, Sun L, Lin YH, Liu D, Londono P, **Song K**, Pino MF, Sparks LM, Smith SR, Scherer PE, Collins S, Seto E, McKinsey TA. (2018). [HDAC11 suppresses the thermogenic program of adipose tissue via BRD2.](https://www.ncbi.nlm.nih.gov/pubmed/30089714) *JCI Insight.* 3(15). PMID: 30089714.
1. **Reprogramming of fibroblasts into induced cardiomyocytes (Postdoctoral training).** Ischemic heart disease leading to myocardial infarction (MI) and heart failure is the leading cause of death, which is majorly due to the limited regenerative capacity of the adult human heart to compensate for the irreversible loss or dysfunction of cardiomyocytes after injury. We have shown that a combination of cardiac transcription factors and microRNAs can cooperatively reprogram cardiac fibroblasts into induced cardiomyocytes in vitro and in vivo. These results suggest a potential strategy for cardiac repair through the reprogramming of fibroblasts resident in the heart into cardiomyocytes. I served as the leading investigator or co-investigator in these studies.
2. **Song K,** Nam YJ, Luo X, Qi X, Tan W, Huang GN, Acharya A, Smith CL, Tallquist MD, Neilson EG, Hill JA, Bassel-Duby R, Olson EN. Heart repair by reprogramming non-myocytes with cardiac transcription factors. *Nature.* 2012 May 13;485(7400):599-604. PMID: 22660318; PMCID: PMC3367390.(2012 top 10 advances in heart disease and stroke research selected by American Heart Association/American Stroke Association)
3. Nam YJ, **Song K,** Luo X, Daniel E, Lambeth K, West K, Hill JA, DiMaio JM, Baker LA, Bassel-Duby R, Olson EN. Reprogramming of human fibroblasts toward a cardiac fate. *Proc Natl Acad Sci U S A.* 2013 Apr 2;110(14):5588-93. PMID: 23487791; PMCID: PMC3619357.
4. Nam YJ, **Song K,** Olson EN. Heart repair by cardiac reprogramming. *Nat Med.* 2013 Apr;19(4):413-5. PMID: 23558630; PMCID: PMC3790637.

|  |  |  |
| --- | --- | --- |
| 1. **Molecular mechanisms underlying cardiomyocyte cell fate decision.** Fibroblasts can be reprogrammed into induced cardiomyocytes at a low efficiency by forced expression of cardiomyogenic factors. We demonstrate that pro-fibrotic signaling potently antagonizes cardiac reprogramming. Remarkably, inhibiting pro-fibrotic signaling using small molecules that target the transforming growth factor-β or Rho-associated kinase pathways efficiently converts embryonic fibroblasts into functional cardiomyocyte-like cells. These findings suggest a negative role of pro-fibrotic signaling in cardiomyocyte regeneration in failing hearts, leading to a concept that inhibiting fibrosis could enhance organ regeneration. We also uncovered that inhibiting inflammatory signaling dramatically enhances the efficiency of cardiac reprogramming. I served as a senior investigator.
	1. Zhao Y, Londono P, Cao Y, Sharpe EJ, Proenza C, O'Rourke R, Jones KL, Jeong MY, Walker LA, Buttrick PM, McKinsey TA, **Song K**. High-efficiency reprogramming of fibroblasts into cardiomyocytes requires suppression of pro-fibrotic signalling. *Nat Commun.* 2015 Sep 10;6:8243. PMID: 26354680; PMCID: PMC4579788.
	2. Riching AS, Zhao Y, Cao Y, Londono P, Xu H, **Song K.** Suppression of Pro-fibrotic Signaling Potentiates Factor-mediated Reprogramming of Mouse Embryonic Fibroblasts into Induced Cardiomyocytes. J Vis Exp. 2018 Jun 3;(136):57687. PMID: 29912202; PMCID: PMC6101528.
	3. Riching AS, Danis E, Zhao Y, Cao Y, Chi C, Bagchi RA, Klein BJ, Xu H, Kutateladze TG, McKinsey TA, Buttrick PM, **Song K**. Suppression of canonical TGF-β signaling enables GATA4 to interact with H3K27me3 demethylase JMJD3 to promote cardiomyogenesis. J Mol Cell Cardiol. 2021 Apr;153:44-59. doi: 10.1016/j.yjmcc.2020.12.005. Epub 2020 Dec 24. PMID: 33359755.
	4. Riching AS, **Song K**. Cardiac Regeneration: New Insights Into the Frontier of Ischemic Heart Failure Therapy. *Front Bioeng Biotechnol*. 2021 Jan 27;8:637538. PMID: 33585427; PMCID: PMC7873479.
2. **Understanding cardiomyopathy and heart failure using the iPSC-based platform and mouse models**. Human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) are a powerful platform for biomedical research. However, they are immature, which is a barrier to modeling adult-onset cardiovascular disease. Recently, we have utilized a combination of fatty acid medium and micropatterned surfaces to induce maturation in hiPSC-CMs. Matured cells display improved sarcomere morphology, metabolic maturation, and contractility. These cells also show increased sensitivity to hypertrophic stimuli, including hypertrophic agonist and genetic mutations in lysosomal-associated membrane protein 2 (*LAMP-2*) gene that are associated with Danon disease, which often leads to cardiomyopathy/heart failure through poorly defined mechanisms. We identify the LAMP-2 isoform B (LAMP-2B) as required for autophagosome-lysosome fusion in human cardiomyocytes (CMs). In combination with mouse models, we have identified an essential role of lncRNA-mediated alternative splicing in cardiac contractile function. I served as a senior investigator.
3. Chi C, Leonard A, Knight WE, Beussman KM, Zhao Y, Cao Y, Londono P, Aune E, Trembley MA, Small EM, Jeong MY, Walker LA, Xu H, Sniadecki NJ, Taylor MR, Buttrick PM, **Song K**. LAMP-2B regulates human cardiomyocyte function by mediating autophagosome-lysosome fusion. *Proc Natl Acad Sci U S A.* 2019 Jan 8;116(2):556-565. PMID: 30584088; PMCID: PMC6329949.
4. Chi C, Riching AS, **Song K**. Lysosomal Abnormalities in Cardiovascular Disease. *Int J Mol Sci.* 2020 Jan 27;21(3):811. doi: 10.3390/ijms21030811. PMID: 32012649; PMCID: PMC7036830.
5. Knight WE, Cao Y, Lin YH, Chi C, Bai B, Sparagna GC, Zhao Y, Du Y, Londono P, Reisz JA, Brown BC, Taylor MRG, Ambardekar AV, Cleveland JC Jr, McKinsey TA, Jeong MY, Walker LA, Woulfe KC, D'Alessandro A, Chatfield KC, Xu H, Bristow MR, Buttrick PM, **Song K**. Maturation of Pluripotent Stem Cell-Derived Cardiomyocytes Enables Modeling of Human Hypertrophic Cardiomyopathy. *Stem Cell Reports.* 2021 Feb 12:S2213-6711(21)00048-5. PMID: 33636116.
6. Zhao Y, Riching AS, Knight WE, Chi C, Broadwell LJ, Du Y, Abdel-Hafiz M, Ambardekar AV, Irwin DC, Proenza C, Xu H, Leinwand LA, Walker LA, Woulfe KC, Bristow MR, Buttrick PM, **Song K**. Cardiomyocyte-Specific Long Noncoding RNA Regulates Alternative Splicing of the Triadin Gene in the Heart. *Circulation.* 2022 Aug 30;146(9):699-714. doi: 10.1161/CIRCULATIONAHA.121.058017. PMID: 35862102.
7. **Inflammatory signaling in heart development and congenital heart defects**. Congenital heart defects (CHDs) are frequent in people with Down syndrome (DS), caused by trisomy of chromosome 21 (T21). However, the underlying mechanisms remain elusive. T21 upregulates IFN signaling, downregulates the canonical WNT pathway, and impairs cardiac differentiation when human iPSCs derived from individuals with DS and CHDs, and healthy euploid controls differentiate into cardiac cells. Genetic and pharmacological normalization of IFN signaling restored canonical WNT signaling and rescued defects in cardiogenesis in DS/CHD iPSCs and the Dp(16)1Yey/+ mouse model of DS. Our findings provide insights into the detrimental effects of interferon hyperactivity on cardiogenesis in DS.
	1. Waugh KA, Minter R, Baxter J, Chi C\*, Galbraith MD, Tuttle KD, Eduthan NP, Kinning KT, Andrysik Z, Araya P, Dougherty H, Dunn LN, Ludwig M, Schade KA, Tracy D, Smith KP, Granrath RE, Busquet N, Khanal S, Anderson RD, Cox LL, Estrada BE, Rachubinski AL, Lyford HR, Britton EC, Fantauzzo KA, Orlicky DJ, Matsuda JL, **Song K**, Cox TC, Sullivan KD, Espinosa JM. Triplication of the interferon receptor locus contributes to hallmarks of Down syndrome in a mouse model. *Nat Genet.* 2023 Jun;55(6):1034-1047. doi: 10.1038/s41588-023-01399-7. PMID: 37277650. (\*trainee)
	2. Chi C, Knight WE, Riching AS, Zhang Z, Tatavosian R, Zhuang Y, Moldovan R, Rachubinski AL, Gao D, Xu H, Espinosa JM, **Song K.** Interferon hyperactivity impairs cardiogenesis in Down syndrome via downregulation of canonical Wnt signaling. *iScience* 26, 107012, 2023

**Book Chapters**Xin M & **Song K**. 2016. Chapter 3: Epigenetic regulations in cardiac development. Backs & Mckinsey (eds.), Epigenetics in Cardiac Disease, Cardiac and Vascular Biology. DOI 10.1007/978-3-319-41457-7\_3. © Springer International Publishing Switzerland 2016.**Song K**, Baskin KK, Wang Z, eds. 2022. Metabolic Regulation in Cardiovascular Homeostasis and Disease. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88976-556-0**Complete List of Published Work in MyBibliography:** <https://www.ncbi.nlm.nih.gov/myncbi/1j3b37l9bkT5z/bibliography/public/> |  |  |
|  |  |  |