BIOGRAPHICAL SKETCH

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NAME: Wang, Da-Zhi

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

POSITION TITLE: Professor of Medicine, University of South Florida

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 | FIELD OF STUDY |
| --- | --- | --- | --- |
| Sichuan University, Chengdu, China | B.S. | 07/1985 | Biology |
| Peking University, Beijing, China | M.S. | 07/1988 | Biology |
| University of Iowa, Iowa City, IA | Ph.D. | 05/1998 | Developmental Biology |
| University of Texas Southwestern Medical Center, Dallas, TX | PostdoctoralFellow | 07/2000 | Molecular Biology(Eric Olson, Mentor) |

**A. Personal Statement**

I am a tenured Professor of Medicine and Director of the Center for Regenerative Medicine at the University of South Florida (USF) Health Heart Institute with a joint appointment in the Departments of Internal Medicine and Molecular Pharmacology and Physiology. I recently relocated to USF from Harvard Medical School/Boston Children’s Hospital. My office and laboratory are located in the newly constructed USF Health Building in downtown Tampa, part of the Morsani College of Medicine, where I have access to staff, trainees, and multiple other scientific resources.

I have dedicated my research career to the study of the molecular mechanisms that regulate mammalian development, cell fate determination, and human disease. My expertise in developmental and molecular biology have enabled me to make important contributions to understanding the fundamental processes regulating myocardial growth. We have extensively studied the myocardin family of transcription factors and their role in the cardiovascular system. In the past fifteen years, we have increasingly focused on non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), to understand how they regulate gene expression in the normal and diseased heart; in fact, my research group was among the first to recognize the importance of miRNAs in the regulation of muscle gene expression. My published studies on the transcriptional and miRNA-mediated post-transcriptional regulation of muscle gene expression are highly cited. This work has now transitioned into studies on the *in vivo* function of the long intergenic noncoding RNA-p21 (lincRNA-p21) in the heart and the description of the mechanisms by which lincRNA-p21 mitigates detrimental hypertrophic remodeling responses due to pressure overload.

We recently determined that the biogenesis, processing, and function of miRNAs is regulated by RNA binding proteins (RBPs). We uncovered a key role of Trbp, a RBP known to bind to HIV RNA, in heart development and function. Our studies on Pcbp1, a multi-functional RBP, revealed that its loss of function in the mouse heart results in ventricular non-compaction and abnormal ventricular apex formation. Interestingly, cardiac-specific Pcbp1-KO disrupts alternative splicing of Aars2, a gene associated with congenital mitochondrial cardiomyopathy; additionally, analysis of hearts from mice lacking Aars2 function reveals a similar phenotype. Pcbp1 also appears to affect the expression and function of a nearby lncRNA, suggesting a crosstalk between RBP and lncRNAs, and linking all three of these categories of regulatory molecules (miRNAs, lncRNAs and RBPs) to cardiac development and growth.

In other recent studies, we have determined that the Hippo/Yap pathway is altered in the Xinβ knock-out (KO) mouse model we developed, and we have further identified a physical and genetic interaction between Xinβ and NF2, a component of the Hippo/Yap pathway. We also showed that the expression of Xinβ is transcriptionally regulated by Mef2a, YAP, and TEAD1, suggesting the presence of a Xinβ/YAP feedback regulatory network in the heart. It is intriguing that the overexpression of YAP is able to rescue the cardiac defects in Xinβ KO mice, since this would indicate a functional and genetic interaction between Xinβ and YAP. We are especially excited about this work given the important roles for Hippo/Yap pathway function in tissue regeneration and self-renewal; we hypothesize that the ICD protein Xinβ mediates expression and function of the Hippo/YAP pathway to regulate cardiomyocyte proliferation and maturation. In summary, we are confident that all these pioneering studies will reveal novel molecular mechanisms that can ultimately be translated into therapeutic approaches to treat patients with cardiovascular disease.

I have also trained more than 60 graduate students and postdoctoral fellows over my 20-year career, including research and medical fellows. These trainees have had great success moving into academic positions at well-established research institutions. My work has resulted in over 100 publications in well-respected journals including Nature, Nature Medicine, Nature Genetics, Cell, and PNAS. I am recognized by my peers for the significant contributions I have made to our understanding of the molecular mechanisms controlling cardiac, skeletal, and smooth muscle gene expression during development and disease. My work has been continuously funded by various agencies including the NIH/NHLBI, American Heart Association, Muscular Dystrophy Association, March of Dimes, as well as by awards from private biotech/pharma.

**Ongoing and recently completed projects that I would like to highlight include:**

R01HL165794

Wang (PI)

01/01/2023-12/31/2026

lncRNA Function and Mechanisms during Cardiac Development and Disease

R01HL149401

Wang (PI)

07/01/2019-06/30/2023

Molecular mechanisms of dystrophic cardiomyopathy

R01HL138757

Wang (PI)

07/15/2017-06/30/2022 (NCE)

MicroRNAs, cardiac function and cardiomyopathy

R01HL141853

Chen, H (contact PI), Wang (co-PI)

01/15/2020-12/31/2023

CD45-mediated endothelial-to-mesenchymal transition in cardiovascular disease

R01HL125925

Wang (PI)

01/01/2016-12/31/2020

Therapeutic applications of miRNAs in myocardial and cardiac regeneration

R01HL116919

Wang (PI)

07/01/2013-06/30/2018

Molecular mechanisms of dilated cardiomyopathy

**Citations:**

1. **Wang, D.-Z.,** Chang, P.S., Wang, Z, Sutherland, L., Small, E., Krieg, P.A. and Olson, E. N., 2001.Activation of cardiac gene expression by Myocardin, a transcriptional cofactor for serum response factor. ***Cell*** 105, 851-862. PMID:11439182.
2. Huang ZP, Kataoka M, Chen J, Wu G, Ding J, Nie M, Lin Z, Liu J, Hu X, Ma L, Zhou B, Wakimoto H,Zeng C, Kyselovic J, Deng ZL, Seidman CE, Seidman JG, Pu WT, **Wang DZ**. 2015. Cardiomyocyte enriched protein CIP protects against pathophysiological stresses and regulates cardiac homeostasis. ***J Clin Invest.*** 125(11):4122-34. PMCID:PMC4639982.
3. Ding J, Chen J, Wang Y, Kataoka M, Ma L, Zhou P, Hu X, Lin Z, Nie M, Deng ZL, Pu WT, **Wang DZ**. 2015. Trbp regulates heart function through miRNA-mediated Sox6 repression. ***Nat Genet.*** 47:776-83. PMCID:PMC4485565.
4. Guo H, Lu YW, Lin Z, Huang ZP, Liu J, Wang Y, Seok HY, Hu X, Ma Q, Li K, Kyselovic J, Wang Q, Lin JL, Lin JJ, Cowan DB, Naya F, Chen Y, Pu WT, **Wang DZ.** 2020. Intercalated disc protein Xinβ is required for Hippo-YAP signaling in the heart. ***Nat Commun.***2020 Sep 16;11(1):4666. doi: 10.1038/s41467-020-18379-8. PMID: 32938943

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

2021-present: Professor, Department of Medicine, University of South Florida, Tampa, FL

2021-present: Director, Center for Regenerative Medicine, USF Health, University of South Florida, Tampa, FL

2017-2021: Professor, Department of Pediatrics, Harvard Medical School, Boston, MA.

2009-2017: Associate Professor, Department of Pediatrics, Harvard Medical School, Boston, MA.

2009-2021: Staff Scientist, Department of Cardiology, Boston Children’s Hospital, MA.

2008-2009: Associate Professor (with Tenure), Dept. of Cell and Development Biology, School of Med., University of North Carolina at Chapel Hill, NC.

2002-2008: Assistant Professor, Dept. of Cell and Developmental Biology; Member, Carolina Cardiovascular Biology Center, School of Med., University of North Carolina at Chapel Hill, NC.

2000-2002: Instructor, Department of Molecular Biology, University of Texas Southwestern, Dallas, TX.

**Professional Activities**

Reviewer for Journals (not exhaustively listed due to space constraints)

Cell and other Cell Press journals, Nature and other Nature Press journals, Science and other Science Press journals, Circulation, Circulation Research, Development, Development Biology, PNAS, and more

*Editorial Experiences:*

2017-present: Editorial board, *Journal of Biological Chemistry*

2014-present: Associate Editor, *Genes & Disease*

2012-present: Editorial board, *Physiological Genomics*

2012, 2017: Guest editor, *PLoS Genetics*

2011-present: Editorial Advisory Panel, *Clinical Science*

2011-2013: Editorial board, *AJP – Heart and Circulatory Physiology*

2010-2015: Editorial board, *Circulation Research*

2008-present: Editorial board, *Journal of Molecular and Cellular Cardiology*

Reviewer for Grants (2 highlighted, not exhaustively listed due to space constraints)

2016-2022: Permanent member. Cardiovascular Development and Disease (CDD). CSR/NIH

2005-2008: Member, Cardiovascular Development Study Section, Mid-Atlantic Affiliate, AHA

*Other activities:*

2019-present: Nominating Committee of the Council on Basic Cardiovascular Sciences, AHA

2018-present: Member, Melvin L. Marcus Young Investigators Award Committee, American Heart Association

2015: Co-organizer, 2015 Weinstein Cardiovascular Development Conference, Boston, MA

Patents: 4 USA issued or pending patents.

*More than 150 invited lectures/seminars at national and international conferences, universities and institutes.*

**Honors and Awards**

2021Endowed chair of cardiovascular medicine, USF Health, University of South Florida, Tampa, FL

**2017 Honorary Master of Art degree, Harvard University**

2014 Elected Fellow of American Heart Association (FAHA)

2008 Established Investigator Award, American Heart Association.

2004 Junior Faculty Award, University of North Carolina, Chapel Hill, NC.

2004 Basil O’Connor Scholar, March of Dimes Birth Defects Foundation.

2004 Medical Alumni Endowment Fund Grant, School of Medicine, University of North Carolina.

2004 Finalist, Katz Basic Research Prize for Young Investigators, American Heart Association.

2001 Young Investigator Award. D.W. Reynolds Center of Cardiovascular Medicine, UTSW, Dallas, TX.

1999 Finalist, D.C. Spriestersbach Dissertation Prize. Graduate College, University of Iowa, Iowa City, IA.

**C. Contributions to Science**

*Our studies have resulted in more than 100 publications, that have been cited more than 18,000 times.*

**1. Transcriptional and epigenetic regulation of gene expression in the cardiovascular system**

We have previously identified the myocardin family of transcription factors, including the founding member myocardin and myocardin-related transcription factors (MRTF-A and –B). We have demonstrated that these factors are essential for heart and vascular smooth muscle development (Wang et al., 2001; Wang, et al., 2002). The discovery of the myocardin family of transcription factors (Wang et al., Cell, 2001) has opened a new area in cardiovascular biology and become the focus of many labs around the world. Our current studies focus on the identification of cell growth and differentiation signals that modulate the transcriptional activities of myocardin. In addition, we study how epigenetic factors impact the function of cardiac transcription factors. It is our hope that those studies will lead to the identification of molecules which might serve as targets for new drug development and diagnosis of cardiovascular diseases.

1. **Wang, D.-Z.,** Chang, P.S., Wang, Z, Sutherland, L., Small, E., Krieg, P.A. and Olson, E. N., 2001.Activation of cardiac gene expression by Myocardin, a transcriptional cofactor for serum response factor. ***Cell*** 105, 851-862. PMID:11439182.

2. **Wang\* D.-Z.,** Li\*, S., Hockemeyer, D., Sutherland, L.B., Wang, Z., Schratt, G., Richardson, J.A., Nordheim, A., and Olson, E.N., 2002. Potentiation of serum response factor activity by a family of myocardin-related transcription factors. ***Proc. Natl. Acad. Sci. U. S. A.*** 99, 14855-14860. PMID:12397177. (\*Equal contribution).

3. Wang Z, **Wang D.-Z,** Hockemeyer D, McAnally J, Nordheim A, Olson EN. 2004. Myocardin and ternary complex factors compete for SRF to control smooth muscle gene expression. ***Nature.*** 428, 185-189. PMID:15014501

4. Guo H, Lu YW, Lin Z, Huang ZP, Liu J, Wang Y, Seok HY, Hu X, Ma Q, Li K, Kyselovic J, Wang Q, Lin JL, Lin JJ, Cowan DB, Naya F, Chen Y, Pu WT, **Wang DZ.** 2020. Intercalated disc protein Xinβ is required for Hippo-YAP signaling in the heart. ***Nat Commun.*** 2020 Sep 16;11(1):4666. doi: 10.1038/s41467-020-18379-8. PMID: 32938943

**2. microRNAs in cardiac development, cardiac function and cardiomyopathy**

Through genome-wide transcriptome profiling in animal models for human cardiomyopathy, our lab identified candidate miRNAs that are dysregulated in diseased hearts. Using a combination of gain- and loss- of function approaches and molecular dissection, our lab showed that loss-of-miRNAs in the cardiovascular system leads to severe cardiac defects and lethality in mice (Chen, et al., 2008). Our lab has generated and studied multiple lines of knockout and transgenic mice for miRNAs (miR-208a, miR-22, miR-17-92 and miR-155). These investigations demonstrated that miRNAs play a key role in controlling cardiac homeostasis in response to pathological and mechanical stress. Our study also uncovered the role of miRNAs in cardiomyocyte proliferation and cardiac regeneration (Chen, et al., 2013). We have been invited to contribute multiple review articles and book chapters on the topic.

1. Chen JF, Murchison EP, Tang R, Callis TE, Tatsuguchi M, Deng Z, Rojas M, Hammond SM, SchneiderMD, Selzman CH, Meissner G, Patterson C, Hannon GJ, **Wang DZ.** 2008. Targeted Deletion of Dicer in the Heart Leads to Dilated Cardiomyopathy and Heart Failure. ***Proc. Natl. Acad. Sci. U. S. A.*** 105: 2111-2116. PMCID:PMC2542870

2. Callis TE, Pandya K, Seok HY, Tang RH, Tatsuguchi M, Huang ZP, Chen JF, Deng Z, Gunn B, Shumate J, Willis MS, Selzman CH, **Wang DZ.** 2009 MicroRNA-208a is a key regulator of cardiac remodeling and conduction. ***J Clin Invest*** 119:2772–2786. PMCID:PMC2735902

3. Chen J, Huang ZP, Seok H, Ding J, Kataoka M, Zhang Z, Hu X, Wang G, Lin Z, Wang S, Pu W, Liao R,**Wang DZ.** 2013. mir-17-92 Cluster is Required for and Sufficient to Induce Cardiomyocyte Proliferation in Postnatal and Adult Hearts. ***Circ Res.*** 112:1557-66. PMCID:PMC3756475.

4. Gao F, Kataoka M, Liu N, Liang T, Huang ZP, Gu F, Ding J, Liu J, Zhang F, Ma Q, Wang Y, Zhang M, Hu X, Kyselovic J, Hu X, Pu WT, Wang J, Chen J, **Wang DZ.** 2019. Therapeutic role of miR-19a/19b in cardiac regeneration and protection from myocardial infarction. ***Nat Commun.*** 2019 Apr 17;10(1):1802. doi: 10.1038/s41467-019-09530-1. PMID: 30996254. PMCID: PMC6470165

**3. The roles of miRNAs and epigenetic regulators in muscle biology**

We are among the first to demonstrate the functional role of microRNAs in skeletal muscle. One of our publications (Chen et al., 2006) has been cited more than 2,000 times. Subsequently, we uncovered a novel function of miRNAs and showed that muscle expressed miRNAs, miR-1 and miR-206 in particular, repress the proliferation of skeletal muscle stem cells (satellite cells). These studies underscore the divergent functions of miRNAs in muscle biology. We have found that an important function of another miRNA, miR-155, in muscle proliferation and differentiation is to repress a key transcription factor, Mef2A (Seok, et al., 2011). We are currently investigating the *in vivo* function of miRNAs in skeletal muscle myocytes and muscle regeneration.

1. Chen JF, Mandel EM, Thomson JM, Wu Q, Callis TE, Hammond SM, Conlon FL, Wang DZ. 2006. Therole of microRNA-1 and microRNA-133 in skeletal muscle proliferation and differentiation. ***Nat Genet.*** 38: 228-233. PMCID:PMC2935565.

2. Chen JF, Tao Y, Li J, Deng Z, Yan Z, Xiao X, **Wang DZ.**, 2010. MicroRNA-1 and miR-206 Regulate Skeletal Muscle Satellite Cell Proliferation and Differentiation by Repressing Pax7. ***J Cell. Biol.*** 190:867-879. PMCID:PMC2935565.

3. Seok HY, Chen J, Kataoka M, Huang ZP, Ding J, Yan J, Hu X, **Wang DZ.** 2014. Loss of microRNA-155 protects the heart from pathological cardiac hypertrophy. ***Circ Res.*** *114:1585-95. PMCID:PMC4033580.*

4*.* Liu J, Huang ZP, Nie M, Wang G, Silva WJ, Yang Q, Freire PP, Hu X, Chen H, Deng Z, Pu WT,**Wang DZ.** 2020. Regulation of myonuclear positioning and muscle function by the skeletal muscle-specific CIP protein.***Proc Natl Acad Sci U S A.*** *2020 Jul 27:201922911.* doi: 10.1073/pnas.1922911117. Online ahead of print. PMID: 32719146

**4. Novel lncRNAs in cardiovascular biology and disease**

In addition to non-coding microRNAs, we recently started to explore the function of long non-coding RNAs (lncRNAs). Our lab showed that one lncRNA, lincRNA-p21, regulates vascular smooth muscle cell proliferation and apoptosis in a p53-dependent manner (Wu, et al., 2014). We documented the expression of lncRNAs in heart samples of human patients with ischemic cardiomyopathy, and we identified many dysregulated lncRNAs (Huang et al, 2016). Similarly, we are studying the expression and function of lncRNAs in mouse models of cardiomyopathy, and we expect to discover important functions of these novel non-coding RNA molecules.

1. Wu G, Cai J, Han Y, Chen J, Huang ZP, Chen C, Cai Y, Huang H, Yang Y, Liu Y, Xu Z, He D, Zhang X, Hu X, Pinello L, Zhong D, He F, Yuan GC, **Wang DZ\***, Zeng C\*. 2014. LincRNA-p21 Regulates Neointima Formation, Vascular Smooth Muscle Cell Proliferation, Apoptosis and Atherosclerosis by Enhancing p53 Activity. ***Circulation*** 130:1452-65. PMCID:PMC4244705. (\*Co-corresponding authors).

2. Huang ZP, Kataoka M, Chen J, Wu G, Ding J, Nie M, Lin Z, Liu J, Hu X, Ma L, Zhou B, Wakimoto H, Zeng C, Kyselovic J, Deng ZL, Seidman CE, Seidman JG, Pu WT, **Wang DZ.** 2015. Cardiomyocyte enriched protein CIP protects against pathophysiological stresses and regulates cardiac homeostasis. ***J Clin Invest.*** 125(11):4122-34. PMCID:PMC4639982.

3. Huang ZP, Ding Y, Chen J, Wu G, Kataoka M, Hu Y, Yang JH, Liu J, Drakos SG, Selzman CH, Kyselovic J, Qu LH, Dos Remedios CG, Pu WT, **Wang DZ.** 2016. Long non-coding RNAs link extracellular matrix gene expression to ischemic cardiomyopathy. ***Cardiovasc Res.*** 112:543-554. PMCID:PMC5079274.

4. Zhang F, Fu X, Kataoka M, Liu N, Wang Y, Gao F, Liang T, Dong X, Pei J, Hu X, Zhu W, Yu H, Cowan DB, Hu X, Huang ZP, Wang J, **Wang DZ\***, Chen J\*. 2020. Long noncoding RNA Cfast regulates cardiac fibrosis. ***Mol Ther Nucleic Acids.*** 2020 Nov 26;23:377-392. doi: 10.1016/j.omtn.2020.11.013. eCollection 2021 Mar 5. PMID: 33473324(\*co-corresponding authors).

**5. Molecular mechanisms of cardiac remodeling and stress-induced cardiac defects**

It has been well documented that the heart undergoes remodeling in response to physiological and pathological stress. However, the molecular mechanism underlying this observation remains largely unknown. We identified CIP as a novel molecule that senses pathological stresses to regulate cardiomyocyte hypertrophy (Huang et al., 2012). Understanding the molecular nature of CIP-mediated cardiac remodeling promises to offer novel therapeutic targets to treat heart disease. We also linked the function of miRNAs and the miRNA pathway to cardiac remodeling and cardiomyopathy. We showed that miR-22 is a key regulator of cardiac hypertrophy (Huang et al., 2013). Most recently, we discovered a surprising linear molecular pathway, including miR-208a and its target Sox6, in regulating cardiac function and heart failure (Ding et al, 2015). We are confident that results of our studies will ultimately allow us to find cure for cardiovascular disease.

1. Huang ZP, Seok HY, Zhou B, Chen J, Chen JF, Tao Y, Pu WT, **Wang DZ.** 2012. CIP, a cardiac Isl1- interacting protein, represses cardiomyocyte hypertrophy ***Circ Res.*** 110:818-830. PMCID:PMC3307880.

2. Huang ZP, Chen J, Seok H, Zhang Z, Kataoka M, Hu X, **Wang DZ.** 2013. MicroRNA-22 Regulates Cardiac Hypertrophy and Remodeling in Response to Stress. ***Circ Res.*** 112:1234-43. PMCID:PMC3720677.

3. Ding J, Chen J, Wang Y, Kataoka M, Ma L, Zhou P, Hu X, Lin Z, Nie M, Deng ZL, Pu WT, **Wang DZ**. 2015. Trbp regulates heart function through miRNA-mediated Sox6 repression. ***Nat Genet.*** 47:776-83. PMCID:PMC4485565.

4. Liang T, Gao F, Jiang J, Lu YW, Zhang F, Wang Y, Liu N, Fu X, Dong X, Pei J, Cowan DB, Hu X, Wang J\*, **Wang DZ**\*, Chen J\*. 2020. Loss of Phosphatase and Tensin Homolog Promotes Cardiomyocyte Proliferation and Cardiac Repair After Myocardial Infarction. ***Circulation*** 2020 Dec;142(22):2196-2199. doi: 10.1161/CIRCULATIONAHA.120.046372. PMID: 33253002 (\*co-corresponding authors).

Complete List of Published Work: <https://www.ncbi.nlm.nih.gov/myncbi/da-zhi.wang.1/bibliography/public/>