Over 20 years, I have commanded a broad background in cardiac muscle physiology and biochemistry. After my Ph.D training with Dr. Henk ter Keurs, I became a post research fellow in Dr. Eduardo Marban's lab at Johns Hopkins and became a faculty there later. For over a decade, my research has been involved in cardiac excitation-contraction coupling with focuses on myofilament Ca^{2+} responsiveness in normal and diseased myocardium. I have been P.I. and co-P.I./co-investigator in several NIH funded projects (i.e. R01, PPG) since. I have published the *most* regarding intact steady-state force-Ca^{2+} relations using fura-2 loaded cardiac trabecular preparation over the years and have established myself as an international leader in utilizing this state-of-the-art technique. My current research focuses on the mechanism of myofilament desensitization of the hypercontractile state by fropofol (a derivative of without anesthetic efficacy) in hypertrophic cardiomyopathy (HCM) and the prevention/reversal of HCM phenotype progression in animal models of HCM. I will be characterizing the changes in cardiac excitation-contraction coupling, especially on changes in myofilament responsiveness to Ca^{2+} in different experimental conditions and ultimately uncover the molecular mechanism of myofilament desensitization of fropofol. Conceptually, our research will not only deepen our understanding of why HCM phenotype develops but also extend our understanding to the pathophysiology of abnormal increase in contractility in the heart. Translationally, our research will help in the design of new strategies to deliver effective therapy to patient with HCM. Other projects in my lab include the role of endothelial-myocyte coupling in the transition from hypertrophy to failure in heart and the effect of anesthetics on failing myocardium.

Other Experience and Professional Memberships

Attending anesthesiologist, Johns Hopkins Hospital, Johns Hopkins University school of Medicine.
Member: Association of University Anesthesiologists, American Heart Association, American Society of Anesthesiologist, American Physiologic Society, Society of Cardiothoracic Anesthesiologists.
Committees: Member, American Heart Association's Cardiac Bio Reg - BSci 2 Peer Review Committee.
Member, Society of Cardiothoracic Anesthesiologists (SCA) Research Committee.
Journal Editor: Associate Editorial Board, Anesthesia & Analgesia (2014-2016)

Honors

5.1987 - 5.1989:	William H. Davis Scholarship for Medical Research, Faculty of Graduate Studies, University of Calgary, Calgary, Canada
9.1992 - 8.1994:	International Research Fellowship, American Heart Association.
7.2002 - 6.2004:	Clinician Scientist Award, Johns Hopkins University.

Contributions to Science.

1. Molecular and Cellular Mechanism of Myocardial Stunning.

My journey to independent research career began when I came to Dr. Marban's lab at Johns Hopkins after I got my Ph.D. in cardiovascular science in Dr. ter Keurs' lab. As a postdoc, I conducted the first successful experiments to compare steady-state force-Ca^{2+} relationship before and after skinning in the same cardiac trabeculae, leading to a landmark *expedited* publication in Circ Res in 1994 (**ref a**). As a key co-investigator of a R01 project, I made important discoveries towards understanding the molecular mechanism of myocardial stunning (**refs b,c**). We were the first to show directly that myocardial stunning is due to decreased myofilament Ca^{2+} responsiveness as a result of partial degradation of TnI (**ref d.e**). Now, this molecular mechanism underlying myocardial stunning has been well accepted in cardiology and our work has been well cited over the years. I later completed one of early studies on changes in cross-bridge kenetics in stunned myocardium (**ref f**).

a. **Gao, W.D.,** P.H. Backx, M.D. Azan-Backx, and E Marban. Myofilament Ca^{2+} sensitivity in intact versus skinned rat ventricular muscle. ***Circ Res.*** **74;**408-415, 1994.
b. **Gao, W.D.,** D. Atar, P.H. Backx, and E. Marban. Relationship between intracellular calcium and contractile force in stunned myocardium: Direct evidence for decreases myofilament Ca^{2+} responsiveness and altered diastolic function in intact ventricular muscle. ***Circ Res.*** **76:**1036-1048, 1995
c. **Gao, W.D.,** Y. Liu and E. Marban. Selective effects of oxygen free radicals on excitation-contraction coupling in ventricular muscle: Implications for the mechanism of stunned myocardium. ***Circulation*** **94:**2597-2604, 1996.
d. **Gao, W.D.,** Y. Liu, R Mellgren and E. Marban. Intrinsic myofilaments alterations underlying the decreased contractility of stunned myocardium: A consequence of calcium-dependent proteolysis? ***Circ Res.*** **78:**455-465, 1996
e. **Gao, W.D.,** D. Atar, Y. Liu, N.G Perez, A.M. Murphy, and E. Marban. Role of Troponin I proteolysis in the pathogenesis of myocardial stunning. ***Circ Res.*** **80:**393-399, 1997.

f. **Gao, W.D.,** T. Dai, and D. Nyhan. Increased cross-bridge cycling rate in stunned myocardium. ***Am J Physiol***. 290:H886-H893, 2006.

2. Excitation-contraction Coupling in Marine Myocardium.

In addition to the studies on the molecular mechanism of myocardial stunning, I continued studies on excitation-contraction coupling (ECC) in cardiac muscles from mice. I was the first person to be able to inject fura-2 salt into mouse trabecular muscle to obtain the steady-state force-$[Ca^{2+}]_i$ relationship in intact mouse cardiac muscle (**ref a**). With the experience of this challenging study, I completed another study charactering changes in ECC in transgenic hypertrophic cardiomyopathy (HCM) mice (**ref b**). Led by these two studies, I have been consistently publishing results from mouse cardiac muscles and have established our lab as one of the most productive labs using cardiac muscles from both normal and transgenic mice (**refs c,d,f**).

a. **Gao, W.D.**, N.G.Perez, E. Marban. Calcium Cycling and Contractile Activation in Intact Mouse Cardiac Muscle. ***J Physiol.*** **507:**175-184, 1998.
b. **Gao, W.D.,** N.G. Perez, C. Seidman, J, Seidman and E. Marban. Altered cardiac excitation-contraction coupling in cardiac muscle from mutant mice with familial hypertrophic cardiomyopathy. ***J Clin Invest.*** **103:**661-666, 1999.
c. Tan, Z., T. Dai, X. Zhong, Y. Tian, M. K. Leppo, **W. D. Gao**. Preservation of Cardiac Contractility after Long-term Therapy with Oxypurinol in Post-ischemic Heart Failure in Mice. ***Eur J Pharma.*** 621:71-77, 2009
d. Ramirez-Correa, G.A., Cortassa, S., Stanley, B., **W.D. Gao**, A.M. Murphy. Calcium sensitivity, force frequency relation and cardiac troponin I: critical role of PKA and PKC phosphorylation sites. ***J Mol Cell Cardiol*****.** 2010 2010 48(5):943-53
f. Sysa-Shah P, Tocchetti CG, Gupta M, Rainer PP, Shen X, Kang BH, Belmonte F, Li J, Xu Y, Guo X, Bedja D, **Gao WD**, et al.. Bidirectional cross-regulation between ErbB2 and β-adrenergic signaling pathways. Cardiovasc Res. 2015 Dec 21. pii: cvv274. [Epub ahead of print]

3. Nitroxyl (HNO) and Myofilment Ca^{2+} Responsiveness.

Several years ago, I collaborated with Dr. Paolocci, who pioneered the research of nitroxyl anion (HNO) on myocardium. We published a landmark study in which we discovered that myofilament Ca^{2+} responsiveness is increased by HNO, which was accompanied by an editorial by ***RJ Solaro*** (**ref a**). We later identified the molecular mechanism of HNO's myofilament action: HNO, by inducing disulfa bonds between actin and tropomyosin, and between myosin and myosin light chain, augments force generation. This novel study was also accompanied by an editorial by ***Y Ge and RL Moss*** (**ref b**).

a. Dai, T., Y. Tian, C. G. Tocchetti, T. Katori, D. Kass, N. Paolocci, **W. D. Gao.** Nitroxyl Anion (HNO/NO^-) Increases Myofilament Ca^{2+} Responsiveness in Rat Cardiac Muscle. ***J Physiol.*** 580(3): 951-960, 2007. (***Editorial by RJ Solaro. Nitroxyl effects on myocardium provide new insights into the significance of altered myofilament response to calcium in the regulation of contractility.J Physiol. 580(3):697, 2007***
b. **Gao, W.D.**, C. I. Murray, X. Zhong, Y. Tian, J. F. DuMond, B. A. Stanley, D. B. Foster, D. A. Wink, S. B. King, J. E. Van Eyk, N. Paolocci. Nitroxyl(HNO)-mediated disulfide bond formation between cardiac myofilament cysteines enhances contractile function. ***Circ Res.*** 111(8):1002-11, 2012. (***Editorial by Y Ge and RL Moss. Nitroxyl, redox switches, cardiac myofilaments, and heart failure: a prequel to novel therapeutics? Circ Res. 111(8):954-6, 2012.***

4. Myofilament Effect of Anesthetic Agents.

A couple of years ago, I became interested studying the effect of anesthetic agents on cardiac muscle contraction using our unique muscle technique. We provided direct evidence that anesthetics, especially at low and clinical relevant doses, desensitize myofilament leading to decreased force development. Furthermore, the decreased force can be prevented and reversed by HNO (**ref a**). We also investigated the effect of anesthetics on myocardial energetics and redox states in diabetic myocardium (**ref b**). Recently, we identified the molecular targets of propofol and isoflurane in myofilament proteins (**ref d**). The findings offered us an important clue that *anesthetics are myofilament desensitizers*. In collaboration with Dr. Eckenhoff of University Pennsylvania, we found that a propofol derivative, ***fropofol***, also depressed cardiac contraction but lacks anesthesia potency (**ref c**). These exciting findings motivated our current pursuit on fropofol's possible disease modifying effect in HCM.

a. Weigang Ding, Z, Li, X, Shen, , J. Martin, B. S. King, V. Sivakumaran, N. Paolocci, **W. D. Gao** Reversal of Isoflurane-induced Depression of Myocardial Contraction by Nitroxyl (HNO) via Myofilament Sensitization to Ca^{2+}. ***J Pharmaco Exp Ther*** 339:825-831, 2011. (***Highlighted paper***).
b. Shen X, N. Bhatt, J. Xu, T. Meng, M. Aon, B. O'Rourke, D.E. Berkowitz, S. Cortassa, **W.D. Gao.** Effect of Isoflurane on Myocardial Energetic and Oxidant Stress in Cardiac Muscle from Zucker Diabetic Fatty Rat. ***J Pharmacol Exp Ther.*** 349:21-28, 2014.
c. Woll KA, Weiser BP, Liang Q, Meng T, McKinstry-Wu A, Pinch B, Dailey WP, **Gao WD**, Covarrubias M, Eckenhoff RG. Role for the Propofol Hydroxyl in Anesthetic Protein Target Molecular Recognition. ***ACS Chem Neurosci.*** 17;6(6):927-35, 2015.
d. Meng T, Bu W, Ren X, Chen X, Yu J, Eckenhoff RG, **Gao WD**. Molecular mechanism of anesthetic-induced depression of myocardial contraction. ***FASEB J.*** 2016 May 11. 2915-25. doi: 10.1096/fj.201600290RR

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