**A. Personal Statement**

My goal of the proposed research is to investigate the underlying mechanism that triggers cardiac remodeling and heart failure using animal models and human cardiac fibroblast cultures. I am a new investigator submitting R01 grant application entitled, “Contribution of Fibulin-2 in Maladaptive Cardiac Remodeling”. Fibulin-2 is an extracellular matrix protein and also newly recognized matricellular protein that I have been working over the last 13 years since I started to work under my previous Research Mentor, Dr. Mon-Li Chu, at Thomas Jefferson University. With experimental myocardial infarction (MI) in the mouse model, we demonstrated that loss of fibulin-2 protected against progressive ventricular dysfunction and markedly improved survival after MI. We further found that preservation of ventricular function in fibulin-2 null mice following MI was accompanied by attenuated TGF-β activation and extracellular matrix synthesis, suggesting that fibulin-2 is required for local TGF-β activation. Additional preliminary data suggest that up-regulation of fibulin-2 drives sustained TGF-β activity leading to down-regulation of brain natriuretic peptide (BNP) signaling, an attenuator of remodeling. In this proposal, we will investigate regulatory role of fibulin-2 over two mutually counteracting signaling pathways, TGF-β and BNP, during maladaptive remodeling in in vivo animal studies and in vitro cardiac fibroblast cell culture studies. We hypothesize that autocrine and paracrine signaling network involving TGF-β and BNP is modulated by fibulin-2 and that targeting fibulin-2 can prevent or reverse remodeling process by attenuating pro-remodeling TGF-β activation and restoring cardio-protective BNP signaling. This hypothesis will be also tested by using isolated human cardiac fibroblasts from explanted hearts of patients with end-stage heart failure and from control non-failing donor hearts. These human samples will be available through my collaborator, Dr. Kenneth Margulies, an established investigator and Director of Heart Failure & Transplant Program at University of Pennsylvania who is in charge of Heart Tissue Bank. Collectively, my proposal will test the validity of a potentially novel therapeutic strategy in treating progressive heart failure. I am independent in my current position and the quality of my research training is commensurate with a career in biomedical research. In addition, I have included two experts in the field, Dr. Thomas Force (Temple University: cardiac stress and signal transduction) and Dr. Roger Markwald (Medical University of South Carolina: extracellular matrix biology and epithelial-mesenchymal transition) as Consultants to support my research progress. In summary, I am proposing the highly innovative research project from a novel viewpoint in investigating a principal mechanism of cardiac remodeling and heart failure. With our established animal models and preliminary data, we are uniquely positioned to test the proposed hypothesis.

**B. Positions and Honors**

**Positions and Employment**

1998-2002 Instructor, Department of Dermatology and Cutaneous Biology, Thomas Jefferson University, Philadelphia, PA
Principal Investigator/Program Director (Last, First, Middle): Tsuda, Takeshi

2002-2008 Assistant Professor, Department of Dermatology and Cutaneous Biology and Department of Pediatrics, Thomas Jefferson University, Jefferson Medical College, Philadelphia, PA
2002-present Staff Pediatric Cardiologist, Nemours Cardiac Center, Alfred I. duPont Hospital for Children, Wilmington, DE
2008-present Associate Professor, Department of Pediatrics, Thomas Jefferson University, Jefferson Medical College, Philadelphia, PA

Honors and Awards
1989-1990 Research Fellowship Award, Noguchi Medical Research Institute, Philadelphia, PA
1990 Scholarship Award, Japan North America Medical Exchange Foundation, Tokyo, Japan
1997-1998 Research Fellowship Award, American Heart Association, South Eastern Pennsylvania Affiliate
1998 Travel Award, Fourth Annual Meeting of Weinstein Conference of Cardiovascular Development
2004-2009 Target Investigator, COBRE (Center for Pediatric Research, 1 P20 RR20173-01, NIH)
2006-2008 Beginning Grant in Aid, American Heart Association, Pennsylvania-Delaware Affiliate

Board Certification
1993-2000 American Board of Pediatrics (#052336)
2008-2015 Re-certified (December 21, 2007)
1996-2003 American Board of Pediatrics, Subboard of Pediatric Cardiology (#001327)
2004-2010 Re-certified (April 30, 2002)
2010-2013 Re-certified (January 1, 2011)
2013-2020 Re-certified (March 31, 2013)

Other Professional Activities
2009-2012 American Heart Association Peer Review Section, Molecular Signaling I

C. Selected Peer-reviewed Publications (Selected from 26 peer-reviewed publications)

Most relevant to the current application

(3 other papers are currently under a review process).

Additional recent publications of importance to the field (in chronological order)


D. Research Support

Pending Research Support

NIH R01 HL 122792-01 Tsuda, T (PI)
2014-2019
“Contribution of fibulin-2 in maladaptive cardiac remodeling”
Role: PI
To determine that excessive fibulin-2-mediated TGF-β activity relative to BNP signaling underlies the transition from compensatory response to maladaptive remodeling that induces ventricular dysfunction and heart failure.

AHA National Innovative Research Grant Tsuda, T (PI)
2014-1016
“Targeting fibulin-2 in preventing myocardial fibrosis”
Role: PI
To determine efficacy of targeting fibulin-2 in preventing human heart failure by testing whether fibulin-2 knockdown will attenuate angiotensin II-induced extracellular remodeling in isolated human cardiac fibroblasts in vitro.

Completed Research Support

7/1/1997-6/30/1998 9704788A Tsuda, T (PI)
AHA Southeastern Pennsylvania Affiliate Fellowship Grant
“Molecular expression of flectin in left-right asymmetry determination and heart looping in avian and murine embryos”
Role: Post-doctoral Fellow (Mentor: Kersti Linask, Ph.D.)
To study how embryonic left-right asymmetry and the directionality of cardiac looping are determined by the
expression pattern of flection and extracellular matrix organization and to investigate how flectin functions in relation to the known embryonic asymmetry determination pathways such as activin-shh-nodal.

7/1/1998-6/30/2004 5R01 GM 55625-08 Chu, M-L (PI)
NIH National Institute of General Medical Sciences, “Function of Fibulins”
Role: Co-Investigator
To study biological role of an emerging family of extracellular matrix proteins, fibulins, in the embryonic cardiovascular development and tissue remodeling process such as wound healing by utilizing genetically ablated mouse model.

9/7/2004 – 7/31/2009 1 P20 RR020173-01 Shaffer, T (PI)
NIH Center of Biological Research Excellence (COBRE), “Center for Pediatric Research”
Role: Target investigator (Title: Fibulin-2 and ventricular remodeling).
To develop a group of target investigators who are competitive for long-term NIH funding, a structured mentoring program that provides guidance to the junior investigators will be implemented. In addition, recruitment of junior and senior investigators to the Center will be started to provide additional research programs and infrastructure for the long-term development of an NIH-funded Translational Research Center at the Nemours Biomedical Research Institute.

7/1/2006-6/30/2008 0665433U Tsuda, T (PI)
AHA Pennsylvanıa/Delaware Affiliate Beginning Grant in Aid
"The Role of Fibulin-2 in the Transition from Compensatory Hypertrophy to Ventricular Remodeling”
Role: PI
To investigate the biological role of fibulin-2 in the transition of physiological adaptation to pathological maladaptation when the heart is exposed to chronic biomechanical overload. Molecular mechanism of how extracellular matrix (ECM) protein fibulin-2 modulates ECM remodeling and functional deterioration will be examined.

5/1/2009 – 4/30/2010 Delaware Health Science Alliance (DHSA) Research and Development Task Force Grant Naik, U (PI)
“JAM-A and Cardiac Morbidity and Mortality after Myocardial Infarction” Role: Co-PI
We will investigate the role of JAM-A in wound healing process after myocardial infarction. Our preliminary data showed that JAM-A deficient mice died prematurely due to cardiac rupture compared with wild type controls. JAM-A can be involved in wound healing process by both modulating (a) neutrophil transmigration to introduce inflammatory processes and (b) angiogenesis to facilitate tissue repair. We will test the hypothesis that JAM-A facilitates a wound healing process by modulating inflammatory processes and angiogenesis during tissue repair.

6/1/2010 - 2/28/2013 IDeA Networks of Biomedical Research Excellence (INBRE)
“Extracellular matrix remodeling and human heart failure” Role: PI
To investigate the role of fibulin-2 in the development of human heart failure. Human myocardial tissue from the patients from advanced heart failure will be studied for up-regulation of fibulin-2, TGF-β, and MMP-2. In our preliminary studies, fibulin-2 is found to be responsible for transition from compensatory adaptive stage to progressive maladaptive stage in the mouse model. This is a pilot study to examine whether the same principle applies to the human and to evaluate whether fibulin-2 can become a target extracellular component to attenuate the development of human heart failure.

“Fibulin-2 mediates positive feedback loop of extracellular TGF-β modulation in cardiac remodeling” Role: PI
To directly address whether fibulin-2 is an essential mediator of TGF-β activation during cardiac remodeling, we will generate double mutant mice between TGF-β over-expression transgenic (TG) mice and fibulin-2 knockout (KO) mice. TGF-β TG mice are known to develop spontaneous cardiac hypertrophy and fibrosis by 8 weeks after birth. We hypothesize that fibulin-2 mediates positive feedback loop in activating TGF-β. By generating double mutant mice, we will be able to demonstrate whether depletion of fibulin-2 can attenuate cardiac remodeling induced by excessive TGF-β activation.