**Significant Publications**


Cells have mechanisms for controlling their protein composition and the cells in the heart are no exception. This manuscript describes a series of experiments in which a critical mechanism for turning over and degrading cardiac proteins, so that their components can be recycled, is manipulated. This recycling process, termed “autophagy,” appears to be critical in the heart and in other organs as well. The Robbins lab upregulated the process but showed that if this was done in a very precise manner, there was no harm to the heart and, during subsequent cardiac disease, the heart was relatively protected. This opens up new therapeutic avenues for the potential treatment of many different forms of cardiac pathology and heart failure as the recycling process is often disrupted in cardiac disease.


During development, the transcription factor Tbx20 is required for heart muscle cell proliferation, which is normally significantly down regulated after birth. In this study, the Yutzey Lab found that developmental overexpression of the transcription factor Tbx20 promotes adult heart muscle cell proliferation and maintains fetal gene expression patterns. Multiple signaling pathways activated by Tbx20 overexpression were identified that could be therapeutic targets for promotion of muscle growth in adult cardiac disease. Current studies are designed to determine if Tbx20 overexpression after adult cardiac injury can improve heart function and promote cardiac muscle cell proliferation.


Retinoic acid, the most important derivative of vitamin A, is required for normal human development. Improper levels of retinoic acid in humans causes numerous birth defects, including heart defects. This paper is important because it identifies a previously unrecognized, yet fundamental, mechanism that controls the levels of retinoic acid during development. Specifically, the Waxman Lab demonstrates that if receptors for retinoic acid are lost, it results in a molecular feedback loop that results in too much retinoic acid and consequently heart defects.

Heart failure is associated with chronically elevated levels of circulating adrenaline that are toxic to the heart. The adrenal glands are key contributors to this chronic excess of adrenaline; ironically, exposure of the adrenal gland to excess adrenaline elicits further, pathologic adrenaline release from the adrenal gland. This manuscript identifies a similar mechanism by which excess adrenaline is toxic to both the heart and the adrenal gland. Importantly, a small molecule drug is identified that can simultaneously mitigate the pathologic effects of excess adrenaline in both the heart and the adrenal gland, suggesting a novel therapeutic approach for heart failure.


Whether or not resident c-kit expressing cardiac progenitor cells contribute new cardiomyocytes to the heart after an injury event is the matter of an intense debate among the scientific community. In this innovative study, the Molkentin laboratory developed two genetic strategies in the mouse to irreversibly mark c-kit expressing cells during development, with ageing or after injury in adulthood. Unexpectedly, c-kit expressing cells did not produce a significant number of cardiomyocytes although they essentially generated endothelial cells during development, with ageing or after injury in adulthood. Unexpectedly, c-kit expressing cells did not produce a significant number of cardiomyocytes although they essentially generated endothelial cells in the heart. This study questions the potential cardiac functional improvement associated to c-kit cells therapies in heart failure patients.

Division Publications


35. Molkentin JD, Houser SR. Are resident c-Kit+ cardiac stem cells really all that are needed to mend a broken heart?. *Circ Res.* 2013; 113:1037-9.


42. Rydeen AB, Waxman JS. Cyp26 enzymes are required to balance the cardiac and vascular lineages within the anterior lateral plate mesoderm. Development. 2014; 141:1638-48.


Faculty, Staff, and Trainees

Faculty Members

Jeffrey Robbins, PhD, FAHA, FISHR, Professor

Leadership Executive Co-Director, Heart Institute; Endowed Chair, Molecular Cardiovascular Biology; Associate Chair for Core Research

Research Interests Mechanisms of Normal and Abnormal Cardiovascular function
Federica Accornero, PhD, Instructor
Research Interests Molecular mechanisms underlying pathologic cardiac remodeling

Md. Shenuarin Bhuiyan, PhD, Instructor
Research Interests Role of Sigma 1 Receptor in Cardiac Biology

Burns C. Blaxall, PhD, FAHA, Professor
Leadership Director, Translational Science; Co-Director, Heart Institute Research Core
Research Interests Molecular and signaling mechanisms of heart failure; cardiac fibrosis; drug and therapeutic discovery

Jennifer Davis, PhD, MA, Instructor
Research Interests Elucidating the mechanistic basis of myocardial repair and the cardiac injury response

James Gulick, MS, Instructor
Research Interests Molecular interactions between certain cardiac contractile proteins and how such interactions can be altered by mutations that are associated with cardiomyopathies

Jeanne James, MD, Associate Professor
Leadership Director, Pediatric Cardiology Fellowship Program; Director, Mouse Echocardiography Core
Research Interests Echocardiography, Translational Research, Cardiovascular Genetics

Zaza Khuchua, PhD, Associate Professor
Research Interests Congenital cardiac disorders caused by inborn errors in mitochondrial energy-producing enzymes, and model systems to study molecular mechanisms of these diseases

Marjorie Maillet, PhD, Instructor
Research Interests Understanding signaling pathways that lead to heart disease

Jeffery Molkentin, PhD, Professor
Leadership Howard Hughes Medical Institute Investigator
Research Interests Molecular pathways that underlie heart disease and muscular dystrophy

Sudarsan Rajan, PhD, Assistant Professor
Research Interests Understanding contractile and regulatory proteins’ gene expression and their role in maintaining normal cardiovascular function

Johannes van Berlo, MD, PhD, Instructor

Stephanie Ware, MD, PhD, Associate Professor
Leadership Director of Research and Development, Associate Medical Director, the Heart Institute Diagnostic Laboratory
Research Interests Genetics of pediatric heart disease

Joshua Waxman, PhD, Assistant Professor
Research Interests Molecular genetics of cardiovascular development

Katherine Yutzey, PhD, Professor
Research Interests Heart development and disease mechanisms

Trainees
- Federica Accornero, PhD, University of Turin, Italy
- Sarah Beckman, PhD, University of Pittsburgh
Bidur Bhandary, PhD, Chonbuk National University, South Korea
Md. Shenuarin Bhuiyan, PhD, Tohoku University, Japan
Justin Boyer, PhD, University of Ottawa, Canada
Caitlin Braitsch, PhD, University of Cincinnati
Matthew Brody, PhD, University of Wisconsin-Madison
Adam Burr, BS, University of Minnesota, Twin Cities
Robert Nathan Correll, PhD, University of Kentucky
Jason Cowan, MS, University of Miami
Angela Damen, MAT, Miami University
Enrico D'Aniello, PhD, Marine Zoological Station Anton Dohrn, Italy
Jennifer Davis, PhD, University of Michigan, Ann Arbor
Allison Dixon, BS, Bellarmine University
Tracy Dohn, BS, Wittenberg University
Ming Fang, MS, Boise State University
Maria Gomez, BS, Xavier University
Ambrose Goonasekera, PhD, University of Rochester
Manish Gupta, PhD, University of Cincinnati
Yan Huang, PhD, University of Wyoming
Alexia Hulin, PhD, Cleveland Clinic
Fadia Kamal, PhD, University of Rochester
Onur Kanisicak, PhD, University of Connecticut
Jason Karch, PhD, University of Cincinnati
Hadi Khalil, PhD, University of Lausanne, Switzerland
Jennifer Kwong, PhD, Weill Medical College of Cornell University
Julie Lander, BS, Brigham Young University
Mary Lee, MS, Ball State University
Ruijie Liu, PhD, University of Illinois at Urbana Champaign
Amrita Mandal, MSc, University of Calcutta, India
Patrick McLendon, PhD, Virginia Polytechnic Institute and State University
Rashmi Ram, PhD, University of Rochester
Md. Abdur Razzaque, PhD, Tokyo Women's Medical University, Japan
Tara Rindler, PhD, University of Cincinnati
Ariel Rydeen, BS, University of Minnesota
Tobias Schips, PhD, Ulm University, Germany
Jeffrey Schubert, BS, College of Mount St. Joseph
Emily Schulz, PhD, University of Cincinnati
Jennifer Schwanekamp, MS, University of Cincinnati
Mardi Sutherland, BS, University of Massachusetts, Boston
Muhammad Tariq, PhD, Quaid-I-Azam University, Pakistan
Andoria Tjondrokoesoemo, PhD, University of Medicine & Dentistry of New Jersey
Joshua Travers, BS, Rochester Institute of Technology
Ronald Vagnozzi, PhD, Thomas Jefferson University
Davy Vanhoutte, PhD, University of Leuven, Belgium
Elaine Wirrig, PhD, Medical University of South Carolina
Erin Wissing, BA, DePauw University
Division Collaboration

Shared interest in pathologic signaling of protease activated receptor 1 (PAR1) and its role in the pathogenesis of fibrotic remodeling and heart failure. (Burns C. Blaxall, PhD)

**Hematology** » Joseph S. Palumbo, MD

Investigating the potential for our novel small molecule inhibitors of G protein beta gamma signaling to attenuate acute and chronic renal fibrosis and inflammation using both animal models and human blood/tissue. (Burns C. Blaxall, PhD)

**Nephrology and Hypertension** » Prasad Devarajan, MD

**Center for Acute Care Nephrology** » Stuart L. Goldstein, MD

Assessment of cardiovascular outcomes in a mouse model of sickle cell disease. Dr. James worked with Dr. Malik and her clinical hematology fellow to develop a mouse echocardiography protocol to obtain model-specific data. She monitors the data for accuracy and meets with her team regularly to discuss the data and to provide clinical interpretation. The data generated was critical for the fellow’s successful application for an Arnold W. Strauss Fellow Award. (Jeanne James, MD)

**Experimental Hematology and Cancer Biology** » Punam Malik, MD

Effects of obesity on cardiovascular function in a mouse model of polymicrobial sepsis. This study is aimed at gaining a better understanding of why obese patients have poorer outcomes in clinical sepsis. Working with Dr. Kaplan’s team, Dr. James designed a customized mouse echocardiography protocol to provide a detailed assessment of cardiac function in mice with polymicrobial sepsis. She monitors the data for accuracy and meet with her team regularly to discuss the data and to provide clinical interpretation. (Jeanne James, MD)

**Critical Care Medicine** » Jennifer Kaplan, MD, MS

Role of AMP-activated protein kinase on cardiac function in polymicrobial sepsis. Dr. James worked with Dr. Zingarelli and her team to develop a mouse echocardiography protocol to provide detailed information about systolic and diastolic function before and after the induction of polymicrobial sepsis. She monitors the data for accuracy and meets with her team to discuss the data and to provide clinical interpretation. (Jeanne James, MD)

**Critical Care Medicine** » Basilia Zingarelli, MD, PhD

Non-invasive assessment of right ventricular function and pressure in a mouse model of pulmonary hypertension. Working with Dr. Nichols’ research team, Dr. James developed a protocol to specifically address right ventricular parameters in mice. She monitors the data for accuracy and meets with his team regularly to discuss the data and to provide clinical interpretation. This is a relatively new collaboration, representing new territory for the Mouse Echocardiography Core. (Jeanne James, MD)

**Human Genetics** » William C. Nichols, PhD

Pre- and post-natal modulation cardiovascular function in a mouse model of intrauterine growth retardation. Drs. James and Habli have worked to develop a reproducible method of assessing umbilical artery and vein flow in fetal mice. They are now able to perform transuterine survival scanning of fetal mice, which is an extension of their previous fetal mouse echo capabilities. Dr. James monitors the data for accuracy and meets with the team regularly to discuss the data and to provide clinical interpretation. (Jeanne James, MD)
Assessment of skeletal muscle contractility in a mouse model of amyotrophic lateral sclerosis (ALS). Dr. Crone came to the Mouse Echocardiography Core with a novel request to assess the movement of respiratory muscles in a mouse model of ALS. This required a novel approach to our usual mouse scanning but has yielded promising (and intriguing) preliminary data. (Jeanne James, MD)

Neurosurgery » Steven A. Crone, PhD

Alteration of mitochondrial dynamics in cardiolipin deficient mitochondria. We use our tafazzin-knockdown mice and human iPS-derived cells to look how mitochondrial fission/fusion is altered in these model systems. (Zaza Khuchua, PhD)

Human Genetics » Taosheng Huang, MD, PhD

Investigating human ACAD9 deficiency which changes folding of mitochondrial complex I. (Zaza Khuchua, PhD)

A student from Tanya Kalin’s laboratory investigates possible interaction of FoxM1 with mitochondrial electron transport chain complexes. (Zaza Khuchua, PhD)

Section of Neonatology, Perinatal and Pulmonary Biology » Tanya V. Kalin, MD, PhD

Identification of shared Twist1 target genes in embryonic development and cancer cells. (Katherine Yutzey, PhD)

Experimental Hematology and Cancer Biology » Nancy Ratner, PhD

Grants, Contracts, and Industry Agreements

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**MBNL1’s Function in Myofibroblast Transformation and Fibrosis**  
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FANG, M

**Wnt/beta-catenin Signaling in Heart Valve Development**  
American Heart Association  
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07/01/13-06/30/15  
$26,000

GOMEZ, M

**BMP Signaling in the Progression of Calcific Aortic Valve Disease**  
American Heart Association  
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$26,000

KAMAL, F

**Targeting Adrenal and Cardiac GPCR Signaling in Heart Failure: A Novel Therapeutic Strategy**  
American Heart Association  
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07/01/13-06/30/15  
$46,000

KHUCHUA, Z

**A Mouse Model of Barth Syndrome, a Mitochondrial Cardiolipin Disorder**  
National Institutes of Health  
R01 HL 108867  
07/07/11-03/31/15  
$245,000

Bezafibrates Pre-Trial on Mice  
Barth Syndrome Foundation, Inc.  
05/01/14-04/30/15  
$38,500

KWONG, J

**Defining the Role of SLC25a35 as a Regulator of the Mitochondrial Permeability Transition Pore and Cardiomyocyte Death**  
American Heart Association  
12POSTDOC11950000  
07/01/12-06/30/14  
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MOLKENTIN, J / ROBBINS, J (MPI)

**Thrombospondin 4 Regulates Adaptive ER Stress Response**  
National Institutes of Health  
R01 HL 105924  
01/01/11-12/31/14  
$305,366

MOLKENTIN, J

**CaMKII and InsP3-Mediated Signaling in Cardiac Myocytes**  
National Institutes of Health(The Regents of the University of California)  
P01 HL 080101  
08/01/11-05/31/16  
$271,987
Improving Cardiac Function after Myocardial Infarction
National Institutes of Health (Temple University School of Medicine)
P01 HL 108806 05/07/12-03/31/17 $260,000

Regulating Fibrosis and Muscle Growth in the Muscular Dystrophies
National Institutes of Health (The University of Chicago)
P01 NS 072027 07/01/11-06/30/16 $215,000

Molecular Pathways Controlling Cardiac Gene Expression
National Institutes of Health
R37 HL 060562 07/01/13-06/30/18 $238,000

RAJAN, S

Translational and Post-Translational Regulation of Tropomyosin in Normal and Cardiomyopathic Hearts
American Heart Association
11SDG4980029 08/01/11-12/31/14 $70,000

ROBBINS, J

A TG Rabbit Model for the Functional Effects of FHC Mutations in B-Cardiac Myosin
National Institutes of Health (University of Vermont)
R21 HL 111847 07/15/12-06/30/14 $24,960

Cardiac Myosin Binding Protein-C: Structure, Function and Regulation
National Institutes of Health (University of Vermont)
P01 HL 059408 02/01/10-01/31/15 $304,920

Proteotoxicity: An Unappreciated Mechanism of Heart Disease
Fondation Leducq
10/01/11-09/30/16 $247,636

Signaling Processes Underlying Cardiovascular Function
National Institutes of Health
P01 HL 069779 06/06/02-05/31/18 $1,149,912

TARIQ, M

Identification of Novel Human X-Linked Heterotaxy Genes
American Heart Association
12POSTDOC10370002 07/01/12-02/28/14 $30,667

VAN BERLO, J

Functional Relevance and Extent of Endogenous Cardiac Regeneration by C-Kit Positive Stem Cells
National Institutes of Health
K99 HL 112852 06/04/12-07/31/13 $32,000

WARE, S

Genetic and Epigenetic Mechanisms in Cardiomyopathy
American Heart Association
13EIA13460001 01/01/13-12/31/14 $72,727

Genetic Registry for Pediatric Heart Disease: The CCVM Consortium
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