**Division Data Summary**

**Research and Training Details**

<table>
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<th>Category</th>
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<tr>
<td>Direct Annual Industry Support</td>
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<td>Peer Reviewed Publications</td>
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**Significant Publications**


> During development, epicardial cells on the surface of the heart invade the myocardium to form the coronary blood vessels and fibrous connective tissue. Michelle Combs, a graduate student in Dr. Katherine Yutzey's lab, discovered that the transcription factor NFATc1 is required for the myocardial invasion of epicardial cells. Studies in mice and chicken embryos demonstrate that loss of NFATc1 in epicardial cells prevents myocardial invasion, thus inhibiting the development of the coronary vessels and fibrous connective tissue of the heart. The invasion of myocardium by epicardial-derived cells is likely mediated by the NFATc1 downstream target gene cathepsin K, that encodes an extracellular matrix-degrading enzyme. Recently, epicardial cells have been identified as a source of regenerative cells in cardiovascular disease. Therefore, manipulation of the NFATc1 pathway could be exploited to promote the invasion or investment of progenitor cells in diseased hearts.


> The Molkentin laboratory published a paper in The Journal of Clinical Investigation this past year in which they identified an entirely novel strategy for treating muscular dystrophy. Mice engineered to overexpress the protein SERCA in skeletal muscle showed substantial protection from mutations that normally lead to muscular dystrophy. Dr. Molkentin and colleagues also showed a gene therapy approach whereby transfer of the SERCA gene in skeletal muscle immediately corrected disease due to a Duchenne-like mutation in mice. These results suggest novel approaches to mitigate the underlying molecular defects that initiate skeletal muscle and cardiac cellular necrosis in muscular dystrophy by enhancing SERCA activity and/or expression. The laboratory is currently working on novel SERCA activating drugs that could also be employed to treat this disease in the near future.

Heineke J, Auger-Messier M, Correll RN, Xu J, Benard MJ, Yuan W, Drexler H, Parise LV, Molkentin JD. **CIB1 is a regulator of pathological cardiac hypertrophy.** *Nature medicine.* [Research Support, N.I.H., Extramural]
This paper from the Molkentin laboratory identified a novel regulatory pathway that functions through the intracellular phosphatase calcineurin to regulate how the heart hypertrophies in response to disease inducing stimuli. The protein CIB1 was shown to modulate calcineurin signaling at the plasma membrane, and inhibition of CIB1 function reduced cardiac hypertrophy through calcineurin. This research suggests novel treatment angles for reducing pathological manifestations to the heart in response to disease inducing states.


This paper describes a mouse model of latent and progressive aortic valve disease. Elastin (Eln) haploinsufficiency was induced by gene targeting. Eln null mice died in the perinatal period due to severe arterial obstruction, but the Eln haploinsufficient mice (Eln+/−) had normal longevity. Valvular interstitial cell activation and TGFβ receptor 1 downregulation is at least in part responsible for the pathogenesis in this model, resulting in hyperproliferation and maladaptive extracellular matrix remodeling. The valve cusp histopathology of the Eln+/− mice mimics the findings of human degenerative aortic valve disease, thus these mice thus have the potential of contributing to the development of novel therapeutics for patients with aortic valve disease.

Division Highlights

Joshua Waxman, PhD

The Waxman lab’s recent work has focused on factors that affect cardiac progenitor specification and indicates that cardiac and forelimb progenitors interact, helping to direct each ones’ development. Specifically, we have found that retinoic acid signaling acting on forelimb progenitors impacts fibroblast growth factor signaling, which acts on cardiac progenitors. Together, these interactions allow proper specification of these different fields. We think elucidating these interactions will allow us to understand developmental syndromes that result in both heart and forelimb defects.

Division Collaboration

Human Genetics » Teresa Smolarek, PhD; Sarah Zimmerman, PhD

Study of microarray abnormalities in patients with cardiovascular malformations, funded by a grant through the March of Dimes.

Allergy and Immunology; Gastroenterology » Marc Rothenberg, MD, PhD; Philip Putnam, MD; James Franciosi, MD, MS, MSCE

TGF beta dysregulation: understanding the relationship in patients with eosionophilic esophagitis and connective tissue abnormalities.

Biomedical Informatics » Bruce Aronow, PhD

Use of systems biology to identify genetic regulatory networks for cardiomyopathy.

Faculty Members

Jeffrey Robbins, PhD, Professor

Executive Co-Director, The Heart Institute
Associate Chair of the CCHMC
Endowed Chair for Molecular Cardiovascular Biology

Research Interests: Mechanisms of Normal and Abnormal Cardiovascular function

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
Director, Mouse Echocardiography Core
Research Interests: Manifestations and etiologies of misfolded protein response and echocardiography

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
Howard Hughes Medical Institute Investigator
Research Interests: Molecular pathways that underlie heart disease and muscular dystrophy

Stephanie Ware, MD, PhD, Associate Professor
Director of Research and Development, Associate Medical Director, The Heart Institute Diagnostic Laboratory
Co-Director, Cardiovascular Genetics
Research Interests: Genetics of pediatric heart disease

Joshua Waxman, PhD, Assistant Professor
Research Interests: Molecular Genetics of Heart Development

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

Joint Appointment Faculty Members

D Woodrow Benson, MD, PhD, Professor
Cardiology
Research Interests: Genetic basis of pediatric heart disease

Trainees
- Federica Accornero, PhD, University of Turin, Italy
- Mannix Auger-Messier, PhD, University of Sherbrooke, Canada
- Md. Shenuarin Bhuiyan, PhD, Tohoku University, Japan
- Caitlin Braitsch, BS, Xavier University
- Adam Burr, BS, University of Minnesota, Twin Cities
- Ashley Cast, BA, Augustana College
- Santanu Chakraborty, PhD, Miami University
- Michelle Combs, BS, Quincy University
- Robert Nathan Correll, PhD, University of Kentucky
- Jason Cowan, MS, University of Miami
- Enrico D'Aniello, PhD, Marine Zoological Station Anton Dohrn, Italy
Division Publications


32. Spicer RL, Ware SM. **Diseases of the Myocardium.** *Nelson textbook of pediatrics*. Philadelphia, PA: Elsevier/Saunders; 2011: 1 online resource (p.).


34. Spicer RL, Ware SM. **Tumors of the Heart.** *Nelson textbook of pediatrics*. Philadelphia, PA: Elsevier/Saunders; 2011: 1 online resource (p.).


37. Sugden PH, Markou T, Fuller SJ, Tham el L, Molkentin JD, Paterson HF, Clerk A. Monophosphothreonyl extracellular signal-regulated kinases 1 and 2 (ERK1/2) are formed endogenously in intact cardiac myocytes and are enzymatically active. *Cellular signalling*. 2011; 23:468-77.


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**Grants, Contracts, and Industry Agreements**

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<td>Tbx18 Regulation of Epicardial-Derived Cell Proliferation, Migration and Differentiation in Cardiac Development</td>
<td>American Heart Association 07/01/09-06/30/11 $23,000</td>
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<td>Regulation of Cardiac Gene Expression by the L-type Calcium Channel, CaV1.2</td>
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<td>The Non-Hypertrophic Role of Calcineurin in Regulating Cardiac Structure-Function</td>
<td>National Institutes of Health F32 HL 095353 12/15/08-12/14/11 $52,154</td>
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<td><strong>KARCH, J</strong></td>
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<td>The Role of Bax and Bak in Necrotic Cell Death</td>
<td>American Heart Association</td>
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KHUCHUA, Z
The shRNA-Mediated Tafazzin Knockdown Mouse Model
Barth Syndrome Foundation, Inc.
01/01/10-12/31/11 $16,361

KRISHNAMURTHY, V
Valve Tissue Mechanics and Cell Phenotype in a Mouse Model of Aortic Valve Disease
American Heart Association
07/01/09-06/30/11 $23,000

MAILLET, M
Role of IP-3 Mediated Calcium Release in Cardiac Hypertrophic Cardiomyopathy
National Institutes of Health
R21 HL 097186 04/15/10-03/31/12 $125,000

MOLKENTIN, J
Calcium as a Molecular Signal in the Heart
National Institutes of Health (Temple University School of Medicine)
R01 HL 089312 08/15/07-06/30/12 $239,303
Cardiac Hypertrophic Intracellular Signaling Pathways
National Institutes of Health
R01 HL 062927 02/01/09-12/31/13 $250,000
Molecular Pathways Controlling Cardiac Gene Expression
National Institutes of Health
R37 HL 060562 07/01/08-06/30/13 $250,000
Thrombospondin 4 Regulates Adaptive ER Stress Response
National Institutes of Health
R01 HL 105924 01/01/11-12/31/11 $315,000

RAZZAQUE, A
Cardiomyopathic Mechanisms in Pediatric Congenital Disease
American Heart Association
07/01/09-06/30/12 $43,000

ROBBINS, J
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 $356,105
Nikon A1 Confocal Microscope
National Institutes of Health
S10 RR 027014 07/01/10-06/30/11 $388,205
Signaling Processes Underlying Cardiovascular Function
National Institutes of Health
P01 HL 069779 01/11/08-12/31/12 $1,219,260

SENGUPTA, A
URC Postdoctoral Fellow Research Grant
University of Cincinnati
01/01/11-12/31/11 $5,000

VAN BERLO, J
GATA-6 Function is Crucial for Cardiac Hypertrophy to Prevent Heart Failure
American Heart Association
07/01/10-06/30/12 $43,000
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<td>Uncovering Novel Genetic Causes and Risk in Congenital Heart Disease Patients</td>
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Current Year Direct Funding: $4,676,640

Industry Contracts

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Current Year Direct Receipts: $5,000

Total Funding: $4,681,640