Division Data Summary

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<th>Research and Training Details</th>
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<td>Number of Faculty</td>
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Significant Publications


cMyBP-C phosphorylation is necessary for basal myocardial function in the β-MyHC background and can preserve function after ischemia/reperfusion injury. Our studies justify exploration of cMyBP-C phosphorylation as a therapeutic target in the human heart.


This publication identified a novel interaction between the calcineurin and the TAK1 signaling pathways in the heart as an integrated circuit for controlling hypertrophy and response to insults that cause heart failure.

Wu X, Chang B, Blair NS, Sargent M, York AJ, Robbins J, Shull GE, Molkentin JD. Plasma membrane Ca2+...
This publication showed that a local pool of subsarcolemmal calcium regulates calcineurin-NFAT signaling in the heart. The calcium pump PMCA4b regulates this subsarcolemmal pool of calcium and can secondarily impact calcineurin signaling and the hypertrophic response, altering the sensitivity of mouse models to heart failure.

This paper is the first to identify and characterize mutations in NODAL, a TGF-beta ligand, in human congenital heart disease.

Demonstrated the necessity of a particular kinase in valve development.

Division Highlights
Jeffrey Robbins, PhD & James Gulick, MS
Demonstrated the importance of altered signaling in the development of valve disease.

Jeffrey Robbins, PhD
Demonstrated the direct linkage between cardiomyocyte accumulations of pre-amyloid oligomers and the development of heart failure.

Jeffrey Robbins, PhD
Showed that altered visco-elastic properties of the myocyte as a result of misfolded proteins can lead to chamber stiffness in the heart.

Jeffrey Robbins, PhD
Showed that altered signal pathways in a single progenitor cell type is responsible for developmental abnormalities in both the heart and skull.

Jeffery Molkentin, PhD
Presented the 2008 Thomas W. Smith Memorial Lecture—Protein Kinase C α as a Novel Therapeutic Target for Treating Heart Failure—to the American Heart Association Scientific Sessions meeting in New Orleans.

Division Collaboration
Collaboration with Experimental Hematology
Collaborating Faculty: Yi Zheng, PhD
The Molkentin Lab used Dr. Zheng's Cdc42 gene targeted mice in a study published in the Journal of Clinical Investigation.

Collaboration with Human Genetics
Collaborating Faculty: Teresa Smolarek, PhD
Dr. Smolarek's Cytogenetics Lab helped Dr. Ware's lab identify novel genetic causes of congenital heart defects.

Faculty Members
Jeffrey Robbins, PhD, Professor; Associate Chair of the CCHMC; Executive Co-Director, The Heart Institute; Endowed Chair for Molecular Cardiovascular Biology
Research Interests: Mechanisms of Normal and Abnormal Cardiovascular function

Christopher Baines, PhD, Research Instructor

James Gulick, MS, Research 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, Research Associate Professor
Zaza Khuchua, PhD, Research 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

Maike Krenz, MD, Research Instructor

Jeffery Molkentin, PhD, Professor; *Howard Hughes Medical Institute Investigator*
**Research Interests:** Molecular pathways that underlie heart disease

Hiroyuki Nakayama, MD, PhD, Research Instructor
**Research Interests:** Role of calcium in cardiac pathogenesis

Sakthivel Sadayappan, PhD, Research Instructor
**Research Interests:** Effects of muscle protein structure on heart function and how certain proteins protect the heart from injury

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

Katherine Yutzey, PhD, Professor; *Director Molecular and Developmental Graduate Program*
**Research Interests:** Heart development and disease mechanisms

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**Joint Appointment Faculty Members**

D. Woodrow Benson, MD, PhD, Professor
Cardiology

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**Trainees**

- Federica Accornero, PhD, University of Turin
- Mannix Auger-Messier, PhD, University of Sherbrooke, Canada
- Caitlin Braitsch, BS, Xavier University
- Matthew Benard, BS, St. Lawrence University
- Ashley Cast, BA, Augustana College
- Santanu Chakraborty, PhD, Miami University
- Michelle Combs, BS, Quincy University
- Robert Nathan Correll, PhD, University of Kentucky
- Jennifer Davis, PhD, University of Michigan, Ann Arbor
- Petra Eder, PhD, University of Graz, Austria
- John Elrod, PhD, Albert Einstein College of Medicine
- Ambrose Goonasekera, PhD, University of Rochester
- Joerg Heineke, MD, Hannover Medical School, Germany
- Mary Horn, MS, Ball State University
- Shawna Hottinger, BS, Marshall University
- Jason Karch, BA, Dakota Wesleyan University
- Izhak Kehat, PhD, Technion-Israel Institute of Technology, Isreal
- Jennifer Kwong, PhD, Weill Medical College of Cornell University
- Qinghang Liu, MD, PhD, University of Tennessee Health Sciences Center
- Jeffrey Lynch, PhD, University of Alberta, Canada
- Marjorie Maillet, PhD, University of Paris XI, France
- Timothy Mead, BS, University of Dayton
- Douglas Millay, PhD, University of Cincinnati
- Arunima Sengupta, PhD, Miami University
- Mardi Sutherland, BS, University of Massachusetts, Boston
- David Terrell, BS, Texas State University
- Anup Tilak, PhD, Industrial Toxicology Research Centre, India
- Jop van Berlo, MD, PhD, University Hospital Maastricht, Netherlands
- Shuyun Wang, MD, PhD, Shandong University, China
Significant Accomplishments

Mechanisms of Congenital Heart Disease

Jeffrey Robbins, PhD, Professor and Director of MCB, was elected a Fellow of The Graduate School at the University of Cincinnati this year. He received the Rieveschel Award for Distinguished Scientific Research and the Daniel Drake Medal, the highest honor that the College of Medicine awards its most distinguished faculty. Dr. Robbins was also appointed Associate Editor of the premier basic science cardiovascular journal, *Circulation Research*.

The Robbins laboratory continues to use novel, genetically engineered models to study pediatric cardiovascular disease. In a pair of seminal studies published in *Proceedings of the National Academy of Sciences, USA*, Dr. Robbins and his colleagues showed the basis of the development of congenital heart abnormalities and the accompanying craniofacial defects as a result of altered developmental signaling due to the mutations in a single gene. Too little of the gene/protein SHP2 interferes with the normal developmental activity of what are called neural crest cells. These cells, which occur very early in embryonic development, migrate to specific regions of the embryo. While doing so, the cells are supposed to differentiate and give rise to certain nerve tissues, craniofacial bones or smooth muscle tissue of the heart. The findings show that a deficiency of SHP2 in neural crest cells results in a failure of cell differentiation at diverse sites in the developing embryo, leading to anatomical and functional deficits so severe that it precludes viability of the developing fetus.

The findings from this study can be used to now develop specific drugs that could target the affected pathway, leading to treatment of heart and cranial-facial malformations. Abnormal heart development is the most common human birth defect, affecting about 1 percent of newborns. The team will now focus on exploring the exact alterations in neural crest cell migration, expansion and differentiation that contribute to birth defects of other organ systems.

Signals for Heart Failure

Jeffrey D. Molkentin, PhD, a professor in MCB, was named one of 56 new Howard Hughes Medical Institute (HHMI) Investigators. The award will place Dr. Molkentin among an elite group of the nation’s most promising scientists who are challenged to extend the boundaries of science by pursuing bold and creative research. His team studies the signaling mechanisms that control muscle cell growth, differentiation and death. This work is creating new knowledge about basic molecular processes that influence cardiac and skeletal development as well as diseases like muscular dystrophy and heart failure.

The Molkentin laboratory continues to investigate the genes and pathways that underlie heart failure and how the chambers in the heart change shape during disease. The heart typically enlarges in response to many different disease states as a way of maintaining proper pump function. This process of heart enlargement has been studied by scientists for decades, because it typically leads to other more serious disease states, including death of the patient. In collaboration with Dr. Yi Zheng in the Division of Experimental Hematology, the Molkentin laboratory uncovered a novel gene that controls how the heart enlarges in response to disease. Mice lacking this gene showed much greater cardiac enlargement and more rapid progression to heart failure when challenged with different disease-inducing insults. The results of this study were recently published in the prestigious medical journal, *Journal of Clinical Investigation*. This study suggests that drugs used to modulate this novel disease modifying gene, Cdc42, might be advantageous in treating select human cardiovascular abnormalities.

Bench to Bedside

Stephanie Ware, MD, PhD, was awarded the prestigious Burroughs Wellcome Fund Clinical Scientist Award in Translational Medicine grant to help bridge bench to bedside research. The $750,000 grant (over five years) will allow Ware, a physician-scientist at Cincinnati Children's Heart Institute, to explore the genetic causes of heterotaxy and how it relates to congenital heart defects. The Burroughs Wellcome Fund Award was exceptionally competitive this year, and the grant is one of only four awarded nationally.

Heterotaxy is the name given to multiple birth defects that occur when the body fails to establish a proper right and left side during early formation. This can affect the heart and other organs. As the heart forms, it follows a blueprint that requires positional information. The heart is particularly sensitive to not having information about left and right. The heart defects in heterotaxy are some of the most complicated cardiologists see. A child's overall prognosis is determined by the severity of the heart defect, and children with heterotaxy frequently have a worse prognosis than other children with similar heart defects. Heterotaxy is present in about three percent of children with congenital heart defects, but loss of
left- and right-sided information causes other heart defects as well. The precise genetic cause is identified in less than 10 percent of children with heterotaxy. The Burroughs Wellcome grant will use a unique heterotaxy patient sample set to perform genetic analyses to identify new candidates for this condition. Through a combination of human genetics and developmental biology, new genetic changes in patients with heterotaxy will be identified, validated, and then tested functionally in animal models.

**Division Publications**


Grants, Contracts, and Industry Agreements

Grants and Contract Awards

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<th>BAINES, C</th>
<th>Mechanisms of Mitochondrial-Dependent Death</th>
<th>American Heart Association - National</th>
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<td>SDG0635134N</td>
<td>07/01/06 - 06/30/10</td>
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<td>Identifying Novel Components of the Cardiac Necrotic Program</td>
<td>National Institutes of Health R21 HL 092327</td>
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| BEDARD, J | Genetic and Molecular Roles of a Novel ZIC3 Isoform in Cardiovascular Development | American Heart Association - Ohio PF0725539B | 07/01/07 - 06/30/09 | $44,000 / $86,000 |

| CHAKRABORTY, S | Twist1 and Tbx20 Function in Heart Valve Development | American Heart Association - Ohio PF0825627D | 07/01/08 - 06/30/10 | $43,000 / $88,000 |

| COMBS, M | NFATc1 Regulation of Extracellular Matrix Remodeling | American Heart Association - Ohio PF0715107B | 07/01/07 - 06/30/09 | $21,000 / $42,000 |

| DAVIS, J | The Non-Hypertrophic Role of Calcineurin in Regulating Cardiac Structure-Function | National Institutes of Health F32 HL 095353 | 12/15/08 - 12/14/11 | $48,826 / $149,750 |

| ELROD, J | Defining the Role of Necrotic Cell Death in the Progression of Heart Failure | National Institutes of Health F32 HL 092737 | 07/25/08 - 07/24/10 | $46,826 / $96,472 |

| GOONASEKERA, A | Role of Cardiac L-type Calcium Channels in the Pathophysiology of Cardiac Hypertrophy and Heart Failure | American Heart Association - Ohio PF0825652D | 07/01/08 - 06/30/10 | $43,000 / $88,000 |

| KRENZ, M | Defective Valvulogenesis in Noonan Syndrome | American Heart Association - National SDG0635472N | 07/01/06 - 06/30/10 | $59,091 / $236,364 |

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<th>Genetic And Molecular Signaling In Heart Failure - Project 4</th>
<th>National Institutes of Health (University of Cincinnati) P50 HL 077101</th>
<th>02/22/05 - 12/31/09</th>
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<td>Adaptive and Maladaptive Signaling in Cardiac Growth and Regeneration</td>
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<td>Role of Calcium Influx in Miyoshi Myopathy and Other Forms of Muscular Dystrophy</td>
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<td>Phosphorylation and Function of Cardiac Myosin Binding Protein-C</td>
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<td>Determination of Cardiac Looping Role of Zic 3 at the Node</td>
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<td>Requirement of the Embryonic Node for Cardiac Looping</td>
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