

Molecular Cardiovascular Biology

Division Photo



First Row: M. Krenz, J. Robbins; **Second Row:** J. Molkentin, K. Yutzey, J. James, Z. Khuchua; **Third Row:** H. Nakayama, J. Gulick, S. Sadayappan, S. Ware, C. Baines

Division Data Summary

Research and Training Details

Number of Faculty	12
Number of Joint Appointment Faculty	1
Number of Research Fellows	25
Number of Research Students	11
Number of Support Personnel	2
Direct Annual Grant Support	\$5,468,739
Direct Annual Industry Support	\$85,085
Peer Reviewed Publications	37

Faculty Members

Jeffrey Robbins, PhD, Professor

Christopher Baines, PhD, Research Instructor

Melissa Colbert, PhD, Research Associate Professor

James Gulick, MS, Research Instructor

Jeanne James, MD, Research Associate Professor

Zaza Khuchua, PhD, Research Associate Professor

Maiké Krenz, MD, Research Instructor

Jeffery Molkentin, PhD, Professor

Hiroyuki Nakayama, MD, PhD, Research Instructor

Sakthivel Sadayappan, PhD, Research Instructor

Stephanie Ware, MD, PhD, Assistant Professor

Katherine Yutzey, PhD, Professor

Joint Appointment Faculty Members

D. Woodrow Benson, MD, PhD, Professor
Cardiology

Trainees

- **Mannix Auger-Messier, PhD**, N/A, University of Sherbrooke, Canada
- **Bedard James, PhD**, N/A, University of Cincinnati
- **Santanu Chakraborty, PhD**, N/A, Miami University
- **Petra Eder, PhD**, N/A, University of Graz, Austria
- **John Elrod, PhD**, N/A, Albert Einstein College of Medicine
- **Heather Evans-Anderson, PhD**, N/A, University of South Carolina School of Medicine
- **Ambrose Goonasekera, PhD**, N/A, University of Rochester
- **Michael Hambleton, PhD**, N/A, University of Cincinnati
- **Joerg Heineke, MD**, N/A, Hannover Medical School, Germany
- **Izhak Kehat, PhD**, N/A, Technion-Israel Institute of Technology, Israel
- **Jennifer Kwong, PhD**, N/A, Weill Medical College of Cornell University
- **Qinghang Liu, MD, PhD**, N/A, University of Tennessee Health Sciences Center
- **Jeffrey Lynch, PhD**, N/A, University of Alberta, Canada
- **Marjorie Maillet, PhD**, N/A, University of Paris XI, France
- **Alina Maloyan, PhD**, N/A, Hebrew University of Jerusalem, Israel
- **Douglas Millay, PhD**, N/A, University of Cincinnati
- **Tomoki Nakamura, MD**, N/A, Jichi Medical School, Japan
- **Hiroyuki Nakayama, MD, PhD**, N/A, Osaka University School of Medicine, Japan
- **J. Scott Pattison, PhD**, N/A, University of Missouri-Columbia
- **Malgorzata Quinn, PhD**, N/A, Polish Academy of Sciences, Poland
- **Arunima Sengupta, PhD**, N/A, Miami University
- **Anup Tilak, PhD**, N/A, Industrial Toxicology Research Centre, India
- **Jop van Berlo, MD, PhD**, N/A, University Hospital Maastricht, Netherlands
- **Shuyun Wang, MD, PhD**, N/A, Shandong University, China
- **Xu Wu, MD, PhD**, N/A, Loyola University Medical Center

Significant Accomplishments in FY08

\$9 Million NIH L&B Grant

The Division received a major program grant totaling over 9 million dollars from the National Institute of Heart, Lung and Blood. The work will be carried out in the laboratories of three divisional faculty and will center around understanding important signaling pathways that underlie heart development and function.

Significant Publications in FY08

Pattison JS, Sanbe A, Maloyan A, Martin L, Osinska H, Klevitsky R, Robbins J (2008) Cardiomyocyte Expression of a Polyglutamine Pre-amyloid Oligomer Causes Heart Failure. Circulation 117: 2743-2751

This manuscript establishes the toxicity of a certain kind of unfolded protein that is found very often in diseased pediatric and adult heart patients. Proving that this protein causes heart disease now allows us to focus on developing ways of interfering with that process.

Millay DP, Sargent MA, Osinska H, Barton ER, Vagniaux G, Sweeney HL, Robbins J, Molkentin JD (2008) Genetic and pharmacologic inhibition of mitochondrial-dependent necrosis attenuates muscular dystrophy. Nat. Med. 14:442-447.

This manuscript shows a novel way to treat muscular dystrophy in mice by blocking mitochondrial-dependent necrosis. It suggests a novel treatment strategy for translation in to Duchenne MD boys.

Evans-Anderson HJ, Alfieri CM, Yutzey KE (2008) Regulation of cardiomyocyte proliferation and myocardial growth during development by FoxO transcription factors. *Circ. Res.* 102:686-694.

Baines CP, Kaiser RA, Sheiko T, Craigen WJ, Molkentin JD (2007) Voltage-dependent anion channels are dispensable for mitochondrial-dependent cell death. *Nat. Cell Biol.* 9:550-555.

Heineke J, Auger-Messier M, Xu J, Oka T, Sargent MA, York A, Klevitsky R, Vaikunth S, Duncan SA, Aronow BJ, Robbins J, Crombleholme TM, Molkentin JD (2007) Cardiomyocyte GATA4 functions as a stress-responsive regulator of angiogenesis in the heart. *J. Clin. Invest.* 117:3198-3210.

Division Collaboration

Collaboration with Molecular Cardiovascular Biology; Cardiology; Cardiology

Collaborating Faculty: Katherine Yutzey; D. Woodrow Benson; Robert Hinton

Hinton RB, Alfieri C, Witt S, Glascock B, Khoury PR, Benson DW, Yutzey KE. (2008) Mouse Heart Valve Structure and Function: Echocardiographic and Morphometric Analyses from the Fetus through the Aged Adult. *Am. J. Physiol. – Heart and Circ. Physiol.* 294:H2480-2488.

Division Publications

1. Baines CP. [The mitochondrial permeability transition pore as a target of cardioprotective signaling](#). *Am J Physiol Heart Circ Physiol.* 2007; 293: H903-4.
2. Millay DP, Sargent MA, Osinska H, Baines CP, Barton ER, Vagniaux G, Sweeney HL, Robbins J, Molkentin JD. [Genetic and pharmacologic inhibition of mitochondrial-dependent necrosis attenuates muscular dystrophy](#). *Nat Med.* 2008; 14: 442-7.
3. Nakayama H, Chen X, Baines CP, Klevitsky R, Zhang X, Zhang H, Jaleel N, Chua BH, Hewett TE, Robbins J, Houser SR, Molkentin JD. [Ca²⁺- and mitochondrial-dependent cardiomyocyte necrosis as a primary mediator of heart failure](#). *J Clin Invest.* 2007; 117: 2431-44.
4. Pattison JS, Waggoner JR, James J, Martin L, Gulick J, Osinska H, Klevitsky R, Kranias EG, Robbins J. [Phospholamban overexpression in transgenic rabbits](#). *Transgenic Res.* 2008; 17: 157-70.
5. Nakamura T, Colbert M, Krenz M, Molkentin JD, Hahn HS, Dorn GW, 2nd, Robbins J. [Mediating ERK 1/2 signaling rescues congenital heart defects in a mouse model of Noonan syndrome](#). *J Clin Invest.* 2007; 117: 2123-32.
6. Diwan A, Krenz M, Syed FM, Wansapura J, Ren X, Koesters AG, Li H, Kirshenbaum LA, Hahn HS, Robbins J, Jones WK, Dorn GW. [Inhibition of ischemic cardiomyocyte apoptosis through targeted ablation of Bnip3 restrains postinfarction remodeling in mice](#). *J Clin Invest.* 2007; 117: 2825-33.
7. Krenz M, Sadayappan S, Osinska HE, Henry JA, Beck S, Warshaw DM, Robbins J. [Distribution and structure-function relationship of myosin heavy chain isoforms in the adult mouse heart](#). *J Biol Chem.* 2007; 282: 24057-64.
8. Ago T, Liu T, Zhai P, Chen W, Li H, Molkentin JD, Vatner SF, Sadoshima J. [A redox-dependent pathway for regulating class II HDACs and cardiac hypertrophy](#). *Cell.* 2008; 133: 978-93.
9. Davies KJ, Ermak G, Rothermel BA, Pritchard M, Heitman J, Ahnn J, Henrique-Silva F, Crawford D, Canaider S, Strippoli P, Carinci P, Min KT, Fox DS, Cunningham KW, Bassel-Duby R, Olson EN, Zhang Z, Williams RS, Gerber HP, Perez-Riba M, Seo H, Cao X, Klee CB, Redondo JM, Maltais LJ, Bruford EA, Povey S, Molkentin JD, McKeon FD, Duh EJ, Crabtree GR, Cyert MS, de la Luna S, Estivill X. [Renaming the DSCR1/Adapt78 gene family as RCAN: regulators of calcineurin](#). *Faseb J.* 2007; 21: 3023-8.
10. Gurda GT, Guo L, Lee SH, Molkentin JD, Williams JA. [Cholecystokinin Activates Pancreatic Calcineurin-NFAT Signaling In Vitro and In Vivo](#). *Mol Biol Cell.* 2008; 19: 198-206.
11. Houser SR, Molkentin JD. [Does contractile Ca²⁺ control calcineurin-NFAT signaling and pathological hypertrophy in cardiac myocytes?](#). *Sci Signal.* 2008; 1: pe31.
12. Jobe SM, Wilson KM, Leo L, Raimondi A, Molkentin JD, Lentz SR, Di Paola J. [Critical role for the mitochondrial permeability transition pore and cyclophilin D in platelet activation and thrombosis](#). *Blood.* 2008; 111: 1257-65.
13. Manicassamy S, Gupta S, Huang Z, Molkentin JD, Shang W, Sun Z. [Requirement of calcineurin a beta for the survival of naive T cells](#). *J Immunol.* 2008; 180: 106-12.
14. Morancho B, Minguillon J, Molkentin JD, Lopez-Rodriguez C, Aramburu J. [Analysis of the transcriptional activity of endogenous NFAT5 in primary cells using transgenic NFAT-luciferase reporter mice](#). *BMC Mol Biol.* 2008; 9: 13.
15. Sahin B, Hawasli AH, Greene RW, Molkentin JD, Bibb JA. [Negative regulation of cyclin-dependent kinase 5](#)

- [targets by protein kinase C](#) . *Eur J Pharmacol*. 2008; 581: 270-5.
16. Snider P, Hinton RB, Moreno-Rodriguez RA, Wang J, Rogers R, Lindsley A, Li F, Ingram DA, Menick D, Field L, Firulli AB, Molkentin JD, Markwald R, Conway SJ. [Periostin is required for maturation and extracellular matrix stabilization of noncardiomyocyte lineages of the heart](#) . *Circ Res*. 2008; 102: 752-60.
 17. Hsieh PC, Segers VF, Davis ME, MacGillivray C, Gannon J, Molkentin JD, Robbins J, Lee RT. [Evidence from a genetic fate-mapping study that stem cells refresh adult mammalian cardiomyocytes after injury](#) . *Nat Med*. 2007; 13: 970-4.
 18. Pattison JS, Sanbe A, Maloyan A, Osinska H, Klevitsky R, Robbins J. [Cardiomyocyte expression of a polyglutamine preamyloid oligomer causes heart failure](#) . *Circulation*. 2008; 117: 2743-51.
 19. Pinz I, Robbins J, Rajasekaran NS, Benjamin IJ, Ingwall JS. [Unmasking different mechanical and energetic roles for the small heat shock proteins CryAB and HSPB2 using genetically modified mouse hearts](#) . *Faseb J*. 2008; 22: 84-92.
 20. Wolf CM, Arad M, Ahmad F, Sanbe A, Bernstein SA, Toka O, Konno T, Morley G, Robbins J, Seidman JG, Seidman CE, Berul CI. [Reversibility of PRKAG2 glycogen-storage cardiomyopathy and electrophysiological manifestations](#) . *Circulation*. 2008; 117: 144-54.
 21. Hambleton M, York A, Sargent MA, Kaiser RA, Lorenz JN, Robbins J, Molkentin JD. [Inducible and myocyte-specific inhibition of PKC \$\alpha\$ enhances cardiac contractility and protects against infarction-induced heart failure](#) . *Am J Physiol Heart Circ Physiol*. 2007; 293: H3768-71.
 22. Heineke J, Auger-Messier M, Xu J, Oka T, Sargent MA, York A, Klevitsky R, Vaikunth S, Duncan SA, Aronow BJ, Robbins J, Crombleholme TM, Molkentin JD. [Cardiomyocyte GATA4 functions as a stress-responsive regulator of angiogenesis in the murine heart](#) . *J Clin Invest*. 2007; 117: 3198-210.
 23. Oka T, Xu J, Kaiser RA, Melendez J, Hambleton M, Sargent MA, Lorts A, Brunskill EW, Dorn GW, 2nd, Conway SJ, Aronow BJ, Robbins J, Molkentin JD. [Genetic manipulation of periostin expression reveals a role in cardiac hypertrophy and ventricular remodeling](#) . *Circ Res*. 2007; 101: 313-21.
 24. Pinz I, Ostroy SE, Hoyer K, Osinska H, Robbins J, Molkentin JD, Ingwall JS. [Calcineurin-induced energy wasting in a transgenic mouse model of heart failure](#) . *Am J Physiol Heart Circ Physiol*. 2008; 294: H1459-66.
 25. Purcell NH, Wilkins BJ, York A, Saba-El-Leil MK, Meloche S, Robbins J, Molkentin JD. [Genetic inhibition of cardiac ERK1/2 promotes stress-induced apoptosis and heart failure but has no effect on hypertrophy in vivo](#) . *Proc Natl Acad Sci U S A*. 2007; 104: 14074-9.
 26. Nagayama T, Takimoto E, Sadayappan S, Mudd JO, Seidman JG, Robbins J, Kass DA. [Control of in vivo left ventricular \[correction\] contraction/relaxation kinetics by myosin binding protein C: protein kinase A phosphorylation dependent and independent regulation](#) . *Circulation*. 2007; 116: 2399-408.
 27. Sadayappan S, Finley N, Howarth JW, Osinska H, Klevitsky R, Lorenz JN, Rosevear PR, Robbins J. [Role of the acidic N' region of cardiac troponin I in regulating myocardial function](#) . *Faseb J*. 2008; 22: 1246-57.
 28. Sadayappan S, Robbins J. [The death of transcriptional chauvinism in the control and regulation of cardiac contractility](#) . *Ann N Y Acad Sci*. 2008; 1123: 1-9.
 29. Yasuda S, Coutu P, Sadayappan S, Robbins J, Metzger JM. [Cardiac transgenic and gene transfer strategies converge to support an important role for troponin I in regulating relaxation in cardiac myocytes](#) . *Circ Res*. 2007; 101: 377-86.
 30. Ware SM, Quinn ME, Ballard ET, Miller E, Uzark K, Spicer RL. [Pediatric restrictive cardiomyopathy associated with a mutation in beta-myosin heavy chain](#) . *Clin Genet*. 2008; 73: 165-70.
 31. Villar AJ, Ware SM. **"Developmental Origins of the Mammalian Body Plan."** New York: Oxford University Press; 2008: 57-68.
 32. Ware SM, Belmont JW. **"ZIC3, CFC1, ACVR2B and EBAF and the Visceral Heterotaxies."** New York: Oxford University Press; 2008: 373-381.
 33. Evans-Anderson HJ, Alfieri CM, Yutzey KE. [Regulation of cardiomyocyte proliferation and myocardial growth during development by FOXO transcription factors](#) . *Circ Res*. 2008; 102: 686-94.
 34. Hinton RB, Jr., Alfieri CM, Witt SA, Glascock BJ, Khoury PR, Benson DW, Yutzey KE. [Mouse heart valve structure and function: echocardiographic and morphometric analyses from the fetus through the aged adult](#) . *Am J Physiol Heart Circ Physiol*. 2008; 294: H2480-8.
 35. Shelton EL, Yutzey KE. [Twist1 function in endocardial cushion cell proliferation, migration, and differentiation during heart valve development](#) . *Dev Biol*. 2008; 317: 282-95.
 36. Shelton EL, Yutzey KE. [Heart development and T-box transcription factors: lessons from avian embryos.](#) Amsterdam ; Boston: Elsevier; 2008: 69-91.
 37. Yutzey KE. [Teed off: cardiac conduction system development requires T-box transcription factors](#) . *Circ Res*.

Grants, Contracts, and Industry Agreements**Grant and Contract Awards****Annual Direct / Project Period Direct****Baines, C****Mechanisms of Mitochondrial-Dependent Myocyte Death**

American Heart Association - National

0635134N

07/01/06 - 06/30/10

\$59,091 / \$236,634

Bedard, J**Genetic and Molecular Roles of a Novel ZIC3 Isoform in Cardiovascular Development**

American Heart Association - Ohio

0725539B

07/01/07 - 06/30/09

\$42,000 / \$86,000

Combs, M**NFATc1 Regulation of Extracellular Matrix Remodeling and Cell Proliferation in Heart Valve Development**

American Heart Association - Ohio

0715107B

07/01/07 - 06/30/09

\$21,000 / \$42,000

Khuchua, Z**Animal Models of Human Barth Syndrome, A Mitochondrial Cardiolipin Disorder**

United Mitochondrial Disease Foundation

07/01/07 - 06/30/09

\$49,500 / \$55,000

Krenz, M**Defective Valvulogenesis in Noonan Syndrome**

American Heart Association - National

0635472N

07/01/06 - 06/30/10

\$59,091 / \$236,364

Liu, Q**The Role of Apoptosis Signal-Regulating Kinase-1 in Regulation of Cardiac Growth and Cell Death in Adult Heart in Vivo**

American Heart Association - Ohio

0625543B

07/01/06 - 06/30/08

\$44,000 / \$86,000

Maillet, M**Calcineurin's Role in Regulating Heart Growth & Hypertrophy**

American Heart Association - Ohio

0625282B

07/01/06 - 06/30/08

\$44,000 / \$86,000

Molkentin, J**Molecular Pathways Controlling Cardiac Gene Expression**

National Institutes of Health

R01 HL 060562

07/01/03 - 06/30/08

\$213,341 / \$1,125,000

Cardiac Hypertrophic Intracellular Signaling Pathways

National Institutes of Health

R01 HL 062927

08/01/03 - 07/31/08

\$189,636 / \$1,000,000

Genetic and Molecular Signaling in Heart Failure: Core D

National Institutes of Health (University of Cincinnati)

P50 HL 077101

01/01/08 - 12/31/09

\$278,020 / \$564,381

Mitochondrial Regulated Cardiac Myocyte Death

National Institutes of Health

R01 HL 081104

08/01/05 - 07/31/09

\$237,045 / \$1,000,000

Genetic and Molecular Signaling in Heart Failure

National Institutes of Health (University of Cincinnati)

P50 HL 077101

02/22/05 - 12/31/09

\$275,962 / \$1,451,722

Role of Calcium Influx in Miyoshi Myopathy and Other Forms of Muscular Dystrophy

Jain Foundation, Inc	05/01/07 - 04/30/10	\$70,000 / \$210,000
Adaptive and Maladaptive Signaling in Cardiac Growth and Regeneration		
Fondation Leducq	10/01/05 - 09/30/10	\$293,618 / \$1,184,852
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	\$249,169 / \$1,245,845
Pattison, S		
The Role of Mitochondrial Dysfunction and Apoptosis in CryABR120G Heart Failure		
National Institutes of Health		
F32 HL 087478	11/18/07 - 11/17/09	\$50,546 / \$66,401
Robbins, J		
Investigation of Amyloid Oligomer in Pediatric Cardiovascular Disease		
National Research Institution for Child Health and Development		
	06/03/07 - 03/31/10	\$38,409 / \$122,557
Molecular Basis of Dilated and Hypertrophic Cardiomyopathy		
National Institutes of Health (University of Vermont)		
P01 HL 059408	12/01/04 - 11/30/09	\$59,059 / \$320,627
Genetic and Molecular Signaling in Heart Failure		
National Institutes of Health (University of Cincinnati)		
P50 HL 077101	02/22/05 - 12/31/09	\$349,154 / \$1,837,616
Cardiomyocyte Toxicity and Heart Failure in Desmin Related Cardiomyopathy		
National Institutes of Health		
R01 HL 087862	02/01/08 - 01/31/11	\$150,000 / \$400,000
Signaling Processes Underlying Cardiovascular Function		
National Institutes of Health		
P01 HL 069779	01/11/08 - 12/31/12	\$1,236,664 / \$6,163,688
SCCOR in Pediatric Heart Development and Disease		
National Institutes of Health		
P50 HL 074728	02/15/04 - 01/31/09	\$342,085 / \$1,041,874
Sadayappan, S		
Phosphorylation and Function of Cardiac Myosin Binding Protein-C		
American Heart Association - National		
0830311N	01/01/08 - 12/31/11	\$70,000 / \$280,000
Shelton, E		
The Functions of Tbx20 and Twist 1 in Endocardial Cushion Development		
American Heart Association - Ohio		
0715360B	07/01/07 - 06/30/08	\$21,000 / \$21,000
Strauss, A		
Adaptation to Long Chain Fatty Acid Oxidation Deficiency		
National Institutes of Health		
R01 HL 075412	08/01/07 - 02/28/09	\$192,050 / \$192,050
A Multi-Center Group to Study Acute Liver Failure in Children		
National Institutes of Health (Children's Hospital of Pittsburgh)		
U01 DK 072146	09/01/07 - 08/31/08	\$26,017 / \$26,017
Wang, S		
Determination of Cardiac Looping: Role of Zic 3 at the Node		
American Heart Association - Ohio		
0725562B	07/01/07 - 06/30/09	\$42,000 / \$86,000

Ware, S

Development of Novel Resequencing Chip to Diagnose Pediatric Cardiomyopathy

Children's Cardiomyopathy Foundation

04/01/08 - 03/31/09

\$49,750 / \$49,750

Requirement of the Embryonic Node for Cardiac Looping

National Institutes of Health

R01 HL 088639

04/01/07 - 03/31/12

\$250,000 / \$1,250,000

Yutzey, K

Tbx20 Regulation of Heart Valve Development

National Institutes of Health

R01 HL 082716

07/01/06 - 05/31/10

\$242,750 / \$1,000,000

SCCOR in Pediatric Development and Disease

National Institutes of Health

P50 HL 074728

02/15/04 - 01/31/09

\$223,782 / \$681,564

Current Year Direct

\$5,468,739

Industry Contracts

Molkentin, J

Boehringer Ingelheim

\$ 46,046

Wyeth Pharmaceutical

\$ 39,039

Current Year Direct Receipts

\$85,085

Total \$5,553,824