

Division of Molecular Cardiovascular Biology

DIVISION PROFILE

Number of Faculty	9
Number of Joint Appointment Faculty	2
Number of Fellows	
Clinical Fellows	0
Research Fellows	19
Number of Graduate Students	7
Number of Other Students (full and part-time)	4
Number of Support Personnel	1
Annual Total Grant Support (direct)	\$4,546,149
Number of Peer Reviewed Publications	43

FACULTY LISTING

Jeffrey Robbins, PhD, Professor of Pediatrics, Director, Molecular Cardiovascular Biology; Associate Chair, Core Initiatives

Christopher P. Baines, PhD, Research Assistant Professor of Pediatrics

Melissa C. Colbert, PhD, Research Associate Professor of Pediatrics, Director, Institutional Biosafety Committee

James D. Gulick, MS, Research Assistant Professor of Pediatrics

Jeanne M. James, MD., Research Assistant Professor of Pediatrics

Maïke Krenz, MD, Research Assistant Professor of Pediatrics

Jeffery D. Molkenntin, PhD, Associate Professor of Pediatrics, Chair, IACUC

Stephanie M. Ware, MD, PhD, Assistant Professor of Pediatrics

Katherine E. Yutzey, PhD, Associate Professor of Pediatrics, Co-Director, Molecular Developmental Biology Graduate Program

FACULTY JOINT APPOINTMENT LISTING

D. Woodrow Benson, MD, PhD, Professor of Pediatrics, Cardiology

Timothy E. Hewett, PhD, Assistant Professor of Pediatrics, Sports Medicine Biodynamics

STAFF PHYSICIAN LISTING

Jeanne M. James, MD

Stephanie M. Ware, MD, PhD

OVERVIEW

The Division of Molecular Cardiovascular Biology has both research and service goals within the Cincinnati Children's Research Foundation with some of its faculty having clinical responsibilities as well. The charges of the division are: 1) to work closely with the Division of Pediatric Cardiology to provide a strong research training component for the overall cardiovascular efforts of Cincinnati Children's Hospital Medical Center, 2) to develop effective interfaces with Molecular and Developmental Biology, as well as with other molecular/developmental biology efforts of Cincinnati Children's Research Foundation, 3) to integrate research efforts with the overall cardiovascular research efforts of the University of Cincinnati School of Medicine, strengthen these endeavors, and provide productive collaborative opportunities for pediatric investigators outside the Cincinnati Children's Research Foundation, 4) to establish a research program within the Cincinnati Children's Research Foundation that is both nationally known and can serve as a model program for the mentoring of selected junior faculty in Pediatric Cardiology. The broad research aims of the division are therefore directed towards understanding the molecular mechanisms that drive normal and abnormal heart and muscle development during mammalian embryogenesis and developing a set of reagents

that allows remodeling of the developing and mature heart and skeletal muscles. The underlying thrust of the division's research is to create suitable models for uncovering the molecular bases of normal and abnormal cardiac and skeletal development and function using the tools of molecular genetics.



Left to Right: (1st row) K. Yutzey, T. Hewett, J. Robbins, M. Krenz, M. Colbert, J. James (2nd row) S. Ware, C. Baines, J. MolKentin, J. Gulick

In addition to the division's director, Jeffrey Robbins, PhD, five other PhD faculty, Katherine Yutzey, Christopher Baines, Jeffrey MolKentin, Timothy Hewett and Melissa Colbert now work within the division. Maike Krenz, MD, was appointed to a faculty Instructor position this year as well. Jeanne James, MD and Woodrow Benson, MD, PhD are shared faculty with the Division of Pediatric Cardiology and, in addition to their research efforts, have clinical responsibilities. Stephanie Ware, MD, PhD has clinical duties in the Division of Human Genetics and has started a new research program within the division that focuses on how the heart's organization is determined. James Gulick, MS, is a Research Instructor. The division's faculty participates in the teaching of graduate students in the Developmental Biology Program, as well as in the graduate and post-graduate programs of the School of Medicine. Dr. James holds a weekly Fellows Clinic in Pediatric Cardiology, is part of the regular attending staff and specializes in echocardiography. Dr. Benson participates in mentoring the clinical fellows in their research training and also runs a weekly clinic. The division also gives a basic series of lectures dealing with molecular approaches to cardiovascular disease to fellows in the Divisions of Pediatric and Adult Cardiology.

HIGHLIGHTS

This year Dr. Robbins' body of work was formally recognized by his receiving the National Research Achievement Award from the American Heart Association. In a series of landmark papers, Dr. Robbins first defined the promoter elements needed to drive high levels of gene expression in the mammalian heart. Identifying the cis-trans interactions lay firmly in the field of basic research but, understanding the implications, Dr. Robbins then took the work further and explored the utility of cardiac-specific gene expression as a method of doing defined genetics in the mammalian four-chambered heart.

After the initial proof-of-principal that cardiac specific transgenesis was feasible, Dr. Robbins defined, built and tested a set of reagents that are now routinely used by hundreds of laboratories to carry out genetic experiments in the mouse cardiovascular system. Dr. Robbins unambiguously showed the utility of the general approach and developed a set of robust reagents that could be used by relatively inexperienced investigators to create animal models of cardiovascular disease.

One focus of Dr. Robbins' work is now establishing important commonalities between the neurodegenerative and cardiovascular diseases. These linkages are teased out by his studies on the effects of protein misfolding during the development of cardiovascular disease. The cellular consequences of aberrant protein aggregation are not fully understood but the most common neurodegenerative disorders, such as Alzheimer's, Parkinson's and Huntington's are each characterized by peptide misfolding or processing in which a protein or protein fragment self associates in such a way as to yield insoluble tangles or plaques consisting of amyloid, a substance with distinct structural properties. Amyloid formation is a common theme in many neurodegenerative disorders and their deposition has formed the framework for a unifying theory across diverse disease types. Amyloidoses are well characterized in many tissues, including the heart and can have diverse effects on function, resulting in dilated cardiomyopathy, restrictive cardiomyopathy or diastolic dysfunction. Dr. Robbins' work this year has shown that these amyloid-based processes are much more widespread in the diseased heart than previously realized and that interfering with the formation of amyloid in the heart may be of significant benefit in maintaining or even restoring cardiac function in a diseased heart. These results were reported this year in The Proceedings of the National Academy of Sciences and in Circulation.

The division's current faculty continue to excel with publications in the premier journals with multiple articles featured on cover pages. The national stature of the faculty is reflected by the more than twenty-five off-site presentations made this year. Faculty continue to be invited to speak at major meetings such as the Keystone Symposium, Gordon Conferences, American Heart National Meetings and FASEB. Numerous seminar invitations from other universities have also been received. International invitations were received to meetings in Italy, France, Australia, Japan, Germany and Switzerland. The division continues to focus on programmatically oriented research with close collaborations leading to the funding of 3 major program grants that are housed mainly within the division.

TRAINING

Mannix Auger-Messier, PhD	University of Sherbrooke
James Bedard, PhD	University of Manitoba
Heather Evans-Anderson, PhD	University of South Carolina School of Medicine
Joerg Heineke, MD	Hannover Medical School
Joy Lincoln, PhD	University of Durham
Qinghang Liu, PhD	University of Tennessee Health Science Center
Jeffrey Lynch, PhD	University of Alberta
Marjorie Maillet, PhD	University of Paris XI
Alina Maloyan, PhD	Hebrew University of Jerusalem
Jaime Melendez, PhD	University of Chili
Tomoki Nakamura, MD	Jichi Medical School
Hiroyuki Nakayama, MD	Osaka University Graduate School of Medicine
Toru Oka, MD	Shinshu University School of Medicine
J. Scott Pattison, PhD	University of Missouri - Columbia
Nicole Purcell, PhD	University of Alabama @ Birmingham
Malgorzata Quinn, PhD	Polish Academy of Sciences
Sadayappan Sakthivel, PhD	Madurai Kamaraj University
Shuyung Wang, MD, PhD	Shandong University

GRANTS, CONTRACTS AND INDUSTRY AGREEMENTS

Grant and Contract Awards	Annual Direct/Project Period Direct
Auger-Messier, M	
Which Roles Play Respectively Both Isoforms of the Calcineurin A Heart & Stroke Foundation of Canada	
	07/01/04 – 06/30/07
	\$33,468/\$66,936

Bueno, O	Dual Specificity Phosphatases as Regulators American Heart Association - National	07/01/04 – 09/05/05	\$59,091/\$70,852
Gulick, J	Molecular Basis of Dilated and Hypertrophic Cardiomyopathy National Institutes of Health (University of Vermont subcontract) P01 HL 059408	12/01/04 – 11/31/09	\$52,707/\$320,627
Howells, E	The Role of Tbx20 in Extra Cellular Matrix Remodeling American Heart Association	07/01/05 – 06/30/07	\$19,000/\$38,000
Kaiser, R	Role of P38 MAPK in the Adult Heart National Institutes of Health F32 HL 007355	05/01/03 – 04/30/06	\$48,296/\$130,972
Lincoln, J	Molecular and Cellular Regulation of Heart Valve Remodeling American Heart Association - Ohio Valley Affiliate	07/01/04 – 06/30/06	\$41,000/\$82,000
Lynch, J	Role of MEF2 Transcription Factors in the Heart Heart & Stroke Foundation of Canada	10/01/05 – 09/30/07	\$34,864/\$69,728
Maloyan, A	Desmin-Related Myopathy in Transgenic Mice American Heart Association – Ohio Valley Affiliate	07/01/05 – 06/30/07	\$41,000/\$84,000
Molkentin, J	Mitochondrial Regulated Cardiac Myocyte Death National Institutes of Health R01 HL 081104	08/01/05 – 07/31/09	\$250,000/\$1,000,000
	Adaptive and Maladaptive Signaling in Cardiac Growth and Regeneration Foundation LeDucq	10/01/05 – 09/30/10	\$98,861/\$593,168
	Molecular Pathways Controlling Cardiac Gene Expression National Institutes of Health R01 HL 060562	07/01/03 – 06/30/08	\$225,000/\$1,125,000
	Cardiac Hypertrophic Intracellular Signaling Pathways National Institutes of Health R01 HL 062927	08/01/03 – 07/31/08	\$200,000/\$1,000,000
	Genetic and Molecular Signaling in Heart Failure National Institutes of Health (University of Cincinnati subcontract) P50 HL 077101	02/22/05 - 12/31/09	\$281,992/\$1,451,722
	JNK MAPK Signaling in Cardiac Hypertrophy American Heart Association - National	01/01/03 – 12/31/07	\$90,909/\$454,545
Nakayama, H	Necessity of Calcinerin as a Regulator of Adaptive vs Maladaptive American Heart Association – Ohio Valley Affiliate	07/01/04 – 06/30/06	\$43,000/\$84,000

Oka, T		
Role of GATA4 as a Necessary Mediator of Gene Program		
American Heart Association – Ohio Valley Affiliate		
	07/01/04 – 06/30/06	\$43,000/\$84,000
Robbins, J		
SCCOR in Pediatric Heart Development and Disease: Project 4		
National Institutes of Health		
P50 HL 074728	02/15/04 – 01/31/09	\$350,723/\$1,856,163
Signaling Processes Underlying Cardiovascular Function		
National Institutes of Health		
P01 HL 069779	06/06/02 – 04/30/07	\$1,435,032/\$7,041,308
Robbins, J	\$248,992	Project 1
Yutzey, K	\$178,492	Project 2
Molkentin, J	\$194,995	Project 3
Robbins, J	\$459,040	Core A
Colbert, M	\$211,526	Core B
Colbert, M	\$141,987	Core C
Genetic and Molecular Signaling in Heart Failure		
National Institutes of Health (University of Cincinnati subcontract)		
P50 HL 077101	02/22/05 – 12/31/09	\$348,632/\$1,837,616
Transgenic Remodeling of the Rabbit Heart		
National Institutes of Health		
R01 HL 056370	02/01/03 – 01/31/07	\$279,433/\$1,106,442
Sakthivel, S		
Phosphorylation and Function of Cardiac Myosin Binding		
American Heart Association – Ohio Valley Affiliate		
	07/01/04 – 06/30/06	\$42,000/\$82,000
Ware, S		
ZIC3 and the Control of Body Pattern Formation		
National Institutes of Health		
K08 HL 067355	08/01/04 – 07/31/06	\$119,425/\$238,850
ZIC3 Function in Axis and Organizer Formation		
March of Dimes		
5-FY04-124	08/01/04 - 01/31/06	\$124,283
Gli Superfamily Interactions in the Development of Heterotaxy		
American Heart Association – Ohio Valley Affiliate		
	07/01/05 - 06/30/07	\$55,000/\$110,000
Yutzey, K		
SCCOR in Pediatric Heart Development and Disease: Project 3		
National Institutes of Health		
P50 HL 074728	02/15/04 – 01/31/09	\$229,433/\$1,223,056
Current Year Direct		\$4,546,149
Industry Contracts		
Current Year Direct Receipts		\$0
TOTAL		\$4,546,149

PUBLICATIONS

1. Nakamura T, Colbert MC, Robbins J. Neural crest cells retain multipotential characteristics in the developing valves and label the cardiac conduction system. *Circ Res* 2006;98(12):1547-54.
2. Sanbe A, Osinska H, Villa C, Gulick J, Klevitsky R, Glabe CG, Kaye R, Robbins J. Reversal of amyloid-induced heart disease in desmin-related cardiomyopathy. *Proc Natl Acad Sci U S A* 2005;102(38):13592-7.
3. Sadayappan S, Gulick J, Osinska H, Martin LA, Hahn HS, Dorn GW, 2nd, Klevitsky R, Seidman CE, Seidman JG, Robbins J. Cardiac myosin-binding protein-C phosphorylation and cardiac function. *Circ Res* 2005;97(11):1156-63.
4. Tallini YN, Ohkura M, Choi BR, Ji G, Imoto K, Doran R, Lee J, Plan P, Wilson J, Xin HB, Sanbe A, Gulick J, Mathai J, Robbins J, Salama G, Nakai J, Kotlikoff MI. Imaging cellular signals in the heart in vivo: Cardiac expression of the high-signal Ca²⁺ indicator GCaMP2. *Proc Natl Acad Sci U S A* 2006;103(12):4753-8.
5. Krenz M, Yutzey KE, Robbins J. Noonan syndrome mutation Q79R in Shp2 increases proliferation of valve primordia mesenchymal cells via extracellular signal-regulated kinase 1/2 signaling. *Circ Res* 2005;97(8):813-20.
6. Parlakian A, Charvet C, Escoubet B, Mericskay M, Molkentin JD, Gary-Bobo G, De Windt LJ, Ludosky MA, Paulin D, Daegelen D, Tuil D, Li Z. Temporally controlled onset of dilated cardiomyopathy through disruption of the SRF gene in adult heart. *Circulation* 2005;112(19):2930-9.
7. Oka T, Dai YS, Molkentin JD. Regulation of calcineurin through transcriptional induction of the calcineurin A beta promoter in vitro and in vivo. *Mol Cell Biol* 2005;25(15):6649-59.
8. Molkentin JD. Locating heart failure. *Nat Med* 2005;11(12):1284-5.
9. Lynch J, Guo L, Gelebart P, Chilibeck K, Xu J, Molkentin JD, Agellon LB, Michalak M. Calreticulin signals upstream of calcineurin and MEF2C in a critical Ca(2+)-dependent signaling cascade. *J Cell Biol* 2005;170(1):37-47.
10. Li J, Patel VV, Kostetskii I, Xiong Y, Chu AF, Jacobson JT, Yu C, Morley GE, Molkentin JD, Radice GL. Cardiac-specific loss of N-cadherin leads to alteration in connexins with conduction slowing and arrhythmogenesis. *Circ Res* 2005;97(5):474-81.
11. Kaiser RA, Lyons JM, Duffy JY, Wagner CJ, McLean KM, O'Neill TP, Pearl JM, Molkentin JD. Inhibition of p38 reduces myocardial infarction injury in the mouse but not pig after ischemia-reperfusion. *Am J Physiol Heart Circ Physiol* 2005;289(6):H2747-51.
12. Kaiser RA, Liang Q, Bueno O, Huang Y, Lackey T, Klevitsky R, Hewett TE, Molkentin JD. Genetic inhibition or activation of JNK1/2 protects the myocardium from ischemia-reperfusion-induced cell death in vivo. *J Biol Chem* 2005;280(38):32602-8.
13. Dai YS, Xu J, Molkentin JD. The DnaJ-related factor Mrj interacts with nuclear factor of activated T cells c3 and mediates transcriptional repression through class II histone deacetylase recruitment. *Mol Cell Biol* 2005;25(22):9936-48.
14. Zhao W, Yuan Q, Qian J, Waggoner JR, Pathak A, Chu G, Mitton B, Sun X, Jin J, Braz JC, Hahn HS, Marreez Y, Syed F, Pollesello P, Annala A, Wang HS, Schultz Jel J, Molkentin JD, Liggett SB, Dorn GW, 2nd, Kranias EG. The presence of Lys27 instead of Asn27 in human phospholamban promotes sarcoplasmic reticulum Ca²⁺-ATPase superinhibition and cardiac remodeling. *Circulation* 2006;113(7):995-1004.
15. Xu J, Kimball TR, Lorenz JN, Brown DA, Bauskin AR, Klevitsky R, Hewett TE, Breit SN, Molkentin JD. GDF15/MIC-1 functions as a protective and antihypertrophic factor released from the myocardium in association with SMAD protein activation. *Circ Res* 2006;98(3):342-50.
16. Xu J, Gong NL, Bodi I, Aronow BJ, Backx PH, Molkentin JD. Myocyte enhancer factors 2A and 2C induce dilated cardiomyopathy in transgenic mice. *J Biol Chem* 2006;281(14):9152-62.

17. Sanna B, Brandt EB, Kaiser RA, Pfluger P, Witt SA, Kimball TR, van Rooij E, De Windt LJ, Rothenberg ME, Tschop MH, Benoit SC, Molkentin JD. Modulatory calcineurin-interacting proteins 1 and 2 function as calcineurin facilitators in vivo. *Proc Natl Acad Sci U S A* 2006;103(19):7327-32.
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19. Parsons SA, Millay DP, Sargent MA, McNally EM, Molkentin JD. Age-dependent effect of myostatin blockade on disease severity in a murine model of limb-girdle muscular dystrophy. *Am J Pathol* 2006;168(6):1975-85.
20. Oka T, Mailliet M, Watt AJ, Schwartz RJ, Aronow BJ, Duncan SA, Molkentin JD. Cardiac-specific deletion of Gata4 reveals its requirement for hypertrophy, compensation, and myocyte viability. *Circ Res* 2006;98(6):837-45.
21. Noh HL, Okajima K, Molkentin JD, Homma S, Goldberg IJ. Acute lipoprotein lipase deletion in adult mice leads to dyslipidemia and cardiac dysfunction. *Am J Physiol Endocrinol Metab* 2006.
22. Nilsson J, Nilsson LM, Chen YW, Molkentin JD, Erlinge D, Gomez MF. High glucose activates nuclear factor of activated T cells in native vascular smooth muscle. *Arterioscler Thromb Vasc Biol* 2006;26(4):794-800.
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26. Kempf T, Eden M, Strelau J, Naguib M, Willenbockel C, Tongers J, Heineke J, Kotlarz D, Xu J, Molkentin JD, Niessen HW, Drexler H, Wollert KC. The transforming growth factor-beta superfamily member growth-differentiation factor-15 protects the heart from ischemia/reperfusion injury. *Circ Res* 2006;98(3):351-60.
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28. Maloyan A, Sanbe A, Osinska H, Westfall M, Robinson D, Imahashi K, Murphy E, Robbins J. Mitochondrial dysfunction and apoptosis underlie the pathogenic process in alpha-B-crystallin desmin-related cardiomyopathy. *Circulation* 2005;112(22):3451-61.
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35. Ware SM, Harutyunyan KG, Belmont JW. Heart defects in X-linked heterotaxy: evidence for a genetic interaction of Zic3 with the nodal signaling pathway. *Dev Dyn* 2006;235(6):1631-7.

36. Chen C, Ware SM, Sato A, Houston-Hawkins DE, Habas R, Matzuk MM, Shen MM, Brown CW. The Vg1-related protein Gdf3 acts in a Nodal signaling pathway in the pre-gastrulation mouse embryo. *Development* 2006;133(2):319-29.
37. Yutzey KE, Colbert M, Robbins J. Ras-related signaling pathways in valve development: ebb and flow. *Physiology (Bethesda)* 2005;20:390-7.
38. Lange AW, Rothermel BA, Yutzey KE. Restoration of DSCR1 to disomy in the trisomy 16 mouse model of Down syndrome does not correct cardiac or craniofacial development anomalies. *Dev Dyn* 2005;233(3):954-63.
39. Lincoln J, Lange AW, Yutzey KE. Hearts and bones: shared regulatory mechanisms in heart valve, cartilage, tendon, and bone development. *Dev Biol* 2006;294(2):292-302.
40. Lincoln J, Alfieri CM, Yutzey KE. BMP and FGF regulatory pathways control cell lineage diversification of heart valve precursor cells. *Dev Biol* 2006;292(2):292-302.
41. Lange AW, Yutzey KE. NFATc1 expression in the developing heart valves is responsive to the RANKL pathway and is required for endocardial expression of cathepsin K. *Dev Biol* 2006;292(2):407-17.
42. Hinton RB, Jr., Lincoln J, Deutsch GH, Osinska H, Manning PB, Benson DW, Yutzey KE. Extracellular matrix remodeling and organization in developing and diseased aortic valves. *Circ Res* 2006;98(11):1431-8.
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