

2015 Research Annual Report

Molecular Cardiovascular Biology

RESEARCH AND TRAINING DETAILS

Faculty	13
Research Fellows	28
Research Students	23
Support Personnel	24
Direct Annual Grant Support	\$4,551,300
Direct Annual Industry Support	\$149,991
Peer Reviewed Publications	41

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Significant Publications

Yutzey KE. [Regenerative biology: Neuregulin 1 makes heart muscle.](#) *Nature*. 2015 Apr 23;520(7548):445-6.

This invited News and Views editorial published in the journal *Nature* highlights three recently published papers on heart regeneration. Until recently, heart muscle cells in adult mammals, including humans, were considered to be unable to proliferate. The featured papers in the editorial show that the neuregulin signaling pathway can induce heart regeneration in zebrafish, as well as proliferation in pediatric heart muscle cells and adult mouse hearts. Dr. Yutzey's lab has published multiple papers on cardiac muscle cell proliferation after birth and she was invited to comment on these papers for *Nature* based on her expertise in this area.

McLendon PM, **Robbins J.** [Proteotoxicity and Cardiac Dysfunction.](#) *Circ Res*. 2015 May 22;116(11):1863-82.

This paper describes the importance of proteins being misfolded and how this occurs during the development of cardiac disease. It goes on to show that misfolded proteins by themselves contribute significantly to disease development and proposes that interfering with the process of protein misfolding would be therapeutically effective.

van Berlo JH, **Molkentin JD.** [An emerging consensus on cardiac regeneration.](#) *Nat Med*. 2014 Dec 4;20(12):1386-93.

This manuscript examined the hypothesis that cKit-expressing cells are capable of making cardiomyocytes during development, with aging, or after cardiac injury such as with myocardial infarction. The paper showed that ckit progenitor cells do not appreciably make new cardiomyocytes in the heart under any conditions, hence cells from this lineage are unlikely to be involved in cardiac regeneration, as least in making new contractile myocardium.

Li L, Chen Y, Doan J, Murray J, **Molkentin JD**, Liu Q. [Transforming growth factor beta-activated kinase 1 signaling pathway](#)

critically regulates myocardial survival and remodeling. *Circulation*. 2014 Dec 9;130(24):2162-72.

For many years, necrosis was thought to be a chaotic, uncontrolled process that invariably led to cell death and tissue destruction. In this study, which was led by a postdoctoral fellow of the Molkentin laboratory, who is now an independent faculty member at the University of Washington Seattle, the lab showed that a particular and specific signaling pathway underlies cellular necrosis in the heart.

Division Publications

1. Accornero F, Kanisicak O, Tjondrokoesoemo A, Attia AC, McNally EM, Molkentin JD. **Myofiber-specific inhibition of TGFbeta signaling protects skeletal muscle from injury and dystrophic disease in mice.** *Hum Mol Genet*. 2014; 23:6903-15.
2. Accornero F, van Berlo JH, Correll RN, Elrod JW, Sargent MA, York A, Rabinowitz JE, Leask A, Molkentin JD. **Genetic Analysis of Connective Tissue Growth Factor as an Effector of Transforming Growth Factor beta Signaling and Cardiac Remodeling.** *Mol Cell Biol*. 2015; 35:2154-64.
3. Barbato E, Lara-Pezzi E, Stolen C, Taylor A, Barton PJ, Bartunek J, Iuzzo P, Judge DP, Kirshenbaum L, Blaxall BC, Terzic A, Hall JL. **Advances in induced pluripotent stem cells, genomics, biomarkers, and antiplatelet therapy highlights of the year in JCTR 2013.** *J Cardiovasc Transl Res*. 2014; 7:518-25.
4. Ceco E, Bogdanovich S, Gardner B, Miller T, DeJesus A, Earley JU, Hadhazy M, Smith LR, Barton ER, Molkentin JD, McNally EM. **Targeting latent TGFbeta release in muscular dystrophy.** *Sci Transl Med*. 2014; 6:259ra144.
5. D'Aniello E, Waxman JS. **Input overload: Contributions of retinoic acid signaling feedback mechanisms to heart development and teratogenesis.** *Dev Dyn*. 2015; 244:513-23.
6. Fang M, Alfieri CM, Hulin A, Conway SJ, Yutzey KE. **Loss of beta-catenin promotes chondrogenic differentiation of aortic valve interstitial cells.** *Arterioscler Thromb Vasc Biol*. 2014; 34:2601-8.
7. Godby R, Munjal C, Opoka A, Smith J, Yutzey K, Narmoneva D, Hinton R. **Cross Talk between NOTCH Signaling and Biomechanics in Human Aortic Valve Disease Pathogenesis.** *J Cardiovasc Dev Dis*. 2014; 1:237-256.
8. Goldstein JA, Bogdanovich S, Beiriger A, Wren LM, Rossi AE, Gao QQ, Gardner BB, Earley JU, Molkentin JD, McNally EM. **Excess SMAD signaling contributes to heart and muscle dysfunction in muscular dystrophy.** *Hum Mol Genet*. 2014; 23:6722-31.
9. Goonasekera SA, Davis J, Kwong JQ, Accornero F, Wei-LaPierre L, Sargent MA, Dirksen RT, Molkentin JD. **Enhanced Ca(2+)(+) influx from STIM1-Orai1 induces muscle pathology in mouse models of muscular dystrophy.** *Hum Mol Genet*. 2014; 23:3706-15.
10. Gupta MK, Gulick J, Liu R, Wang X, Molkentin JD, Robbins J. **Sumo E2 enzyme UBC9 is required for efficient protein quality control in cardiomyocytes.** *Circ Res*. 2014; 115:721-9.
11. Gutierrez-Aguilar M, Douglas DL, Gibson AK, Domeier TL, Molkentin JD, Baines CP. **Genetic manipulation of the cardiac mitochondrial phosphate carrier does not affect permeability transition.** *J Mol Cell Cardiol*. 2014; 72:316-25.
12. Hong YH, Martin LA, Mulvaney JM, Burhans MS, Blaxall BC, Hinton RB. **RNA extraction from healthy and failing human myocardium: a comparative evaluation.** *Biopreserv Biobank*. 2015; 13:123-30.

13. Huang Y, Powers C, Madala SK, Greis KD, Haffey WD, Towbin JA, Purevjav E, Javadov S, Strauss AW, Khuchua Z. **Cardiac metabolic pathways affected in the mouse model of Barth syndrome.** *PLoS One*. 2015; 10:e0128561.
14. Huby AC, Mendsaikhan U, Takagi K, Martherus R, Wansapura J, Gong N, Osinska H, James JF, Kramer K, Saito K, Robbins J, Khuchua Z, Towbin JA, Purevjav E. **Disturbance in Z-disk mechanosensitive proteins induced by a persistent mutant myopalladin causes familial restrictive cardiomyopathy.** *J Am Coll Cardiol*. 2014; 64:2765-76.
15. Karch J, Kanisicak O, Brody MJ, Sargent MA, Michael DM, Molkenin JD. **Necroptosis Interfaces with MOMP and the MPTP in Mediating Cell Death.** *PLoS One*. 2015; 10:e0130520.
16. Karch J, Molkenin JD. **Regulated Necrotic Cell Death: The Passive Aggressive Side of Bax and Bak.** *Circ Res*. 2015; 116:1800-1809.
17. Karch J, Molkenin JD. **Identifying the components of the elusive mitochondrial permeability transition pore.** *Proc Natl Acad Sci U S A*. 2014; 111:10396-7.
18. Khatlani T, Pradhan S, Da Q, Gushiken FC, Bergeron AL, Langlois KW, Molkenin JD, Rumbaut RE, Vijayan KV. **The beta isoform of the catalytic subunit of protein phosphatase 2B restrains platelet function by suppressing outside-in alphaIIb beta3 integrin signaling.** *J Thromb Haemost*. 2014; 12:2089-101.
19. Kwong JQ, Davis J, Baines CP, Sargent MA, Karch J, Wang X, Huang T, Molkenin JD. **Genetic deletion of the mitochondrial phosphate carrier desensitizes the mitochondrial permeability transition pore and causes cardiomyopathy.** *Cell Death Differ*. 2014; 21:1209-17.
20. Kwong JQ, Molkenin JD. **Physiological and pathological roles of the mitochondrial permeability transition pore in the heart.** *Cell Metab*. 2015; 21:206-14.
21. Lauriol J, Keith K, Jaffe F, Couvillon A, Saci A, Goonasekera SA, McCarthy JR, Kessinger CW, Wang J, Ke Q, Kang PM, Molkenin JD, Carpenter C, Kontaridis MI. **RhoA signaling in cardiomyocytes protects against stress-induced heart failure but facilitates cardiac fibrosis.** *Sci Signal*. 2014; 7:ra100.
22. Lee MP, Ratner N, Yutzey KE. **Genome-wide Twist1 occupancy in endocardial cushion cells, embryonic limb buds, and peripheral nerve sheath tumor cells.** *BMC Genomics*. 2014; 15:821.
23. Li L, Chen Y, Doan J, Murray J, Molkenin JD, Liu Q. **Transforming growth factor beta-activated kinase 1 signaling pathway critically regulates myocardial survival and remodeling.** *Circulation*. 2014; 130:2162-72.
24. Makarewich CA, Zhang H, Davis J, Correll RN, Trapanese DM, Hoffman NE, Troupes CD, Berretta RM, Kubo H, Madesh M, Chen X, Gao E, Molkenin JD, Houser SR. **Transient receptor potential channels contribute to pathological structural and functional remodeling after myocardial infarction.** *Circ Res*. 2014; 115:567-80.
25. Mandal A, Waxman J. **Retinoic acid negatively regulates dact3b expression in the hindbrain of zebrafish embryos.** *Gene Expr Patterns*. 2014; 16:122-9.
26. Mazala DA, Pratt SJ, Chen D, Molkenin JD, Lovering RM, Chin ER. **SERCA1 overexpression minimizes skeletal muscle damage in dystrophic mouse models.** *Am J Physiol Cell Physiol*. 2015; 308:C699-709.
27. McLendon PM, Ferguson BS, Osinska H, Bhuiyan MS, James J, McKinsey TA, Robbins J. **Tubulin hyperacetylation is adaptive in cardiac proteotoxicity by promoting autophagy.** *Proc Natl Acad Sci U S A*. 2014; 111:E5178-86.
28. McLendon PM, Robbins J. **Proteotoxicity and Cardiac Dysfunction.** *Circ Res*. 2015; 116:1863-1882.
29. Millay DP, Sutherland LB, Bassel-Duby R, Olson EN. **Myomaker is essential for muscle regeneration.** *Genes Dev*.

2014; 28:1641-6.

30. Molkentin JD. **Letter by Molkentin regarding article, "The absence of evidence is not evidence of absence: the pitfalls of Cre Knock-Ins in the c-Kit Locus"**. *Circ Res*. 2014; 115:e21-3.
31. Munjal C, Opoka AM, Osinska H, James JF, Bressan GM, Hinton RB. **TGF-beta mediates early angiogenesis and latent fibrosis in an Emilin1-deficient mouse model of aortic valve disease**. *Dis Model Mech*. 2014; 7:987-96.
32. Parrott A, James J, Goldenberg P, Hinton RB, Miller E, Shikany A, Aylsworth AS, Kaiser-Rogers K, Ferns SJ, Lalani SR, Ware SM. **Aortopathy in the 7q11.23 microduplication syndrome**. *Am J Med Genet A*. 2015; 167A:363-70.
33. Previs MJ, Prosser BL, Mun JY, Previs SB, Gulick J, Lee K, Robbins J, Craig R, Lederer WJ, Warshaw DM. **Myosin-binding protein C corrects an intrinsic inhomogeneity in cardiac excitation-contraction coupling**. *Sci Adv*. 2015; 1.
34. Sopariwala DH, Pant M, Shaikh SA, Goonasekera SA, Molkentin JD, Weisleder N, Ma J, Pan Z, Periasamy M. **Sarcolipin overexpression improves muscle energetics and reduces fatigue**. *J Appl Physiol (1985)*. 2015; 118:1050-8.
35. Tanner BC, Wang Y, Robbins J, Palmer BM. **Kinetics of cardiac myosin isoforms in mouse myocardium are affected differently by presence of myosin binding protein-C**. *J Muscle Res Cell Motil*. 2014; 35:267-78.
36. van Berlo JH, Molkentin JD. **An emerging consensus on cardiac regeneration**. *Nat Med*. 2014; 20:1386-93.
37. Ware SM, Shikany A, Landis BJ, James JF, Hinton RB. **Twins with progressive thoracic aortic aneurysm, recurrent dissection and ACTA2 mutation**. *Pediatrics*. 2014; 134:e1218-23.
38. Wirrig EE, Gomez MV, Hinton RB, Yutzey KE. **COX2 inhibition reduces aortic valve calcification in vivo**. *Arterioscler Thromb Vasc Biol*. 2015; 35:938-47.
39. Wissing ER, Boyer JG, Kwong JQ, Sargent MA, Karch J, McNally EM, Otsu K, Molkentin JD. **P38alpha MAPK underlies muscular dystrophy and myofiber death through a Bax-dependent mechanism**. *Hum Mol Genet*. 2014; 23:5452-63.
40. Yutzey KE. **Regenerative biology: Neuregulin 1 makes heart muscle**. *Nature*. 2015; 520:445-6.
41. Yutzey KE, Demer LL, Body SC, Huggins GS, Towler DA, Giachelli CM, Hofmann-Bowman MA, Mortlock DP, Rogers MB, Sadeghi MM, Aikawa E. **Calcific aortic valve disease: a consensus summary from the Alliance of Investigators on Calcific Aortic Valve Disease**. *Arterioscler Thromb Vasc Biol*. 2014; 34:2387-93.

Faculty, Staff, and Trainees

Faculty Members

Jeffrey Robbins, PhD, FAHA, FISHR, Professor

Leadership Executive Co-Director, Heart Institute; Endowed Chair, Molecular Cardiovascular Biology

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, FACC, FAPS, Professor

Leadership Director, Translational Science; Co-Director, Heart Institute Research Core; Co-Director, Heart Institute Biorepository

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, Professor

Leadership Medical Director, Cardiovascular Genetics; 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.

Douglas Millay, PhD, Assistant Professor

Research Interests Muscle development; regeneration; membrane fusion; cell therapy.

Jeffery Molkentin, PhD, Professor

Leadership Howard Hughes Medical Institute Investigator

Research Interests Molecular pathways that underlie heart disease and muscular dystrophy.

Joshua Waxman, PhD, Assistant Professor

Research Interests Molecular genetics of cardiovascular development.

Katherine Yutzey, PhD, Professor

Research Interests Heart development and disease mechanisms.

Trainees

- **Aaron Adams**, , University of Cincinnati
- **Dorothy Amofa**, , Miami University
- **Sarah Beckman, PhD**, University of Pittsburgh
- **Bidur Bhandary, PhD**, Chonbuk National University, South Korea
- **Justin Boyer, PhD**, University of Ottawa, Canada
- **Matthew Brody, PhD**, University of Wisconsin-Madison
- **Adam Burr, BS**, University of Minnesota, Twin Cities
- **Robert Nathan Correll, PhD**, University of Kentucky
- **Angela Damen, MAT**, Miami University

- **Allison Dixon, BS**, Bellarmine University
- **Tracy Dohn, BS**, Wittenberg University
- **Ming Fang, MS**, Boise State University
- **Dilani Gigiriwala Gamage, PhD**, Wayne State University
- **Qingnian Goh, PhD**, University of Toledo
- **Maria Gomez, BS**, Xavier University
- **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
- **Andrew Kim, BS**, Duke University
- **Jennifer Kwong, PhD**, Weill Medical College of Cornell University
- **Kelsey Linstrum, BS**, Saint Vincent College
- **Ruijie Liu, PhD**, University of Illinois at Urbana Champaign
- **Bryan Maliken, BA**, Benaroya Research Institute
- **Amrita Mandal, MSc**, University of Calcutta, India
- **Patrick McLendon, PhD**, Virginia Polytechnic Institute and State University
- **Qinghang Meng, PhD**, University of Cincinnati
- **Demetria Michael, BS**, Bellarmine University
- **Yasuyuki Mitani, PhD**, Astellas Pharma US, Inc.
- **Ariel Rydeen, BS**, University of Minnesota
- **Tobias Schips, PhD**, Ulm University, Germany
- **Catherine Schomaker, ,** University of Cincinnati
- **Emily Schulz, PhD**, University of Cincinnati
- **Jennifer Schwanekamp, MS**, University of Cincinnati
- **Yuntao Song, MS**, University of Texas at San Antonio
- **Andoria Tjondrokoesoemo, PhD**, University of Medicine & Dentistry of New Jersey

- **Joshua Travers, BS**, Rochester Institute of Technology
- **Ronald Vagnozzi, PhD**, Thomas Jefferson University
- **Iñigo Valiente Alandí, PhD**, Spanish National Centre for Cardiovascular Research, Spain
- **Davy Vanhoutte, PhD**, University of Leuven, Belgium
- **Elaine Wirrig, PhD**, Medical University of South Carolina
- **Fuli Xiang, MD, PhD**, University of Western Ontario, Canada
- **Na Xu, PhD**, Nanjing University, China

Grants, Contracts, and Industry Agreements

Grant and Contract Awards

Annual Direct

Accornero, F

BEX1 and the Control of Protein Translation in Cardiac Hypertrophy

National Institutes of Health

K99 HL121284

12/20/2013-11/30/2015

\$121,375

Bhuiyan, S

Sigma-1 Receptor and Cardioprotection

National Institutes of Health

K99 HL122354

4/9/2014-6/30/2015

\$121,750

Brody, M

The Role of Thrombospondin-4 in the Secretory Pathway, Extracellular Matrix Production and Homeostasis, and ER Stress

National Institutes of Health

F32 HL124698

8/1/2014-7/31/2017

\$49,850

Davis, J

MBNL1's Function in Myofibroblast Transformation and Fibrosis

National Institutes of Health

K99 HL119353

8/9/2013-7/31/2015

\$121,375

Fang, M

Wnt/beta-catenin Signaling in Heart Valve Development

American Heart Association

7/1/2013-6/30/2015

\$26,000

Gomez, M**BMP Signaling in the Progression of Calcific Aortic Valve Disease**

American Heart Association

7/1/2013-6/30/2015

\$26,000

Kamal, F**Targeting Adrenal and Cardiac GPCR Signaling in Heart Failure: A Novel Therapeutic Strategy**

American Heart Association

7/1/2013-6/30/2015

\$47,000

Millay, D**Molecular Control of Mammalian Myoblast Fusion**

Muscular Dystrophy Association

7/1/2014-7/31/2016

\$59,633

Molkentin, J**Ca Signaling Domains Programming Cardiac Hypertrophy**

National Institutes of Health(The Regents of the Univ of California)

P01 HL080101

8/1/2011-5/31/2016

\$257,130

Improving Cardiac Function after Myocardial Infarction

National Institutes of Health(Temple University School of Medicine)

P01 HL108806

5/7/2012-3/31/2017

\$260,000

Mechanisms of TGF Regulated Fibrosis in Muscular Dystrophy

National Institutes of Health(Northwestern University Medical School)

P01 NS072027

10/1/2014-6/30/2016

\$219,943

Thrombospondin 4 Regulates Adaptive ER Stress Response

National Institutes of Health

R01 HL105924

1/1/2015-12/31/2018

\$314,526

TRPC Channel Regulation of Cardiac Hypertrophy and Contractility

National Institutes of Health(Temple University School of Medicine)

R01 HL119229 9/1/2014-3/31/2018 \$76,760

Molecular Pathways Controlling Cardiac Gene Expression

National Institutes of Health

R37 HL060562 7/1/2013-6/30/2018 \$245,000

Understanding Cardiovascular Disease Mechanisms

National Institutes of Health

T32 HL125204 12/1/2014-11/30/2019 \$277,471

Robbins, J

Proteotoxicity: An Unappreciated Mechanism of Heart Disease

Fondation Leducq

10/1/2011-9/30/2016 \$247,636

Signaling Processes Underlying Cardiovascular Function

National Institutes of Health

P01 HL06779 9/1/2013-5/31/2018 \$1,191,592

Vagnozzi, R

The Role of Sca-1+ and ABCG2+ Cardiac Progenitor Cells in Endogenous Heart Regeneration

National Institutes of Health

F32 HL128083 4/1/2015-3/31/2018 \$52,406

Waxman, J

Coup-tf Dependent Mechanisms of Ventricular and Hemangioblast Specification

National Institutes of Health

R01 HL112893 1/15/2013-2/28/2018 \$221,625

Wirrig, E

The Role of COX2 in the Progression of Human and Mouse Calcific Aortic Valve Disease

National Institutes of Health

F32 HL110390 7/1/2012-4/3/2015 \$56,978

Xiang, F

Tbx20 Function in Cardiomyocyte Cell Cycle Re-entry and Cardiac Regeneration Post-myocardial Infarction

American Heart Association

1/1/2015-12/31/2016

\$46,000

Yutzey, K

Cincinnati Children's SURF Program

American Heart Association

2/1/2014-1/31/2016

\$20,000

Wnt Signaling in Heart Valve Development and Disease

National Institutes of Health

R01 HL094319

4/15/2012-2/28/2016

\$246,250

Cell Signaling Mechanisms of Calcific Aortic Valve Disease

National Institutes of Health

R01 HL114682

8/23/2012-6/30/2016

\$245,000

Current Year Direct

\$4,551,300

Industry Contracts

Molkentin, J

Janssen Research & Development, LLC

\$49,959

Morales, D

CorMatrix

\$100,032

Current Year Direct Receipts

\$149,991

Total

\$4,701,291
