2014 Research Annual Report

Molecular Cardiovascular Biology

Cincinnati Children's

Significant Publications

Bhuiyan MS, Pattison JS, Osinska H, **James J**, **Gulick J**, McLendon PM, Hill JA, Sadoshima J, **Robbins J**.Enhanced autophagy ameliorates cardiac proteinopathy. *J Clin Invest*. 2013 Dec 2;123(12):5284-97.

Cells have mechanisms for controlling their protein composition and the cells in the heart are no exception. This manuscript describes a series of experiments in which a critical mechanism for turning over and degrading cardiac proteins, so that their components can be recycled, is manipulated. This recycling process, termed “autophagy,” appears to be critical in the heart and in other organs as well. The Robbins lab upregulated the process but showed that if this was done in a very precise manner, there was no harm to the heart and, during subsequent cardiac disease, the heart was relatively protected. This opens up new therapeutic avenues for the potential treatment of many different forms of cardiac pathology and heart failure as the recycling process is often disrupted in cardiac disease.

Chakraborty S, Sengupta A, **Yutzey KE**. Tbx20 promotes cardiomyocyte proliferation and persistence of fetal characteristics in adult mouse hearts. *J Mol Cell Cardiol*. 2013 Sep;62:203-13.

During development, the transcription factor Tbx20 is required for heart muscle cell proliferation, which is normally significantly down regulated after birth. In this study, the Yutzey Lab found that developmental overexpression of the transcription factor Tbx20 promotes adult heart muscle cell proliferation and maintains fetal gene expression patterns. Multiple signaling pathways activated by Tbx20 overexpression were identified that could be therapeutic targets for promotion of muscle growth in adult cardiac disease. Current studies are designed to determine if Tbx20 overexpression after adult cardiac injury can improve heart function and promote cardiac muscle cell proliferation.

D'Aniello E, Rydeen AB, Anderson JL, Mandal A, **Waxman JS**. Depletion of retinoic acid receptors initiates a novel positive feedback mechanism that promotes teratogenic increases in retinoic acid. *PLoS Genet*. 2013 Aug;9(8):e1003689.

Retinoic acid, the most important derivative of vitamin A, is required for normal human development. Improper levels of retinoic acid in humans causes numerous birth defects, including heart defects. This paper is important because it identifies a previously unrecognized, yet fundamental, mechanism that controls the levels of retinoic acid during development. Specifically, the Waxman Lab demonstrates that if receptors for retinoic acid are lost, it results in a molecular feedback loop that results in too much retinoic acid and consequently heart defects.

Kamal FA, Mickelsen DM, Wegman KM, Travers JG, Moalem J, Hammes SR, Smrcka AV, **Blaxall BC**. Simultaneous adrenal and cardiac g-protein-coupled receptor-gbetagamma inhibition halts heart failure progression.

Division Summary

RESEARCH AND TRAINING DETAILS	
Number of Faculty	**15**
Number of Research Fellows	**31**
Number of Research Students	**17**
Number of Support Personnel	**23**
Direct Annual Grant Support	**$6,474,506**
Direct Annual Industry Support	**$75,024**
Peer Reviewed Publications	**55**

CLINICAL ACTIVITIES AND TRAINING	
Number of Other Students	**9**

J Am Coll Cardiol. 2014 Jun 17;63(23):2549-57.

Heart failure is associated with chronically elevated levels of circulating adrenaline that are toxic to the heart. The adrenal glands are key contributors to this chronic excess of adrenaline; ironically, exposure of the adrenal gland to excess adrenaline elicits further, pathologic adrenaline release from the adrenal gland. This manuscript identifies a similar mechanism by which excess adrenaline is toxic to both the heart and the adrenal gland. Importantly, a small molecule drug is identified that can simultaneously mitigate the pathologic effects of excess adrenaline in both the heart and the adrenal gland, suggesting a novel therapeutic approach for heart failure.

van Berlo JH, Kanisicak O, **Maillet M**, Vagnozzi RJ, Karch J, Lin SC, Middleton RC, Marban E, **Molkentin JD**. c-kit+ cells minimally contribute cardiomyocytes to the heart. *Nature*. 2014 May 15;509(7500):337-41.

Whether or not resident c-kit expressing cardiac progenitor cells contribute new cardiomyocytes to the heart after an injury event is the matter of an intense debate among the scientific community. In this innovative study, the Molkentin laboratory developed two genetic strategies in the mouse to irreversibly mark c-kit expressing cells during development, with ageing or after injury in adulthood. Unexpectedly, c-kit expressing cells did not produce a significant number of cardiomyocytes although they essentially generated endothelial cells in the heart. This study questions the potential cardiac functional improvement associated to c-kit cells therapies in heart failure patients.

Division Publications

1. Abonia JP, Wen T, Stucke EM, Grotjan T, Griffith MS, Kemme KA, Collins MH, Putnam PE, Franciosi JP, von Tiehl KF, Tinkle BT, Marsolo KA, Martin LJ, Ware SM, Rothenberg ME. **High prevalence of eosinophilic esophagitis in patients with inherited connective tissue disorders**. *J Allergy Clin Immunol*. 2013; 132:378-86.
2. Alves ML, Dias FA, Gaffin RD, Simon JN, Montminy EM, Biesiadecki BJ, Hinken AC, Warren CM, Utter MS, Davis RT, 3rd, Sadayappan S, Robbins J, Wieczorek DF, Solaro RJ, Wolska BM. **Desensitization of myofilaments to Ca2+ as a therapeutic target for hypertrophic cardiomyopathy with mutations in thin filament proteins**. *Circ Cardiovasc Genet*. 2014; 7:132-43.
3. Belmonte SL, Ram R, Mickelsen DM, Gertler FB, Blaxall BC. **Cardiac overexpression of Mammalian enabled (Mena) exacerbates heart failure in mice**. *Am J Physiol Heart Circ Physiol*. 2013; 305:H875-84.
4. Bhuiyan MS, Pattison JS, Osinska H, James J, Gulick J, McLendon PM, Hill JA, Sadoshima J, Robbins J. **Enhanced autophagy ameliorates cardiac proteinopathy**. *J Clin Invest*. 2013; 123:5284-97.
5. Braitsch CM, Kanisicak O, van Berlo JH, Molkentin JD, Yutzey KE. **Differential expression of embryonic epicardial progenitor markers and localization of cardiac fibrosis in adult ischemic injury and hypertensive heart disease**. *J Mol Cell Cardiol*. 2013; 65:108-19.
6. Braitsch CM, Yutzey KE. **Transcriptional Control of Cell Lineage Development in Epicardium-Derived Cells**. *Journal of Developmental Biology*. 2013; 1:92-111.
7. Burr AR, Millay DP, Goonasekera SA, Park KH, Sargent MA, Collins J, Altamirano F, Philipson KD, Allen PD, Ma J, Lopez JR, Molkentin JD. **Na+ dysregulation coupled with Ca2+ entry through NCX1 promotes muscular dystrophy in mice**. *Mol Cell Biol*. 2014; 34:1991-2002.
8. Chakraborty S, Sengupta A, Yutzey KE. **Tbx20 promotes cardiomyocyte proliferation and persistence of fetal characteristics in adult mouse hearts**. *J Mol Cell Cardiol*. 2013; 62:203-13.
9. Cole CR, Yutzey KE, Brar AK, Goessling LS, Van Vickle-Chavez SJ, Cunningham MW, Eghtesady P. **Congenital heart disease linked to maternal autoimmunity against cardiac myosin**. *J Immunol*. 2014; 192:4074-82.

10. Connor JA, Hinton RB, Miller EM, Sund KL, Ruschman JG, Ware SM. **Genetic testing practices in infants with congenital heart disease**. *Congenit Heart Dis*. 2014; 9:158-67.
11. Correll RN, Eder P, Burr AR, Despa S, Davis J, Bers DM, Molkentin JD. **Overexpression of the Na+/K+ ATPase alpha2 but not alpha1 isoform attenuates pathological cardiac hypertrophy and remodeling**. *Circ Res*. 2014; 114:249-56.
12. Cowan J, Tariq M, Ware SM. **Genetic and functional analyses of ZIC3 variants in congenital heart disease**. *Hum Mutat*. 2014; 35:66-75.
13. D'Aniello E, Rydeen AB, Anderson JL, Mandal A, Waxman JS. **Depletion of retinoic acid receptors initiates a novel positive feedback mechanism that promotes teratogenic increases in retinoic acid**. *PLoS Genet*. 2013; 9:e1003689.
14. Davis J, Kwong JQ, Kitsis RN, Molkentin JD. **Apoptosis repressor with a CARD domain (ARC) restrains Bax-mediated pathogenesis in dystrophic skeletal muscle**. *PLoS One*. 2013; 8:e82053.
15. Davis J, Molkentin JD. **Myofibroblasts: trust your heart and let fate decide**. *J Mol Cell Cardiol*. 2014; 70:9-18.
16. Dhandapany PS, Razzaque MA, Muthusami U, Kunnoth S, Edwards JJ, Mulero-Navarro S, Riess I, Pardo S, Sheng J, Rani DS, Rani B, Govindaraj P, Flex E, Yokota T, Furutani M, Nishizawa T, Nakanishi T, Robbins J, Limongelli G, Hajjar RJ, Lebeche D, Bahl A, Khullar M, Rathinavel A, Sadler KC, Tartaglia M, Matsuoka R, Thangaraj K, Gelb BD. **RAF1 mutations in childhood-onset dilated cardiomyopathy**. *Nat Genet*. 2014; 46:635-9.
17. Ehrman LA, Nardini D, Ehrman S, Rizvi TA, Gulick J, Krenz M, Dasgupta B, Robbins J, Ratner N, Nakafuku M, Waclaw RR. **The protein tyrosine phosphatase Shp2 is required for the generation of oligodendrocyte progenitor cells and myelination in the mouse telencephalon**. *J Neurosci*. 2014; 34:3767-78.
18. Gupta MK, Gulick J, James J, Osinska H, Lorenz JN, Robbins J. **Functional dissection of myosin binding protein C phosphorylation**. *J Mol Cell Cardiol*. 2013; 64:39-50.
19. Gupta MK, Robbins J. **Post-translational control of cardiac hemodynamics through myosin binding protein C**. *Pflugers Arch*. 2014; 466:231-6.
20. Haaning AM, Quinn ME, Ware SM. **Heterotaxy-spectrum heart defects in Zic3 hypomorphic mice**. *Pediatr Res*. 2013; 74:494-502.
21. Hernandez JS, Barreto-Torres G, Kuznetsov AV, Khuchua Z, Javadov S. **Crosstalk between AMPK activation and angiotensin II-induced hypertrophy in cardiomyocytes: the role of mitochondria**. *J Cell Mol Med*. 2014; 18:709-20.
22. Hobson MJ, Hake PW, O'Connor M, Schulte C, Moore V, James JM, Piraino G, Zingarelli B. **Conditional deletion of cardiomyocyte peroxisome proliferator-activated receptor gamma enhances myocardial ischemia-reperfusion injury in mice**. *Shock*. 2014; 41:40-7.
23. Hoffman NE, Chandramoorthy HC, Shamugapriya S, Zhang X, Rajan S, Mallilankaraman K, Gandhirajan RK, Vagnozzi RJ, Ferrer LM, Sreekrishnanilayam K, Natarajaseenivasan K, Vallem S, Force T, Choi ET, Cheung JY, Madesh M. **MICU1 motifs define mitochondrial calcium uniporter binding and activity**. *Cell Rep*. 2013; 5:1576-88.
24. Hoffman NE, Chandramoorthy HC, Shanmughapriya S, Zhang XQ, Vallem S, Doonan PJ, Malliankaraman K, Guo S, Rajan S, Elrod JW, Koch WJ, Cheung JY, Madesh M. **SLC25A23 augments mitochondrial Ca(2)(+) uptake, interacts with MCU, and induces oxidative stress-mediated cell death**. *Mol Biol Cell*. 2014; 25:936-47.
25. Kamal FA, Mickelsen DM, Wegman KM, Travers JG, Moalem J, Hammes SR, Smrcka AV, Blaxall BC. **Simultaneous adrenal and cardiac g-protein-coupled receptor-gbetagamma inhibition halts heart**

failure progression. *J Am Coll Cardiol*. 2014; 63:2549-57.
26. Kamal FA, Travers JG, Blaxall BC. **Embracing bias: beta1-adrenergic receptor-biased ligands and nuclear miRNA processing**. *Circ Res*. 2014; 114:742-5.
27. Karch J, Kwong JQ, Burr AR, Sargent MA, Elrod JW, Peixoto PM, Martinez-Caballero S, Osinska H, Cheng EH, Robbins J, Kinnally KW, Molkentin JD. **Bax and Bak function as the outer membrane component of the mitochondrial permeability pore in regulating necrotic cell death in mice**. *Elife*. 2013; 2:e00772.
28. Lalani SR, Ware SM, Wang X, Zapata G, Tian Q, Franco LM, Jiang Z, Bucasas K, Scott DA, Campeau PM, Hanchard N, Umana L, Cast A, Patel A, Cheung SW, McBride KL, Bray M, Craig Chinault A, Boggs BA, Huang M, Baker MR, Hamilton S, Towbin J, Jefferies JL, Fernbach SD, Potocki L, Belmont JW. **MCTP2 is a dosage-sensitive gene required for cardiac outflow tract development**. *Hum Mol Genet*. 2013; 22:4339-48.
29. Lange AW, Haitchi HM, LeCras TD, Sridharan A, Xu Y, Wert SE, James J, Udell N, Thurner PJ, Whitsett JA. **Sox17 is required for normal pulmonary vascular morphogenesis**. *Dev Biol*. 2014; 387:109-20.
30. Liu Y, Lu X, Xiang FL, Poelmann RE, Gittenberger-de Groot AC, Robbins J, Feng Q. **Nitric oxide synthase-3 deficiency results in hypoplastic coronary arteries and postnatal myocardial infarction**. *Eur Heart J*. 2014; 35:920-31.
31. Maiellaro-Rafferty K, Wansapura JP, Mendsaikhan U, Osinska H, James JF, Taylor MD, Robbins J, Kranias EG, Towbin JA, Purevjav E. **Altered regional cardiac wall mechanics are associated with differential cardiomyocyte calcium handling due to nebulette mutations in preclinical inherited dilated cardiomyopathy**. *J Mol Cell Cardiol*. 2013; 60:151-60.
32. Mandal A, Rydeen A, Anderson J, Sorrell MR, Zygmunt T, Torres-Vazquez J, Waxman JS. **Transgenic retinoic acid sensor lines in zebrafish indicate regions of available embryonic retinoic acid**. *Dev Dyn*. 2013; 242:989-1000.
33. Miller BA, Hoffman NE, Merali S, Zhang XQ, Wang J, Rajan S, Shanmughapriya S, Gao E, Barrero CA, Mallilankaraman K, Song J, Gu T, Hirschler-Laszkiewicz I, Koch WJ, Feldman AM, Madesh M, Cheung JY. **TRPM2 channels protect against cardiac ischemia-reperfusion injury: role of mitochondria**. *J Biol Chem*. 2014; 289:7615-29.
34. Molkentin JD, Houser SR. **Response to Torella et al**. *Circ Res*. 2014; 114:e27.
35. Molkentin JD, Houser SR. **Are resident c-Kit+ cardiac stem cells really all that are needed to mend a broken heart?**. *Circ Res*. 2013; 113:1037-9.
36. Mun JY, Previs MJ, Yu HY, Gulick J, Tobacman LS, Beck Previs S, Robbins J, Warshaw DM, Craig R. **Myosin-binding protein C displaces tropomyosin to activate cardiac thin filaments and governs their speed by an independent mechanism**. *Proc Natl Acad Sci U S A*. 2014; 111:2170-5.
37. Oikawa M, Wu M, Lim S, Knight WE, Miller CL, Cai Y, Lu Y, Blaxall BC, Takeishi Y, Abe J, Yan C. **Cyclic nucleotide phosphodiesterase 3A1 protects the heart against ischemia-reperfusion injury**. *J Mol Cell Cardiol*. 2013; 64:11-9.
38. Rainer PP, Hao S, Vanhoutte D, Lee DI, Koitabashi N, Molkentin JD, Kass DA. **Cardiomyocyte-specific transforming growth factor beta suppression blocks neutrophil infiltration, augments multiple cytoprotective cascades, and reduces early mortality after myocardial infarction**. *Circ Res*. 2014; 114:1246-57.
39. Rajan S, Pena JR, Jegga AG, Aronow BJ, Wolska BM, Wieczorek DF. **Microarray analysis of active cardiac remodeling genes in a familial hypertrophic cardiomyopathy mouse model rescued by a phospholamban knockout**. *Physiol Genomics*. 2013; 45:764-73.
40. Ram R, Wescott AP, Varandas K, Dirksen RT, Blaxall BC. **Mena associates with Rac1 and modulates connexin 43 remodeling in cardiomyocytes**. *Am J Physiol Heart Circ Physiol*. 2014; 306:H154-9.

41. Razzaque MA, Gupta M, Osinska H, Gulick J, Blaxall BC, Robbins J. **An endogenously produced fragment of cardiac myosin-binding protein C is pathogenic and can lead to heart failure**. *Circ Res*. 2013; 113:553-61.
42. Rydeen AB, Waxman JS. **Cyp26 enzymes are required to balance the cardiac and vascular lineages within the anterior lateral plate mesoderm**. *Development*. 2014; 141:1638-48.
43. Sandri M, Robbins J. **Proteotoxicity: an underappreciated pathology in cardiac disease**. *J Mol Cell Cardiol*. 2014; 71:3-10.
44. Sorrell MR, Dohn TE, D'Aniello E, Waxman JS. **Tcf7l1 proteins cell autonomously restrict cardiomyocyte and promote endothelial specification in zebrafish**. *Dev Biol*. 2013; 380:199-210.
45. Su H, Li J, Osinska H, Li F, Robbins J, Liu J, Wei N, Wang X. **The COP9 signalosome is required for autophagy, proteasome-mediated proteolysis, and cardiomyocyte survival in adult mice**. *Circ Heart Fail*. 2013; 6:1049-57.
46. Tagashira H, Bhuiyan MS, Fukunaga K. **Diverse regulation of IP3 and ryanodine receptors by pentazocine through sigma1-receptor in cardiomyocytes**. *Am J Physiol Heart Circ Physiol*. 2013; 305:H1201-12.
47. Tagashira H, Bhuiyan MS, Shioda N, Fukunaga K. **Fluvoxamine rescues mitochondrial Ca2+ transport and ATP production through sigma(1)-receptor in hypertrophic cardiomyocytes**. *Life Sci*. 2014; 95:89-100.
48. Tane S, Kubota M, Okayama H, Ikenishi A, Yoshitome S, Iwamoto N, Satoh Y, Kusakabe A, Ogawa S, Kanai A, Molkentin JD, Nakamura K, Ohbayashi T, Takeuchi T. **Repression of Cyclin D1 Expression Is Necessary for the Maintenance of Cell Cycle Exit in Adult Mammalian Cardiomyocytes**. *J Biol Chem*. 2014; 289:18033-18044.
49. van Berlo JH, Kanisicak O, Maillet M, Vagnozzi RJ, Karch J, Lin SC, Middleton RC, Marban E, Molkentin JD. **c-kit+ cells minimally contribute cardiomyocytes to the heart**. *Nature*. 2014; 509:337-41.
50. Wang X, Robbins J. **Proteasomal and lysosomal protein degradation and heart disease**. *J Mol Cell Cardiol*. 2014; 71:16-24.
51. Wirrig EE, Yutzey KE. **Conserved transcriptional regulatory mechanisms in aortic valve development and disease**. *Arterioscler Thromb Vasc Biol*. 2014; 34:737-41.
52. Witayavanitkul N, Ait Mou Y, Kuster DW, Khairallah RJ, Sarkey J, Govindan S, Chen X, Ge Y, Rajan S, Wieczorek DF, Irving T, Westfall MV, de Tombe PP, Sadayappan S. **Myocardial infarction-induced N-terminal fragment of cardiac myosin-binding protein C (cMyBP-C) impairs myofilament function in human myocardium**. *J Biol Chem*. 2014; 289:8818-27.
53. Xiong D, He H, James J, Tokunaga C, Powers C, Huang Y, Osinska H, Towbin JA, Purevjav E, Balschi JA, Javadov S, McGowan FX, Jr., Strauss AW, Khuchua Z. **Cardiac-specific VLCAD deficiency induces dilated cardiomyopathy and cold intolerance**. *Am J Physiol Heart Circ Physiol*. 2014; 306:H326-38.
54. Yutzey KE. **Cardiovascular biology: Switched at birth**. *Nature*. 2014; 509:572-3.
55. Yutzey KE. **A twist of proepicardial fate**. *Circ Res*. 2013; 113:1106-8.

Faculty, Staff, and Trainees

Faculty Members

Jeffrey Robbins, PhD, FAHA, FISHR, Professor

Leadership Executive Co-Director, Heart Institute; Endowed Chair, Molecular Cardiovascular Biology; Associate Chair for Core Research

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, Professor

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

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, Associate Professor

Leadership 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

Jeffery Molkentin, PhD, Professor

Leadership Howard Hughes Medical Institute Investigator

Research Interests Molecular pathways that underlie heart disease and muscular dystrophy

Sudarsan Rajan, PhD, Assistant Professor

Research Interests Understanding contractile and regulatory proteins' gene expression and their role in maintaining normal cardiovascular function

Johannes van Berlo, MD, PhD, Instructor

Stephanie Ware, MD, PhD, Associate Professor

Leadership Director of Research and Development, Associate Medical Director, the Heart Institute Diagnostic Laboratory

Research Interests Genetics of pediatric heart disease

Joshua Waxman, PhD, Assistant Professor

Research Interests Molecular genetics of cardiovascular development

Katherine Yutzey, PhD, Professor

Research Interests Heart development and disease mechanisms

Trainees

- **Federica Accornero, PhD**, University of Turin, Italy
- **Sarah Beckman, PhD**, University of Pittsburgh

- **Bidur Bhandary, PhD**, Chonbuk National University, South Korea
- **Md. Shenuarin Bhuiyan, PhD**, Tohoku University, Japan
- **Justin Boyer, PhD**, University of Ottowa, Canada
- **Caitlin Braitsch, PhD**, University of Cincinnati
- **Matthew Brody, PhD**, University of Wisconsin-Madison
- **Adam Burr, BS**, University of Minnesota, Twin Cities
- **Robert Nathan Correll, PhD**, University of Kentucky
- **Jason Cowan, MS**, University of Miami
- **Angela Damen, MAT**, Miami University
- **Enrico D'Aniello, PhD**, Marine Zoological Station Anton Dohrn, Italy
- **Jennifer Davis, PhD**, Univeristy of Michigan, Ann Arbor
- **Allison Dixon, BS**, Bellarmine University
- **Tracy Dohn, BS**, Wittenberg University
- **Ming Fang, MS**, Boise State University
- **Maria Gomez, BS**, Xavier University
- **Ambrose Goonasekera, PhD**, University of Rochester
- **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
- **Jennifer Kwong, PhD**, Weill Medical College of Cornell University
- **Julie Lander, BS**, Brigham Young University
- **Mary Lee, MS**, Ball State University
- **Ruijie Liu, PhD**, University of Illinois at Urbana Champaign
- **Amrita Mandal, MSc**, University of Calcutta, India
- **Patrick McLendon, PhD**, Virginia Polytechnical Institute and State University
- **Rashmi Ram, PhD**, University of Rochester
- **Md. Abdur Razzaque, PhD**, Tokyo Women's Medical University, Japan
- **Tara Rindler, PhD**, University of Cincinnati
- **Ariel Rydeen, BS**, University of Minnesota
- **Tobias Schips, PhD**, Ulm University, Germany
- **Jeffrey Schubert, BS**, College of Mount St. Joseph
- **Emily Schulz, PhD**, University of Cincinnati
- **Jennifer Schwanekamp, MS**, University of Cincinnati
- **Mardi Sutherland, BS**, University of Massachusetts, Boston
- **Muhammad Tariq, PhD**, Quaid-I-Azam University, Pakistan
- **Andoria Tjondrokoesoemo, PhD**, University of Medicine & Dentistry of New Jersey
- **Joshua Travers, BS**, Rochester Institute of Technology
- **Ronald Vagnozzi, PhD**, Thomas Jefferson University
- **Davy Vanhoutte, PhD**, University of Leuven, Belgium
- **Elaine Wirrig, PhD**, Medical University of South Carolina
- **Erin Wissing, BA**, DePauw University

- **Fuli Xiang, MD, PhD**, University of Western Ontario, Canada

Division Collaboration

Shared interest in pathologic signaling of protease activated receptor 1 (PAR1) and its role in the pathogenesis of fibrotic remodeling and heart failure.(Burns C. Blaxall, PhD)

Hematology » Joseph S. Palumbo, MD

Investigating the potential for our novel small molecule inhibitors of G protein beta gamma signaling to attenuate acute and chronic renal fibrosis and inflammation using both animal models and human blood/tissue. (Burns C. Blaxall, PhD)

Nephrology and Hypertension » Prasad Devarajan, MD

Center for Acute Care Nephrology » Stuart L. Goldstein, MD

Assessment of cardiovascular outcomes in a mouse model of sickle cell disease. Dr. James worked with Dr. Malik and her clinical hematology fellow to develop a mouse echocardiography protocol to obtain model-specific data. She monitors the data for accuracy and meets with her team regularly to discuss the data and to provide clinical interpretation. The data generated was critical for the fellow's successful application for an Arnold W. Strauss Fellow Award. (Jeanne James, MD)

Experimental Hematology and Cancer Biology » Punam Malik, MD

Effects of obesity on cardiovascular function in a mouse model of polymicrobial sepsis. This study is aimed at gaining a better understanding of why obese patients have poorer outcomes in clinical sepsis. Working with Dr. Kaplan's team, Dr. James designed a customized mouse echocardiography protocol to provide a detailed assessment of cardiac function in mice with polymicrobial sepsis. She monitors the data for accuracy and meet with her team regularly to discuss the data and to provide clinical interpretation. (Jeanne James, MD)

Critical Care Medicine » Jennifer Kaplan, MD, MS

Role of AMP-activated protein kinase on cardiac function in polymicrobial sepsis. Dr. James worked with Dr. Zingarelli and her team to develop a mouse echocardiography protocol to provide detailed information about systolic and diastolic function before and after the induction of polymicrobial sepsis. She monitors the data for accuracy and meets with her team to discuss the data and to provide clinical interpretation. (Jeanne James, MD)

Critical Care Medicine » Basilia Zingarelli, MD, PhD

Non-invasive assessment of right ventricular function and pressure in a mouse model of pulmonary hypertension. Working with Dr. Nichols' research team, Dr. James developed a protocol to specifically address right ventricular parameters in mice. She monitors the data for accuracy and meets with his team regularly to discuss the data and to provide clinical interpretation. This is a relatively new collaboration, representing new territory for the Mouse Echocardiography Core. (Jeanne James, MD)

Human Genetics » William C. Nichols, PhD

Pre- and post-natal modulation cardiovascular function in a mouse model of intrauterine growth retardation. Drs. James and Habli have worked to develop a reproducible method of assessing umbilical artery and vein flow in fetal mice. They are now able to perform transuterine survival scanning of fetal mice, which is an extension of their previous fetal mouse echo capabilities. Dr. James monitors the data for accuracy and meets with the team regularly to discuss the data and to provide clinical interpretation. (Jeanne James, MD)

Maternal Fetal Medicine » Mounira Habli, MD

Assessment of skeletal muscle contractility in a mouse model of amyotrophic lateral sclerosis (ALS). Dr. Crone came to the Mouse Echocardiography Core with a novel request to assess the movement of respiratory muscles in a mouse model of ALS. This required a novel approach to our usual mouse scanning but has yielded promising (and intriguing) preliminary data. (Jeanne James, MD)

Neurosurgery » Steven A. Crone, PhD

Alteration of mitochondrial dynamics in cardiolipin deficient mitochondria. We use our tafazzin-knockdown mice and human iPS-derived cells to look how mitochondrial fission/fusion is altered in these model systems. (Zaza Khuchua, PhD)

Human Genetics » Taosheng Huang, MD, PhD

Investigating human ACAD9 deficiency which changes folding of mitochondrial complex I. (Zaza Khuchua, PhD)

Human Genetics » Taosheng Huang, MD, PhD

A student from Tanya Kalin's laboratory investigates possible interaction of FoxM1 with mitochondrial electron transport chain complexes. (Zaza Khuchua, PhD)

Section of Neonatology, Perinatal and Pulmonary Biology » Tanya V. Kalin, MD, PhD

Identification of shared Twist1 target genes in embryonic development and cancer cells. (Katherine Yutzey, PhD)

Experimental Hematology and Cancer Biology » Nancy Ratner, PhD

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 HL 121284	12/20/13-11/30/15	$121,375
BHUIYAN, S		
Sigma-1 Receptor and Cardioprotection		
National Institutes of Health		
K99 HL 122354	04/09/14-03/31/19	$121,750
BLAXALL B		
Extracellular Matrix Remodeling and Fibrosis		
National Institutes of Health(University of Rochester)		
R01 GM 097347	08/15/12-11/30/15	$38,513
Small Molecule Targeting of MLK3 for Heart Failure		
American Heart Association		
13IRG14670079	01/01/13-12/31/14	$68,183

DAVIS, J

MBNL1's Function in Myofibroblast Transformation and Fibrosis
National Institutes of Health

K99 HL 119353	08/09/13-07/31/15	$121,375

FANG, M

Wnt/beta-catenin Signaling in Heart Valve Development
American Heart Association

13PRE16410009	07/01/13-06/30/15	$26,000

GOMEZ, M

BMP Signaling in the Progression of Calcific Aortic Valve Disease
American Heart Association

13PRE1623006	07/01/13-06/30/15	$26,000

KAMAL, F

Targeting Adrenal and Cardiac GPCR Signaling in Heart Failure: A Novel Therapeutic Strategy
American Heart Association

13POST16670003	07/01/13-06/30/15	$46,000

KHUCHUA, Z

A Mouse Model of Barth Syndrome, a Mitochondrial Cardiolipin Disorder
National Institutes of Health

R01 HL 108867	07/07/11-03/31/15	$245,000

Bezafibrates Pre-Trial on Mice
Barth Syndrome Foundation, Inc.

	05/01/14-04/30/15	$38,500

KWONG, J

Defining the Role of SLC25a35 as a Regulator of the Mitochondrial Permeability Transition Pore and Cardiomyocyte Death
American Heart Association

12POSTDOC11950000	07/01/12-06/30/14	$47,999

MOLKENTIN, J / ROBBINS, J (MPI)

Thrombospondin 4 Regulates Adaptive ER Stress Response
National Institutes of Health

R01 HL 105924	01/01/11-12/31/14	$305,366

MOLKENTIN, J

CaMKII and InsP3-Mediated Signaling in Cardiac Myocytes
National Institutes of Health(The Regents of the University of California)

P01 HL 080101	08/01/11-05/31/16	$271,987

Improving Cardiac Function after Myocardial Infarction
National Institutes of Health(Temple University School of Medicine)

P01 HL 108806	05/07/12-03/31/17	$260,000

Regulating Fibrosis and Muscle Growth in the Muscular Dystrophies
National Institutes of Health(The University of Chicago)

P01 NS 072027	07/01/11-06/30/16	$215,000

Molecular Pathways Controlling Cardiac Gene Expression
National Institutes of Health

R37 HL 060562	07/01/13-06/30/18	$238,000

RAJAN, S

Translational and Post-Translational Regulation of Tropomyosin in Normal and Cardiomyopathic Hearts
American Heart Association

11SDG4980029	08/01/11-12/31/14	$70,000

ROBBINS , J

A TG Rabbit Model for the Functional Effects of FHC Mutations in B-Cardiac Myosin
National Institutes of Health(University of Vermont)

R21 HL 111847	07/15/12-06/30/14	$24,960

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	$304,920

Proteotoxicity: An Unappreciated Mechanism of Heart Disease
Fondation Leducq

	10/01/11-09/30/16	$247,636

Signaling Processes Underlying Cardiovascular Function
National Institutes of Health

P01 HL069779	06/06/02-05/31/18	$1,149,912

TARIQ, M

Identification of Novel Human X-Linked Heterotaxy Genes
American Heart Association

12POSTDOC10370002	07/01/12-02/28/14	$30,667

VAN BERLO, J

Functional Relevance and Extent of Endogenous Cardiac Regeneration by C-Kit Positive Stem Cells
National Institutes of Health

K99 HL 112852	06/04/12-07/31/13	$32,000

WARE, S

Genetic and Epigenetic Mechanisms in Cardiomyopathy
American Heart Association

13EIA13460001	01/01/13-12/31/14	$72,727

Genetic Registry for Pediatric Heart Disease: The CCVM Consortium

March of Dimes National

06/01/13-05/31/16 $79,182

Genotype-Phenotype Association in Pediatric Cardiomyopathy
National Institutes of Health(University of Miami)

R01 HL 111459 04/01/12-03/31/14 $987,826

Uncovering Novel Genetic Causes and Risk in Congenital Heart Disease Patients
Burroughs Wellcome Foundation(University of Cincinnati)

07/01/09-02/28/14 $150,000

WAXMAN, J

Coup-tf Dependent Mechanisms of Ventricular and Hemangioblast Specification
National Institutes of Health

R01 HL 112893 01/15/13-02/28/18 $220,500

Mechanisms of Retinoic Acid Signaling Induced Congenital Heart Defects
March of Dimes

6FY14389 06/01/14-05/31/17 $113,636

WIRRIG, E

The Role of COX2 in the Progression of Human Calcific Aortic Valve Disease
National Institutes of Health

F32 HL 110390 07/01/12-06/30/15 $53,942

YUTZEY, K

Cell Signaling Mechanisms of Calcific Aortic Valve Disease
National Institutes of Health

R01 HL 114682 08/23/12-06/30/16 $238,000

Cincinnati Children's SURF Program
American Heart Association

14UFEL19160000 02/01/14-01/31/16 $20,000

Twist 1 Regulation of Valve Progenitors
National Institutes of Health

R01 HL 082716 07/01/10-05/31/15 $242,550

Wnt Signaling in Heart Valve Development and Disease
National Institutes of Health

R01 HL 094319 04/15/12-02/28/16 $245,000

Current Year Direct $6,474,506

Industry Contracts

ROBBINS, J / MORALES, D

CorMatrix Cardiovascular, Inc $75,024

Current Year Direct Receipts $75,024

Total	**$6,549,530**