

Molecular Cardiovascular Biology

Division Details

RESEARCH AND TRAINING DETAILS

Faculty	11
Research Fellows and Post Docs	21
Research Graduate Students	11
Total Annual Grant Award Dollars	\$7,161,163
Total Annual Industry Award Dollars	\$75,001
Total Publications	46

Significant Publications

Davis J, Davis LC, Correll RN, Makarewich CA, Schwanekamp JA, Moussavi-Harami F, Wang D, York AJ, Wu H, Houser SR, Seidman CE, Seidman JG, Regnier M, Metzger JM, Wu JC, **Molkentin JD. A Tension-Based Model Distinguishes Hypertrophic versus Dilated Cardiomyopathy.** *Cell*. 2016 May 19;165(5):1147-59.

During cardiac disease the heart changes form, growing larger and more muscular or dilating with the walls becoming stretched and thin. The processes responsible for these different pathogenic pathways remain obscure. This manuscript defines one of the underlying mechanisms which dictates the pathway taken. By using genetically engineered mouse hearts, the paper shows that muscle tension can be the major force in dictating the choice and predicts whether a dilated or hypertrophy heart will result from how a particular gene mutation changes how the muscle develops internal tension during contraction.

Gupta MK, McLendon PM, **Gulick J, James J**, Khalili K, **Robbins J. UBC9-Mediated Sumoylation Favorably Impacts Cardiac Function in Compromised Hearts.** *Circ Res*. 2016 Jun 10;118(12):1894-905.

The process of cellular self-digestion, called autophagy, is critical for normal cell function and is often altered in cardiovascular disease. We have found the modification of cardiac proteins during development of disease can have significant functional consequences. One of these processes adds small peptide groups to the existing protein, modifying it and changing its activity. This process, called SUMOylation, can in cardiac disease result in a heart that is more resistant to the pathogenic stimuli. Modulating this pathway's activity may represent a novel strategy for increasing autophagic flux and ameliorating morbidity in proteotoxic cardiac disease.

Millay DP, Gamage DG, Quinn ME, Min YL, Mitani Y, Bassel-Duby R, Olson EN. **Structure-function analysis of myomaker domains required for myoblast fusion.** *Proc Natl Acad Sci U S A*. 2016 Feb 23;113(8):2116-21.

Skeletal muscle forms from the fusion of stem cells during development and regeneration. Manipulation of stem cell fusion could offer strategies to treat muscle diseases such as muscular dystrophy and age-related atrophy. Myomaker is a membrane protein that governs muscle cell fusion, however the details of how this protein functions remains unknown. In this manuscript we show that

myomaker contains seven membrane-spanning regions with an intracellular C-terminal tail that is necessary for fusion. These results are an important first step to understand fusion and how it might be therapeutically controlled to mitigate muscle diseases.

Division Publications

1. Bernardo BC, Blaxall BC. **From Bench to Bedside: New Approaches to Therapeutic Discovery for Heart Failure.** *Heart Lung Circ.* 2016; 25:425-34.
2. Bhandary B, Robbins J. **Giving Credence to Controls: Avoiding the False Phenotype.** *J Mol Cell Cardiol.* 2015; 86:136-7.
3. Brody M, Schips T, Vanhoutte D, Kanisicak O, Karch J, Maliken B, Blair N, Sargent M, Prasad V, Molkentin J. **Dissection of Thrombospondin-4 Domains Involved in Intracellular Adaptive Endoplasmic Reticulum Stress-Responsive Signaling.** *Mol Cell Biol.* 2016; 36:2-12.
4. Burr AR, Molkentin JD. **Genetic Evidence in the Mouse Solidifies the Calcium Hypothesis of Myofiber Death in Muscular Dystrophy.** *Cell Death Differ.* 2015; 22:1402-12.
5. Correll R, Goonasekera S, van Berlo J, Burr A, Accornero F, Zhang H, Makarewich C, York A, Sargent M, Chen X. **Stim1 Elevation in the Heart Results in Aberrant Ca²⁺ Handling and Cardiomyopathy.** *J Mol Cell Cardiol.* 2015; 87:38-47.
6. D'Aniello E, Ravisankar P, Waxman JS. **Rdh10a Provides a Conserved Critical Step in the Synthesis of Retinoic Acid During Zebrafish Embryogenesis.** *PLoS One.* 2015; 10:e0138588.
7. Davis J, Davis LC, Correll RN, Makarewich CA, Schwaneckamp JA, Moussavi-Harami F, Wang D, York AJ, Wu H, Houser SR, Seidman CE, Seidman JG, Regnier M, Metzger JM, Wu JC, Molkentin JD. **A Tension-Based Model Distinguishes Hypertrophic Versus Dilated Cardiomyopathy.** *Cell.* 2016; 165:1147-59.
8. Davis J, Salomonis N, Ghearing N, Lin SC, Kwong JQ, Mohan A, Swanson MS, Molkentin JD. **Mbnl1-Mediated Regulation of Differentiation Rnas Promotes Myofibroblast Transformation and the Fibrotic Response.** *Nat Commun.* 2015; 6:10084.
9. Fang M, Xiang FL, Braitsch CM, Yutzey KE. **Epicardium-Derived Fibroblasts in Heart Development and Disease.** *J Mol Cell Cardiol.* 2016; 91:23-7.
10. Gainutdinov T, Molkentin JD, Siemen D, Ziemer M, Debska-Vielhaber G, Vielhaber S, Gizatullina Z, Orynbayeva Z, Gellerich FN. **Knockout of Cyclophilin D in Ppif(-)/(-) Mice Increases Stability of Brain Mitochondria against Ca(2+)(+) Stress.** *Arch Biochem Biophys.* 2015; 579:40-6.
11. Gomez-Stallons MV, Wirrig-Schwendeman EE, Hassel KR, Conway SJ, Yutzey KE. **Bone Morphogenetic Protein Signaling Is Required for Aortic Valve Calcification.** *Arterioscler Thromb Vasc Biol.* 2016; 36:1398-405.
12. Gupta MK, McLendon PM, Gulick J, James J, Khalili K, Robbins J. **Ubc9-Mediated Sumoylation Favorably Impacts Cardiac Function in Compromised Hearts.** *Circ Res.* 2016; 118:1894-905.
13. Huby AC, Turdi S, James J, Towbin JA, Purevjav E. **Fasl Expression in Cardiomyocytes Activates the Erk1/2 Pathway, Leading to Dilated Cardiomyopathy and Advanced Heart Failure.** *Clin Sci (Lond).* 2016; 130:289-99.
14. James J, Robbins J. **Healing a Heart through Genetic Intervention.** *Circ Res.* 2016; 118:920-2.
15. James J, Robbins J. **Bringing It All Together: Bedside to Bench and Back Again.** *Circ Res.* 2015; 117:987-9.
16. Jin S, Orabi AI, Le T, Javed TA, Sah S, Eisses JF, Bottino R, Molkentin JD, Husain SZ. **Exposure to Radiocontrast Agents Induces Pancreatic Inflammation by Activation of Nuclear Factor-Kappab, Calcium Signaling, and Calcineurin.** *Gastroenterology.* 2015; 149:753-64 e11.

17. Kamal FA, Travers JG, Schafer AE, Ma Q, Devarajan P, Blaxall BC. **G Protein-Coupled Receptor-G-Protein Betagamma-Subunit Signaling Mediates Renal Dysfunction and Fibrosis in Heart Failure.** *J Am Soc Nephrol.* 2016.
18. Klionsky D, Abdelmohsen K, Abe A, Abedin M, Abeliovich H, Arozena A, Adachi H, Adams C, Adams P, Adeli Kea. **Guidelines for the Use and Interpretation of Assays for Monitoring Autophagy (3rd Edition).** *Autophagy.* 2016; 12:1-222.
19. Kwong JQ, Lu X, Correll RN, Schwanekamp JA, Vagnozzi RJ, Sargent MA, York AJ, Zhang J, Bers DM, Molkentin JD. **The Mitochondrial Calcium Uniporter Selectively Matches Metabolic Output to Acute Contractile Stress in the Heart.** *Cell Rep.* 2015; 12:15-22.
20. Lamar KM, Bogdanovich S, Gardner BB, Gao QQ, Miller T, Earley JU, Hadhazy M, Vo AH, Wren L, Molkentin JD, McNally EM. **Overexpression of Latent Tgfbeta Binding Protein 4 in Muscle Ameliorates Muscular Dystrophy through Myostatin and Tgfbeta.** *PLoS Genet.* 2016; 12:e1006019.
21. Landis BJ, Ware SM, James J, Shikany AR, Martin LJ, Hinton RB. **Clinical Stratification of Pediatric Patients with Idiopathic Thoracic Aortic Aneurysm.** *J Pediatr.* 2015; 167:131-7 e1-5.
22. Leslie N, Wang X, Peng Y, Valencia CA, Khuchua Z, Hata J, Witte D, Huang T, Bove KE. **Neonatal Multiorgan Failure Due to Acad9 Mutation and Complex I Deficiency with Mitochondrial Hyperplasia in Liver, Cardiac Myocytes, Skeletal Muscle, and Renal Tubules.** *Hum Pathol.* 2016; 49:27-32.
23. Li L, Chen Y, Li J, Yin H, Guo X, Doan J, Molkentin JD, Liu Q. **Tak1 Regulates Myocardial Response to Pathological Stress Via Nfat, Nfkappab, and Bnip3 Pathways.** *Sci Rep.* 2015; 5:16626.
24. Liu R, Correll RN, Davis J, Vagnozzi RJ, York AJ, Sargent MA, Nairn AC, Molkentin JD. **Cardiac-Specific Deletion of Protein Phosphatase 1beta Promotes Increased Myofilament Protein Phosphorylation and Contractile Alterations.** *J Mol Cell Cardiol.* 2015; 87:204-13.
25. Lu X, Kwong JQ, Molkentin JD, Bers DM. **Individual Cardiac Mitochondria Undergo Rare Transient Permeability Transition Pore Openings.** *Circ Res.* 2016; 118:834-41.
26. Martherus R, Jain R, Takagi K, Mendsaikhan U, Turdi S, Osinska H, James JF, Kramer K, Purevjav E, Towbin JA. **Accelerated Cardiac Remodeling in Desmoplakin Transgenic Mice in Response to Endurance Exercise Is Associated with Perturbed Wnt/Beta-Catenin Signaling.** *Am J Physiol Heart Circ Physiol.* 2016; 310:H174-87.
27. Millay DP, Gamage DG, Quinn ME, Min YL, Mitani Y, Bassel-Duby R, Olson EN. **Structure-Function Analysis of Myomaker Domains Required for Myoblast Fusion.** *Proc Natl Acad Sci U S A.* 2016; 113:2116-21.
28. Moore-Morris T, Guimaraes-Camboa N, Yutzey KE, Puceat M, Evans SM. **Cardiac Fibroblasts: From Development to Heart Failure.** *J Mol Med (Berl).* 2015; 93:823-30.
29. Pfluger PT, Kabra DG, Aichler M, Schriever SC, Pfuhlmann K, Garcia VC, Lehti M, Weber J, Kutschke M, Rozman J, Elrod JW, Hevener AL, Feuchtinger A, Hrabe de Angelis M, Walch A, Rollmann SM, Aronow BJ, Muller TD, Perez-Tilve D, Jastroch M, et al. **Calcineurin Links Mitochondrial Elongation with Energy Metabolism.** *Cell Metab.* 2015; 22:838-50.
30. Previs MJ, Mun JY, Michalek AJ, Previs SB, Gulick J, Robbins J, Warshaw DM, Craig R. **Phosphorylation and Calcium Antagonistically Tune Myosin-Binding Protein C's Structure and Function.** *Proc Natl Acad Sci U S A.* 2016; 113:3239-44.
31. Rydeen A, Voisin N, D'Aniello E, Ravisankar P, Devignes CS, Waxman JS. **Excessive Feedback of Cyp26a1 Promotes Cell Non-Autonomous Loss of Retinoic Acid Signaling.** *Dev Biol.* 2015; 405:47-55.
32. Schwanekamp JA, Lorts A, Vagnozzi RJ, Vanhoutte D, Molkentin JD. **Deletion of Periostin Protects against Atherosclerosis in Mice by Altering Inflammation and Extracellular Matrix Remodeling.** *Arterioscler Thromb Vasc Biol.* 2016; 36:60-8.
33. Shojaee S, Caeser R, Buchner M, Park E, Swaminathan S, Hurtz C, Geng H, Chan LN, Klemm L, Hofmann WK, Qiu YH, Zhang N, Coombes KR, Paietta E, Molkentin J, Koeffler HP, Willman CL, Hunger SP, Melnick A, Kornblau SM, et al. **Erk Negative Feedback**

- Control Enables Pre-B Cell Transformation and Represents a Therapeutic Target in Acute Lymphoblastic Leukemia.** *Cancer Cell*. 2015; 28:114-28.
34. Taylor EN, Hoffman MP, Barefield DY, Aninwene GE, 2nd, Abrishamchi AD, Lynch TL, Govindan S, Osinska H, Robbins J, Sadayappan S, Gilbert RJ. **Alterations in Multi-Scale Cardiac Architecture in Association with Phosphorylation of Myosin Binding Protein-C.** *J Am Heart Assoc*. 2016; 5:e002836.
35. Tjondrokoesoemo A, Schips T, Kanisicak O, Sargent MA, Molkentin JD. **Genetic Overexpression of Serpina3n Attenuates Muscular Dystrophy in Mice.** *Hum Mol Genet*. 2016; 25:1192-202.
36. Tjondrokoesoemo A, Schips TG, Sargent MA, Vanhoutte D, Kanisicak O, Prasad V, Lin SC, Maillet M, Molkentin JD. **Cathepsin S Contributes to the Pathogenesis of Muscular Dystrophy in Mice.** *J Biol Chem*. 2016; 291:9920-8.
37. Topkara V, Chambers K, Yang K, Tzeng H, Evans S, Weinheimer C, Kovacs A, Robbins J, Barger P, Mann D. **Functional Significance of the Discordance between Transcriptional Profile and Left Ventricular Structure/Function During Reverse Remodeling.** *JCI Insight*. 2016; 1:e86038.
38. Travers JG, Kamal FA, Robbins J, Yutzey KE, Blaxall BC. **Cardiac Fibrosis: The Fibroblast Awakens.** *Circ Res*. 2016; 118:1021-40.
39. Travers JG, Schafer AE, Blaxall BC. **Grk2 in Lymphocytes: Expanding the Arsenal of Heart Failure Prognostics.** *Circ Res*. 2016; 118:1049-51.
40. Valiente-Alandi I, Schafer AE, Blaxall BC. **Extracellular Matrix-Mediated Cellular Communication in the Heart.** *J Mol Cell Cardiol*. 2016; 91:228-37.
41. van Berlo J, Molkentin J. **Most of the Dust Has Settled Ckit(+) Progenitor Cells Are an Irrelevant Source of Cardiac Myocytes in Vivo.** *Circ Res*. 2016; 118:17-19.
42. Wang Y, Wu B, Farrar E, Lui W, Lu P, Zhang D, Alfieri C, Mao K, Chu M, Yang D. **Notch-Tnf Signalling Is Required for Development and Homeostasis of Arterial Valves.** *Eur Heart J*. 2015.
43. Xiang FL, Guo M, Yutzey KE. **Overexpression of Tbx20 in Adult Cardiomyocytes Promotes Proliferation and Improves Cardiac Function after Myocardial Infarction.** *Circulation*. 2016; 133:1081-92.
44. Zevel D, Millay D, Seo J, Graff J. **Exercise-Induced Skeletal Muscle Adaptations Alter the Activity of Adipose Progenitor Cells.** *Plos One*. 2016; 11.
45. Zhang X, Ai X, Nakayama H, Chen B, Harris DM, Tang M, Xie Y, Szeto C, Li Y, Li Y, Zhang H, Eckhart AD, Koch WJ, Molkentin JD, Chen X. **Persistent Increases in Ca(2+) Influx through Cav1.2 Shortens Action Potential and Causes Ca(2+) Overload-Induced Afterdepolarizations and Arrhythmias.** *Basic Res Cardiol*. 2016; 111:4.
46. Zhu X, Hogan S, Molkentin J, Zimmermann N. **Cyclophilin D Regulates Necrosis, but Not Apoptosis, of Murine Eosinophils.** *Am J Physiol Gastrointest Liver Physiol*. 2016; 310:G609-G17.

Grants, Contracts, and Industry Agreements

Annual Grant Award Dollars

Investigator	Title	Sponsor	ID	Dates	Amount
Burns C Blaxall, PHD	Extracellular Matrix Remodeling and Fibrosis	National Institutes of Health (University of Rochester)	R01 GM097347	8/15/2012 - 5/31/2016	\$66,664
Burns C Blaxall, PHD	Small Molecule Targeting of MLK3 for Heart Failure	National Institutes of Health	R01 HL129772	12/14/2015 -	\$390,000

				11/30/2019	
Burns C Blaxall, PHD	Targeting Gáý-GRK2 Signaling in Fibrotic Remodeling	National Institutes of Health	R01 HL132551	3/1/2016 - 2/29/2020	\$390,000
Matthew J Brody, PHD	The Role of Thrombospondin-4 in the Secretary Pathway, Extracellular Matrix Production and Homeostasis and ER Stress	National Institutes of Health	F32 HL124698	8/1/2014 - 7/31/2017	\$52,406
Alexia Hulin, PHD	Neural Crest Cell-derived Melanocytes Contribute to Myxomatous Valve Disease	American Association of Anatomists	AAA PF Hulin	1/15/2016 - 1/14/2017	\$20,000
Onur Kanisicak, PHD	In Vivo Characterization and Ablation of Murine Cardiac	American Heart Association	15POST25480009	7/1/2015 - 6/30/2017	\$47,000
Zaza Khuchua, PHD	New Therapeutics for Barth Syndrome: Mouse Model Studies	Barth Syndrome Foundation, Inc.		5/1/2016 - 5/1/2017	\$50,000
Jennifer Q Kwong, PHD	Defining the Role of MCUb in the Regulation of Cardiac Mitochondrial Calcium Sensing, Metabolism and Survival	American Heart Association	16SDG26420043	1/1/2016 - 12/31/2019	\$77,000
Douglas P Millay, PHD	Molecular Dissection of Cell Fusion	The Pew Charitable Trusts	28646	8/1/2015 - 7/31/2019	\$60,000
Douglas P Millay, PHD	Molecular Control of Mammalian Myoblast Fusion	Muscular Dystrophy Association	MDA275271	7/1/2014 - 7/31/2016	\$60,000
Douglas P Millay, PHD	Deciphering Mechanisms of Myoblast Fusion	National Institutes of Health	R01 AR068286	7/1/2015 - 6/30/2020	\$343,200
Jeffery D Molkenin, PHD	Ca Signaling Domains Programming Cardiac Hypertrophy	National Institutes of Health (The Regents of the Univ of California)	P01 HL080101	8/1/2011 - 5/31/2017	\$393,409
Jeffery D Molkenin, PHD	Improving Cardiac Function after Myocardial Infarction	National Institutes of Health (Temple University School of Medicine)	P01 HL108806	5/7/2012 - 3/31/2017	\$397,800
Jeffery D Molkenin, PHD	Mechanisms of TGF Regulated Fibrosis in Muscular Dystrophy	National Institutes of Health (Northwestern University Medical School)	P01 NS072027	10/1/2014 - 6/30/2016	\$336,513
Jeffery D Molkenin, PHD	Thrombospondin 4 Regulates Adaptive ER Stress Response	National Institutes of Health	R01 HL105924	1/1/2015 - 12/31/2018	\$484,444

Jeffery D Molkenin, PHD	Role of Ca ²⁺ Flux through TRP Channels in Cardiac Stress Molecular Pathways	National Institutes of Health (Temple University School of Medicine)	R01 HL119229	9/1/2014 - 8/31/2015	\$115,680
Jeffery D Molkenin, PHD	Controlling Cardiac Gene Expression	National Institutes of Health	R37 HL060562	7/1/2013 - 6/30/2016	\$376,762
Jeffery D Molkenin, PHD	Understanding Cardiovascular Disease Mechanisms	National Institutes of Health	T32 HL125204	12/1/2014 - 11/30/2019	\$305,222
Jeffrey Robbins, PHD	Proteotoxicity: An Unappreciated Mechanism of Heart Disease and its Potential for Novel Therapeutics	Fondation Leducq	Leducq Robbins	10/1/2011 - 9/30/2017	\$272,400
Jeffrey Robbins, PHD	Signaling Processes Underlying Cardiovascular Function	National Institutes of Health	P01 HL069779	6/1/2016 - 5/31/2018	\$1,781,113
Ariel Rydeen	Requirements for Cyp26 Enzymes in Second Heart Field Addition and Ventricular Maintenance	American Heart Association	15PRE25090070	7/1/2015 - 6/30/2016	\$26,000
Ronald J Vagnozzi, PHD	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	\$56,118
Joshua Waxman, PHD	Mechanisms of Retinoic Acid Signaling Induced Congenital Heart Defects	March of Dimes	6FY14389	6/1/2014 - 5/31/2017	\$250,000
Joshua Waxman, PHD	Coup-1f Dependent Mechanisms of Ventricular and Hemangioblast Specifications	National Institutes of Health	R01 HL112893	3/1/2016 - 2/28/2018	\$344,250
Jeffrey A Whitsett, MD	Cleveland Clinic Center for Accelerated Innovations (CCCAI)	National Institutes of Health (Cleveland Clin Lerner Col of Med of CWRU)	U54 HL119810	9/26/2013 - 7/31/2020	\$21,420
Fuli Xiang, PHD	Tbx20 Function in Cardiomyocyte Cell Cycle Re-entry and Cardiac Regeneration Post-myocardial Infarction	American Heart Association	15POST22060001	1/1/2015 - 5/31/2016	\$47,000
Katherine E Yutzey, PHD	Cincinnati Children's SURF Program	American Heart Association	16UFEL27940011	2/1/2016 - 1/31/2018	\$20,000
Katherine E Yutzey, PHD	Cell Signaling Mechanisms	National Institutes of Health	R01 HL114682	8/23/2012 -	\$376,762

of Calcific Aortic Valve
Disease

6/30/2017

Total Annual Grant Award Dollars

\$7,161,163

Annual Industry Award Dollars

Investigator	Industry Sponsor	Amount
Jeffery D Molkenin, PHD	Merck & Company, Inc.	\$75,001
Total Annual Industry Award Dollars		\$75,001