2014 Research Annual Report

Heart Institute

Institute Summary

RESEARCH AND TRAINING DETAILS

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CLINICAL ACTIVITIES AND TRAINING

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Significant Accomplishments

Can the Heart Regenerate

Worms can do it, tadpoles can do it; can humans? After a heart attack, large areas of heart muscle are lost and replaced with scar tissue. Not only does this tissue not effectively pump blood, it can actively interfere with the remaining, functional muscle tissue. Researchers have been working to replace this scar tissue with new, contracting muscle grown from stem cells. Data in animal models suggest that certain types of cardiac stem cells have the capacity to regenerate damaged heart muscle. However, clinical trials so far have been controversial and the results have been mixed.

Stem cells used in most human clinical trials have been identified by a certain type of protein they produce, known as “c-kit.” Identifying stem cells for subsequent injection into humans on the basis of this marker has been widely used for the clinical trials. Jeffery Molkentin, PhD, and colleagues recently published a paper in the journal *Nature* that definitively shows that endogenous stem cells in the heart, expressing c-kit, are not a significant source for making new heart cells in the mouse. The Molkentin lab used sophisticated genetic tracing techniques to demonstrate that c-kit expressing stem cells have extremely limited capacity to make new cardiac myocytes and contribute to new, beating muscle in the heart, even after heart attack injury. These results suggest that any potential benefit of injecting c-kit cells into the hearts of human patients is unlikely to result from generation of new contracting heart tissue.

3D Heart Disease Models Help With Surgery Planning, Educating Families

During the past year, the Heart Institute developed the infrastructure and expertise to create patient-specific 3-
dimensional (3D) complex congenital heart disease models. These 3D heart models have proven to be extremely valuable to our surgical team for both patient education and pre-surgical planning. In a recent case, a 3D-printed model of a patient with interrupted aortic arch was needed to help understand the basic anatomy prior to surgery. We delivered the model to the surgeon within six hours, and the resulting pre-surgical planning ultimately changed the surgeon’s approach. The model also was used to educate the family about their child’s heart condition, providing them with additional insight into the surgical approach. We have begun tracking the impact 3D heart modeling has upon surgical outcomes. If there is a proven benefit, this would represent the first evidence to support the paradigm shift of using 3D-printed heart models for routine surgical planning.

In a related project aimed at patients, parents, and trainees, we have created “Heartpedia,” the first fully interactive 3D congenital heart disease mobile application. The initial version of this free app contains seven 3D heart models of the most common and complex congenital heart defects. Each defect also has an interactive model of the most commonly used surgical palliation. All the detailed information from the popular Heart Institute Encyclopedia website is contained within the app and it links to the recently updated Heart Encyclopedia animated videos. The primary aim of the Heartpedia app is to help patients and parents understand these defects. We hope it also helps parents share this complex information with relatives and friends. The Heartpedia app is being used clinically for counseling families about diagnoses and therapy options. It has received excellent initial reviews from parents and practitioners. The team responsible for both projects is headed by Michael Taylor, MD; and includes Peace Madueme, MD, (Cardiology faculty); Ryan Moore, MD, (Cardiology fellow); Ken Tegtmeyer, MD, (Critical Care faculty); and Jeff Cimprich (Critical Care Media Lab animator).

Community Outreach: Healthy Kids

More than 40 percent of Norwood Public School children are overweight or obese. With this in mind, we have collaborated with the school system to create the Norwood Schools Center for Better Health and Nutrition Clinic, which opened in November 2013. The clinic delivers a comprehensive pediatric weight management program directly to the students of an entire city. The clinic features the services of a pediatrician, dietitian, exercise physiologist, nurse, and social worker. These complete services are offered twice a month at Norwood High School.

The Norwood clinic is the centerpiece of “Healthy Kids Norwood,” a comprehensive initiative between Cincinnati Children’s and the City of Norwood to lower obesity rates in children. This effort has several community-based interventions, including Fun2BFit, a youth exercise program offered at the Richard E. Lindner YMCA, and Norwood Grows, an augmentation of the Woven Oak Initiative’s student gardening program. Efforts to improve nutrition and activity for Norwood Public School students include redesigning cafeteria serving strategies, cooking classes, student taste testing and 100-mile walking/running clubs. The clinic also issues a “Healthy Kids Norwood” newsletter with health information and activities for the entire community. To further these health efforts outside of school, the clinic has been working to increase the availability of fruits, vegetables and other healthy foods at the Zion Food Pantry and Lydia’s House (a residential facility for single parent families in distress). In August 2014, we also launched a pilot Norwood Farmer’s Market. All of these initiatives will be monitored closely. Once we know what the most effective approaches are, we can scale those efforts up so that more children in our region are reached.

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


89. Lorts A, Hirsch R. **Development and Recognition of Cardiopulmonary Complications in a Child with...**


104. Molina K, Denfield S, Fan Y, Moulik M, Towbin J, Dreyer W, Rossano J. Viral endomyocardial infection...
in the 1st year post transplant is associated with persistent inflammation in children who have undergone cardiac transplant. *Cardiol Young*. 2014; 24:331-6.


106. 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.


120. Ram R, Wescott AP, Varandas K, Dirksen RT, Blaxall BC. *Mena associates with Rac1 and modulates


126. 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.


Grants, Contracts, and Industry Agreements

Cardiology
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MICHELFELDER, E

**Hypoplastic Left Heart Syndrome: Expression of RHD in the Fetus?**
National Institutes of Health (Washington University)

R01 HL 098634 05/15/11-12/31/14 $34,672

TOWBIN, J

**Biomarkers in Pediatric Cardiomyopathy**
National Institutes of Health (University of Miami)

R01 HL 109090 08/06/12-07/31/16 $34,637

**Genetics, Mechanisms and Clinical Phenotypes of Arrhythmogenic Cardiomyopathy**
National Institutes of Health

R01 HL 116906 08/23/13-06/30/18 $1,858,137

URBINA, E

**Accelerated CV Aging in Youth Related to CV Risk Factor Clusters**
National Institutes of Health

R01 HL 105591 01/01/11-12/31/15 $354,654

**Early Identification of World Trade Center Conditions in Adolescents**
Centers for Disease Control and Prevention (New York University School of Medicine)

U01 OH 010394 07/01/13-06/30/16 $18,000

**Pediatric HIV/AIDS Cohort Study**
National Institutes of Health (Tulane University)

U01 HD 052104 08/01/13-07/31/15 $12,490

WEBB, G

**ACHD Conference**
Medtronic, Inc.

06/10/14-06/09/15 $10,000

**Current Year Direct** $3,100,807

Industry Contracts

BEEKMAN, R

The Johns Hopkins University $6,044

COOPER, D

Cadence Pharmaceuticals, Inc. $67,783

HIRSCH, R

AGA Medical, LLC $2,832
Lilly USA, LLC $8,701
Pfizer, Inc. $3,608
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**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

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**Current Year Direct** $6,474,506

**Industry Contracts**

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**Current Year Direct Receipts** $75,024

**Total** $6,549,530