# Emory+Children's Pediatric Research Center

A newsletter from the Children's Heart Research and Outcomes Center (HeRO)

February 2015

Issue 3



## Center Update: Mike Davis, PhD

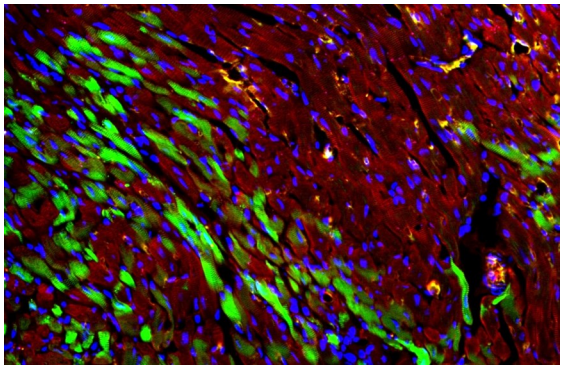
It's been another fantastic 6 months at HeRO as we continue to grow in exciting areas. We welcomed Dr. Hee Cheol Cho to Atlanta, our new Urowsky-Sahr Scholar in Pediatric Bioengineering with a generous philanthropic contribution from Janet Sahr and Todd and Amy Urowsky. We also are pleased to announce the successful recruiting of Dr. Lazaros Kochilas from the University of Minnesota. Dr. Kochilas is a world renowned clinician with an active research program in pediatric cardiology outcomes. In fact, he is only one of several investigators in the country with a major NIH award to study outcomes and will help bridge our clinical enterprise with newly formed adult congenital clinic. We received funds from the Children's Miracle Network to supplement our ongoing research efforts and fund exciting high-risk, high-reward projects. One of these projects involves the purchase of a new 3D Bioprinter. Not only can this machine print complex structures (like valves and tissues) but can also print patient cells to go within those tissues. This is an exciting area and we have projects to print new valves, tissue replacements, and possibly even model hearts prior to surgery. We are on a trajectory to be one of the finer research programs in the country and we thank everyone for their continued support.

## Welcome New Faculty: Hee Cheol Cho, PhD

Urowsky-Sahr Scholar in Pediatric Bioengineering Associate Professor, Depts. of Biomedical Engineering and Pediatrics Emory University

Hee Cheol Cho, PhD, joined the Emory+Children's Centers for Cardiovascular Biology and the Department of Biomedical Engineering at Emory University and Georgia Tech in September 2014. He received his doctoral degree in physiology and biophysics from the University of Toronto, Canada. He completed his post-doctoral fellowship in the cardiology division of the Johns Hopkins Medical Institute, and began his independent research career at the Cedars-Sinai Medical Center in Los Angeles before he arrived in Atlanta.

Dr. Cho is an Urowsky-Sahr Scholar in Pediatric Bioengineering and an associate professor in the Departments of Pediatrics and Biomedical Engineering. Cho and his team are developing innovative therapies to treat patients with abnormally slow heart rhythm. "When our heart beats too slow, we end up having electronic pacemaker devices implanted. They work, but these machines are fraught with problems." says Cho.



The team is developing 'BioPacers' which is made up of genes and stem cells, but free of hardware. They published a breakthrough study, demonstrating that a single gene can transform ordinary heart muscle cells into a BioPacer (Nature Biotech, 2013). In a follow-up study (Science Transl Med, 2014), the therapy cured complete heart block in a clinically-relevant, large animal model. Combined with stem cell-based BioPacers (Stem Cell Reports, 2014) and tissue-engineered electrical conduits (J of Am Coll Cardiol, 2014), Cho and his team are at the cutting-edge of gene- and cell-based therapies for cardiac rhythm-associated diseases.

# Cardiac Fiber Imaging Using Ultrasound and DTI

*Children's Heart and Research Outcomes Center Newsletter -Pilot Project*

Baowei Fei, PhD,
Mary Wagner, PhD
Zhang Xiaodong, PhD

Cardiac fibers directly affect the mechanical, physiological and pathological properties of the heart. Heart failure (HF) is a leading cause of hospitalization, death, and disability in most developed countries, creating a significant social and economic burden for patients, families, and health care systems. Abnormal cardiac fiber orientations such as those in heart failure patients directly affect cardiac function such as ejection fraction, and also contribute to arrhythmias that can lead to sudden death. Personalized cardiac fiber orientation mapping allows us to study the development and progression of cardiac diseases in individuals as well as provides insight into the mechanism of cardiac failure. Innovative imaging technology for early detection of heart failure can have a significant impact on the management of this disease that affects more than 5 million Americans.

Imaging and quantification of cardiac fiber orientations is a challenging task. As compared to the brain where magnetic resonance diffusion tensor imaging (MR-DTI) technology has been successfully developed to visualize brain fiber orientations, it is more difficult to directly measure the cardiac fiber orientations of a beating heart because of motion artifacts. On the other hand, cardiac ultrasound or echocardiography has become one of the most widely utilized modalities in cardiac imaging. Each year approximately 20% of enrollees in the fee-for-service system receive at least one echocardiogram. The number of echocardiography procedures by Medicare beneficiaries is 7 million each year. Echocardiography has larger patient volumes and lower costs as compared to MRI that accounts for 4% of the total expenditures for cardiac imaging. Unfortunately, echocardiography does not currently have the capability of estimating cardiac fiber orientations.

This pilot research is to develop imaging tools to measure cardiac fiber orientations based three-dimensional (3D) ultrasound. We hypothesize that cardiac fiber orientation can be indirectly estimated through the 3D ultrasound geometry of an individual heart based on a cardiac fiber atlas from MR-DTI. In this study, we are testing the hypothesis in *in vivo* beating hearts. This research is the first study that combines MR-DTI fiber atlas information with real-time 3D ultrasound to study heart failure. By adding new information on cardiac fiber orientation to widely-used echocardiography, this research will develop novel and cost-effective imaging tools for early detection of heart failure, which can have a significant impact on the clinical management of millions of patients with heart diseases.

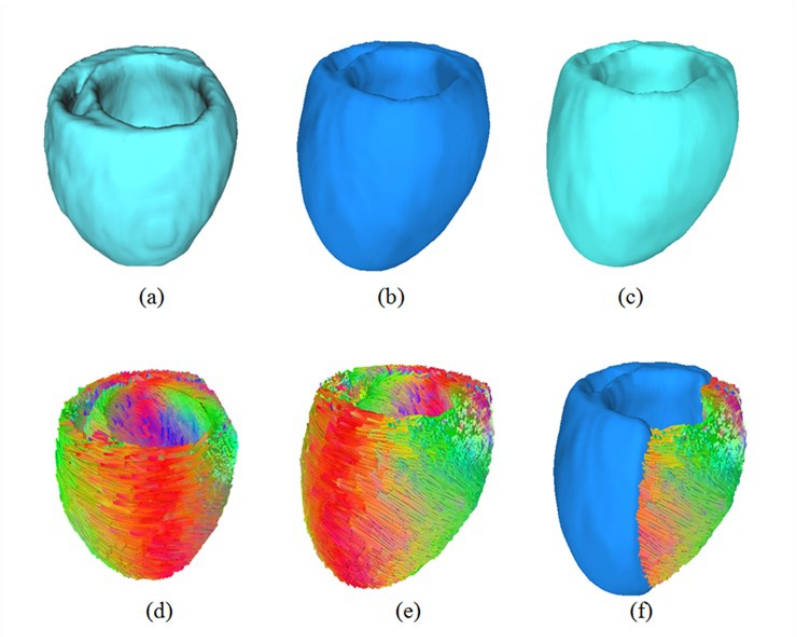



Figure 1. Mapping cardiac fiber orientations to the ultrasound volume based on the deformation field of both ultrasound and MRI volumes.

(a) The reconstructed ultrasound volume

(b) (b) The reconstructed MRI volume

(c) (c) Deformed MRI volume after image registration

(d) The cardiac fiber orientations from MR-DTI

(e) The relocated and reoriented fiber orientations based on the deformation fields from MRI to ultrasound

(f) The mapping results of both fiber orientations and the ultrasound volume

# 2015 Pediatric Research Pilot Grant Call

## Children's Heart Research and Outcomes Center Accepting Applications

Children's Healthcare of Atlanta with partners at Emory University, Georgia Tech, and Morehouse School of Medicine are pleased to offer an annual research pilot program that is aligned with the aims of the Pediatric Research Centers. These pilot award funds are designed to stimulate new research projects and build new collaborations in child health-related research areas. For questions regarding your particular area of interest, please contact the director listed for the center, or Paul Spearman, MD, Chief Research Officer and Vice-Chair for Research, Children's Healthcare of Atlanta and Emory University Department of Pediatrics.

## 2015 CALL FOR APPLICATIONS

## TO LEARN MORE, AND APPLY, CLICK HERE

***Quick Facts:***

1. ***Deadline-*** April 1, 2015, by 6pm
2. ***Funding Limit***- $50,000
3. ***Funding Term***-12 months
4. ***Eligibility*** *:*

· All proposals must include a member of the Emory Department of Pediatrics or someone on the medical staff at Children's Healthcare of Atlanta

· GA Tech-based centers (CPN, CPI and CTPHD) must also include member of GA Tech faculty

5. ***Post Award Expectations***-Must provide annual report specifying related publications, grant applications submitted and extramural funding received. Must apply for extramural funding within one year of project conclusion date.

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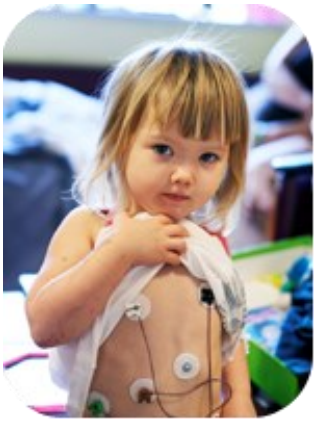
| **Children's Heart Research & Outcomes Center (HeRO)**<br><br>**Key Contacts:**<br><br>**Michael Davis, PhD**<br>**Director**<br><br>**Kristen Herzegh, MPH**<br>**Center Program Coordinator**<br><br>**Kcoshau@emory.edu** | **Children's Heart Research & Outcomes 2015 Themes**<br><br>• *Research towards enhancing the diagnosis and treatment of infants and children with pediatric heart disease.*<br>• *Developing regenerative medicine therapies and nanotechnology that will be directed toward treatment of the pediatric heart and developing new collaborations with clinicians to address critical issues in the care of children with pediatric heart disease.*<br>• *Discovering novel genes and pathways associated with pediatric heart failure.*<br>• *Better understanding of pathways that lead to cardiac arrhythmias and novel therapies.*<br>• *Improved imaging and detection of pediatric cardiovascular disease/function.* |



# Children's Receives First Grant from Enduring Hearts to Support Pediatric Heart Transplant Research

Chrissie Gallentine

Enduring Hearts, a nonprofit organization that awards operating grants to established members of academic staff at universities, transplant centers, and research institutes for research projects in organ transplantation, announced today the approval of their first research grant of approximately $25,000 to Children's Healthcare of Atlanta and Emory University. The research will focus on Chimerism of Cardiac Myocytes in a transplanted heart.

"Through Enduring Heart's research grant, we hope to gain a better understanding of the transplant recipient's contribution to a transplanted heart, which will help us identify new targets for therapies that would prolong the life and quality of these transplanted organs and the patients themselves," said Shriprasad Deshpande, M.D., M.S., Pediatric Cardiologist and Associate Director of Mechanical Circulatory System Program at Children's Sibley Heart Center and Assistant Professor of Pediatrics at Emory University.

Enduring Hearts seeks to enhance lives by funding research to increase the longevity of organ transplants. The results of the funded research projects will contribute to the knowledge about many aspects of the clinical and scientific transplantation, including the mechanisms of long-term organ deterioration, the consequence of tissue injury and the opportunities to intervene in these processes.

"Thanks to the support of everyone who believes in our cause, we are pleased to announce that Enduring Hearts is funding its first research effort to improve the long-term outcomes of pediatric transplant recipients like our daughter Mya," said Patrick Gahan, Treasurer of Enduring Hearts.

A transplanted heart is very unique in how it 'adopts' to a new body; quite unlike any other transplanted organ. The new host contributes very little to ongoing upkeep and repair of a transplanted heart. This limits to a large degree how long the transplanted organ is able to survive. The host, however, does play major role in rejecting the organ via immunologic mechanisms as well as the aging process via development of coronary blood vessel disease. "Our understanding of the host contribution to the transplanted heart is very limited and derived from some very basic studies," said Deshpande. "Here, we are attempting to answer these questions using state of art research tools."

# 2nd Annual Greater Atlanta Congenital Heart

The Congenital Heart Walk is a national fundraising event series benefitting the Adult Congenital Heart Association (ACHA) and The Children's Heart Foundation (CHF). We walk to honor and remember the millions who have been impacted by congenital heart disease (CHD).

The Congenital Heart Walk shows the nation how a team of inspired individuals can join together to make a difference. Funds raised will support the missions of both national nonprofit organizations who are uniting to fight CHD! Since 2010, CHW has raised more than $4 million in total. For more information visit, www.congenitalheartwalk.org.

**Event Information:**
When: 04/25/2015
Where: North Georgia State Fairgrounds - Jim Miller Park, 2245 Callaway Road SW, Marietta GA 30008
Time: Registration opens at 8:00 AM
Walk kicks off at 9:30 AM

Offering family friendly 1 mile and 3 mile walk routes!

Honorary Chair: Dr. Brian Kogon, Children's Healthcare of Atlanta

# Chimerism of Cardiac Myoctes in a Transplanted Heart

Shriprasad Deshpande, M.D.

Heart transplant (HT) is one of the current therapies for end-stage heart failure. Currently, around 400 pediatric heart transplants are performed throughout the North America. Roughly 15-20 pediatric heart transplants are performed at Children's Healthcare of Atlanta.

Although the early mortality after HT has improved significantly in the recent years, the long term graft survival continues to be static. The 10 year survival for adults after transplant is 55%, while it is 60% in pediatric patients. One of the main reasons for mortality is graft failure – either related to rejection or graft loss due to coronary vasculopathy. The transplanted organs appear to have an accelerated aging process. It has been postulated that some of the accelerated aging process may result in inadequate repair mechanism as well as in development of the coronary vasculopathy. The contribution of the host cells towards both these processes is unclear. Immunologic basis for cellular or antibody mediated rejection is reasonably well understood. However, the interactions between the host and the graft beyond certain immunologic processes are very unclear.

Heart is unique as it pertains to cell turnover and regeneration even as a native organ. This may be further modified when we are talking about a transplanted heart. The contribution of the host may be important because of two reasons viz. 1) as a mechanism for repair and regeneration 2) as a mechanism for injury (immunologically mediated or not) and development of coronary vascular disease and eventual graft failure.

Previous studies have attempted to look at the repopulation of cardiac myocytes after injury or transplantation. Angert et al have suggested that, after injury, cardiac progenerator cells can differentiate in to myocytes during repair process. The reserve of progenerator cells (of donor origin) is not well documented within the transplanted heart. The repair mechanism innate to the donor heart may be inadequate. Host progenerator cells are known to repopulate most of the vascular smooth muscle cells, endothelium as well as schwann cells , but not cardiomyocytes. This is based on very limited data looking at gender mismatched transplants and assessing the presence of Y chromosome positive cardiomyocytes in a male recipient of a female heart. The degree of chimerism may reflect inadequate host participation in the repair mechanisms. However, using Y chromosome signals in a gender mismatched heart transplantation is not a sensitive way of assessing cell origins and has very limited application (only in gender mismatched candidates).

Dr. Deshpande proposed a study utilizing a cutting edge methodology to assess degree of chimerism in pediatric heart transplant patients. This is a first of its kind study using a highly sensitive real time PCR technology to detect HLA markers to assign origin (host or donor ) to the cells. The methods involved isolating DNA from the pathology samples of heart from patients with rejection as well as stable transplanted heart. A qRT-PCR assay (Allele-SEQR, Celera Corp.) using bi-allelic insertion/deletion (indel) polymorphisms was used to assess chimerism in 11 pediatric explanted cardiac allografts and 11 biopsies from stable transplant patients. Pre-transplant DNA from both the recipient and the donor were screened to identify informative markers. DNA isolated from paraffin embedded tissue was then compared to pre-transplant DNA of the recipient to determine the percentage of chimerism within the allograft. Further, to analyze the source of host cells, we used qPCR to detect mRNA markers specific for cardiomyocytes (NKX2.5) and endothelial cells (VE-Cadherin) after RNA extraction using Qiagen AllPrep DNA/RNA FFPE kit.

In tissue from explanted patients, chimerism analysis revealed that the DNA was 46% (±9%) recipient compared to recipient DNA of 7% (±2%) in stable patients ($p<0.0005$). mRNA markers showed chimerism patterns were different between explanted and stable patients. Explanted samples had a cardiomyocyte : endothelial signal ratio of 16:1 compared to 3:1 in the stable sample ($p=0.061$). This increased allograft repopulation by host cells is potentially a marker of cellular injury and may represent a risk factor for graft survival. This study shows a novel application of qRT-PCR that presents a wide applicability for assessment of chimerism. Current work is focusing on further refinement of the tools to assess cellular origins of the DNA using RNA markers.
This study has been accepted for an oral presentation at the 35$^{th}$ ISHLT (International Society for Heart and Lung Transplantation) Annual Meeting and Scientific Sessions (April 2015, France).

# PEDIATRIC BIOENGINEERING RESEARCH SUMMER EXPERIANCE (PERSE)

Ten undergraduate students from across the country will once again have the unprecedented opportunity to participate in the Nation's only pediatric bioengineering program. The program is made possible due to the collaborative efforts of Emory and Georgia Tech's Biomedical Engineering Department, the Department of Pediatrics within Emory University's School of Medicine, Emory College's Summer Undergraduate Research Program (SURE), and Children's Healthcare of Atlanta. Students will have the opportunity to not only work in a lab doing Pediatric Engineering research, but also will shadow clinicians to better understand pediatric medicine.

This is one of the only training programs in the country focused solely on pediatric bioengineering. Nearly $500,000 in funding over five years will allow 10 talented undergraduate students each year from around the United States to work for a pediatric engineering project over the summer. The students also will shadow clinicians to better understand childhood diseases and receive training in scientific reading, writing, and scientific processes.

Feedback from the 2014 cohort, included below, documents the programs initial success. We look forward to continuing to establish the nation's premier program in pediatric bioengineering.

### *How did participation in PERSE change your interest in participating in MD/PhD programs?*

- It helped me further define my interest in MD/PhD programs. I had always considered taking that approach, and now I have a much more clear idea of what the PhD portion of my career would include.
- I was set on a PhD program but PERSE really made me consider MD/PhD
- It gave me real insight to clinical research, where before I was completely unaware of what the field encompasses

### *If you were to describe the PERSE program to a student considering applying, what would you tell them?*

- It is one of the best experiences one could have the privilege of attaining. The program is very well rounded and is an excellent way to invest your summer.
- PERSE is a truly unique experience in that the program encourages you to explore the interaction between science and medicine.
- PERSE is a wonderful research program in which you not only can do research in pediatric bioengineering but also shadow clinicians at the children's hospital.
- The PERSE program allows students with little previous background in bioengineering an immersive experience as a full-time member of a lab, building competency and confidence in a particular field. The shadowing component allows fellows to leave the bench to witness the compassionate care necessary for the employment and continued development of research products.
- If you are still confusing between going to MED school or being a researcher, this program will give you the opportunities to do both.

2014 PERSE Students:

Morgan Taylor, Siddhant Thukral, and Brittney Browning