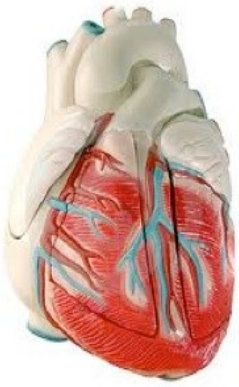
Emory+Children's Pediatric Research Center

An Atlanta-based research alliance

Children's Healthcare of Atlanta | Emory University | Georgia Institute of Technology | Morehouse School of Medicine



Center for Cardiovascular Biology

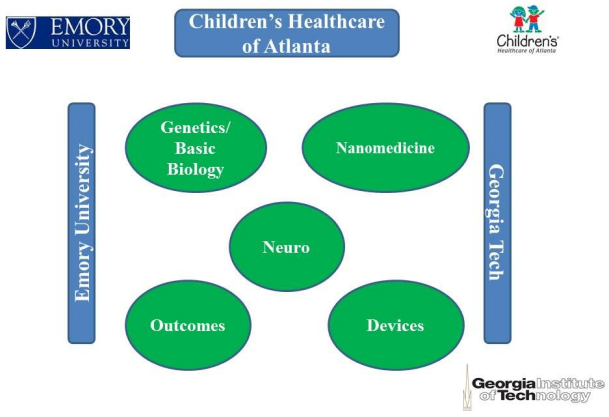
January 2014

Welcome from Dr. Mike Davis, Center Director

I would like to thank you for reading the inaugural newsletter for the Emory+Children's Center for Cardiovascular Biology.

It has been an amazing year for the Center and for Emory Pediatrics as a whole. The Emory Department of Pediatrics has jumped to 5th overall in NIH funding and Pediatric Cardiology and Surgery was ranked 4th in the recent U.S. News and World Report rankings. It is certainly cause for celebration, but also a reminder that there is room to grow and build on our successes. In this time of growth, we are pleased that Children's Healthcare of Atlanta has invested in our success. We were able to hire new faculty such as Dr. Chunhui Xu, who received funding in 2013 from the NIH and NASA to study stem cell approaches to understanding and treating pediatric heart disease. In the next 2 years, we will more than double our faculty and work harder to integrate our basic science and clinical research programs. Our focus will be to build partnerships with local institutions and to utilize the strengths in the Atlanta area to advance pediatric cardiology research. In fact, we recently received the only NIH training grant to groom the next generation of undergraduate researchers in pediatric engineering with a focus on cardiovascular medicine. This involved 3 institutions, 10 departments, and over 30 faculty members, and epitomizes the partnerships we are building to improving treatments for pediatric heart disease. We thank you for sharing in our success and hope you will support us in any way possible as we work to improve children's health.

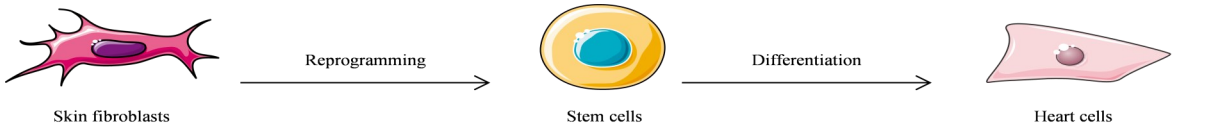
Inside this issue:

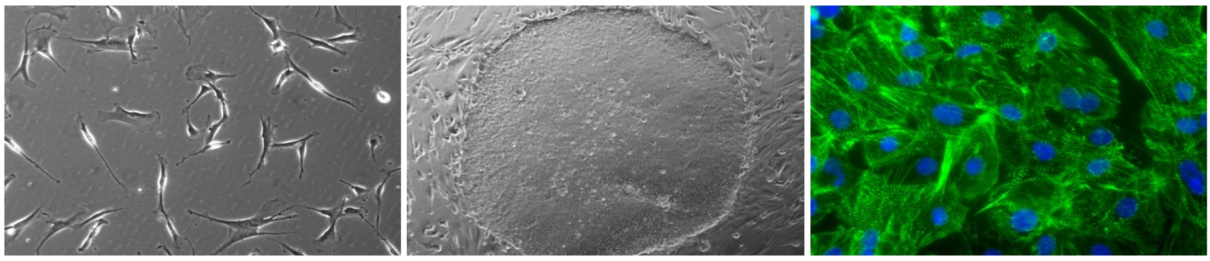


Research Hot Topics

In collaboration with researchers at Emory University, Georgia Institute of Technology, and Children's Healthcare of Atlanta, we are developing stem cell models to study pediatric cardiac diseases. Currently, we are focusing on two inherited cardiac diseases, Duchenne muscular dystrophy (DMD) and catecholamine induced polymorphic ventricular tachycardia (CPVT). DMD is the most common and devastating form of muscular dystrophies in children. Muscle weakness is the earliest and most noticeable clinical feature; however, heart problems have now become the leading cause of death in DMD patients. CPVT can lead to life-threatening arrhythmias that are often induced by physical or emotional stress in pediatric patients.

There is an urgent need to develop novel targeted therapies to treat heart problems in DMD and CPVT patients and for that purpose adequate disease models. We are trying to establish human cell models that can recapitulate cardiac phenotype using the technology of induced pluripotent stem (iPS) cells. iPS cells can be derived from skin biopsies from patients and can then be induced to form heart cells. We plan to use these heart cells to investigate mechanisms contributing to cardiomyopathy and arrhythmias and to evaluate potential therapies.





Discov Med 2013;15:349

NIH Funded Bioengineering Summer Program

Ten undergraduate students will have the unprecedented opportunity to participate in the Nation's only pediatric bioengineering program. Initiating this June, the summer program has received NIH funding for five years. The program is made possible due to the collaborative efforts of Emory University 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.

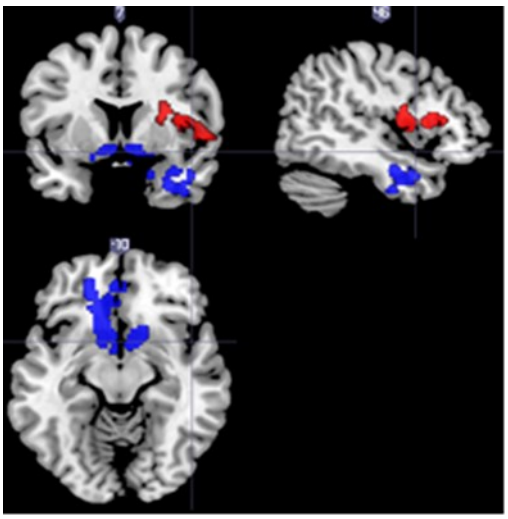
Details on the application process will be shared in March.

Research Hot Topics Continued

Emerging Adults with Congenital Heart Disease Use Brain Differently

Researchers in the Center for Cardiovascular Biology have been working together with colleagues at Georgia State University and Children's Healthcare Department of Neuropsychology to better understand the working memory of adolescents and young adults with congenital heart disease (CHD). It is known that young children with CHD may have injury to their brain following newborn heart surgery. However, it has not been clear whether this has any impact later in life. By asking emerging adults with CHD to perform memory tasks inside an MRI scanner, we have been able to show that these patients tend to "compensate" by using other parts of their brain to complete the task.

This finding, led by Dr William Mahle of the Sibley Heart Center, would support the idea that the injury to the brain that we see within the first weeks of life does have later effects. We have also demonstrated that these emerging adults with CHD do not perform as well in a number of areas including memory and attention. We hope to use these findings to design supportive strategies to enhance brain function. Functional MRI, MRI scanning done while performing mental tasks, is critical to understanding how such therapies might help.



Activation of brain area during a test of memory

Blue region- CHD patients used less

Red region- CHD patients used more

Welcome Brandon Aylward, PhD

Dr. Aylward joined the Emory+Children's Centers for Cardiovascular Biology and Neurosciences in July 2013. He received his doctoral degree in clinical child psychology with a minor in quantitative psychology from the University of Kansas. He completed his predoctoral residency program and two fellowships at Cincinnati Children's Hospital Medical Center. His research interests encompass a broad range of health-related issues for children and adolescents within the context of pediatric psychology. To this end, his work has focused on three main areas: (1) predictors and correlates of children's psychosocial, developmental, and physical functioning; (2) trends and correlates of adherence and self-management behaviors; and 3) use of advanced statistical methodology and digital health technology to examine predictors and outcomes for chronic health issues. Dr. Aylward has received a Pediatric Innovation seed grant and is currently developing a mobile platform to assist caregivers of infants with CHD with daily feeding and provide a way for caregivers to communicate with the medical team.

Research Hot Topics Continued

The Creation of a Biological Pacemaker Using Human Pluripotent Stem Cells

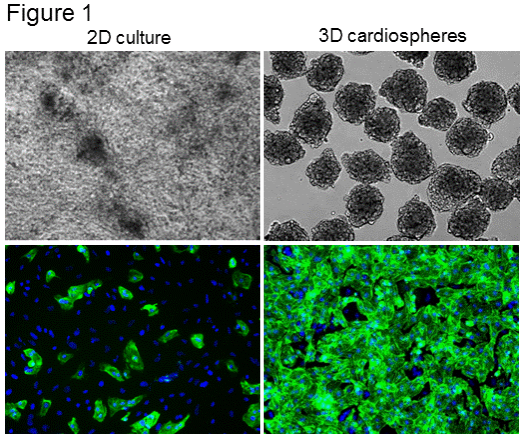
Children's Healthcare of Atlanta, Emory University, and Georgia Institute of Technology are collaborating to develop novel therapies for children with congenital heart defects, or other pediatric heart diseases, using regenerative medicine and nanomedicine technologies. One of these potential transformational projects is working to create a biological pacemaker using human pluripotent stem cells.

When the electrical signal of the heart is abnormal, cardiologists will prescribe drug therapy, or for some patients a pacemaker may be necessary. There are several conditions in children that may lead to the need of a pacemaker. These include sick sinus syndrome, congenital atrioventricular node block, and damage done to the electrical system during surgery to repair congenital heart defects. Unfortunately, there are many potential complications associated with pacemakers, especially those placed in young children.

The goal of the study is to use pluripotent stem cells to create a biological pacemaker which would; 1)alleviate the need for lead and battery replacements, 2) provide a normal electrical conduction path improving heart function, and 3) grow with the child throughout their life.

Patient skin cells would be turned into pluripotent stem cells which can then be turned into any type of cell, in this case, pacemaker cells. These cells would be implanted onto a matrix to create a biological construct one to two centimeters in circumference. This construct would be implanted into the heart via catheter to replace the natural pacemaker in the heart that is not functioning properly.

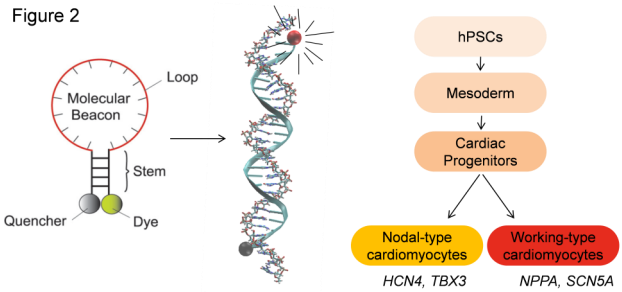
Figure 1



Drs. Xu, Wagner, Bao, and McDevitt's collaborative efforts have resulted in numerous achievements. Dr. Xu's lab is currently able to obtain cardiomyocytes differentiated from stem cells using an improved procedure based on growth factors. In collaboration with Dr. McDevitt, they have recently developed a 3D tissue engineering approach to enrich cardiomyocytes to nearly 100% purity.

Dr. Bao is utilizing molecular technology to develop a population of stem cells derived from cardiomyocytes that have a pacemaker phenotype. Molecular beacons are florescent molecules that glow when they bind to a specific molecule.

Figure 2



Recent Publications

Marching towards regenerative cardiac therapy with human pluripotent stem cells

Maher KO, Xu C.

Early postoperative bleeding is independently associated with increased surgical mortality in infants after cardiopulmonary bypass.

Wolf MJ[1], Maher KO[2], Kanter KR[3], Kogon BE[3], Guzzetta NA[4], Mahle WT[2].

Hemodynamic effects of implanting a unidirectional valve in the inferior vena cava of the Fontan circulation pathway: an in vitro investigation

Santhanakrishnan A, Maher KO, Tang E, Khiabani RH, Johnson J, Yoganathan AP.

Purification of cardiomyocytes from differentiating pluripotent stem cells using molecular beacons that target cardiomyocyte-specific mRNA.

Ban K, Wile B, Kim S, Park HJ, Byun J, Cho KW, Saafir T, Song MK, Yu SP, Wagner M, Bao G, Yoon YS

Delivery of Nox2-NADPH oxidase siRNA with polyketal nanoparticles for improving cardiac function following myocardial infarction

Somasuntharam I, Boopathy AV, Khan RS, Martinez MD, Brown ME, Murthy N, Davis ME.

Cellular encapsulation enhances cardiac repair

Levit RD, Landázuri N, Phelps EA, Brown ME, García AJ, Davis ME, Joseph G, Long R, Safley SA, Suever JD, Lyle AN, Weber CJ, Taylor WR

Acute preconditioning of cardiac progenitor cells with hydrogen peroxide enhances angiogenic pathways following ischemia-reperfusion injury

Pendergrass KD, Boopathy AV, Seshadri G, Maiellaro-Rafferty K, Che PL, Brown ME, Davis ME.

Caloric intake during the perioperative period and growth failure in infants with congenital heart disease

Nicholson GT, Clabby ML, Kanter KR, Mahle WT.

Relationship between Resource Utilization and Length of Stay Following Tetralogy of Fallot Repair

Oster ME, Dawson AL, Batenhorst CM, Strickland MJ, Kleinbaum DG, Mahle WT

Awarded Pilots

Prevention of Antibody Mediated Rejection in Cardiac Transplant Recipients
Primary Principal Investigator: Dr. Jean Kwun
Collaborators: Drs. Stuart Knechtle, William Mahle, and Malcom MacConmara

---

The Impact of Weight Loss on Arterial Health in Morbidly Obese Adolescents
Primary Principal Investigators: Drs. Luke Brewster, Mark Wulkan, and Don Giddens
Collaborators: Drs. Hanjoong Jo, Stephanie Walsh, and Ritu Sachdeva

---

Genomic Characterization of Inflammatory Response and Prediction of Clinical Outcome after Infant Cardiac Surgery
Primary Principal Investigators: Drs. May Wang and William Mahle
Collaborators: Drs. Kevin Maher and John Phan

Identification of Novel Biomarkers for Pediatric Heart Transplant Rejection
Primary Principal Investigator: Dr. Hanjoong Jo
Collaborators: Drs. William Mahle and Charles Searles

Dr. Chunhui Xu Receives CASIS Grant

The Center for the Advancement of Science in Space (CASIS), the nonprofit organization responsible for managing and promoting research aboard the International Space Station U.S. National Laboratory, has announced grant awards for seven researchers focused on non-embryonic stem cell biology. Congratulations to Dr. Xu for receiving one of the seven awards. CASIS continues to facilitate groundbreaking research through solicitations for proposals that are designed to expand the knowledge of the scientific community and advance research processes, technologies and treatments.

The winning experiments were chosen from among numerous submissions in response to the CASIS request for proposals titled “The Impact of Microgravity on Fundamental Stem Cell Properties.” Dr. Xu’s research seeks to develop small-scale tissue engineering technology for studying the growth and differentiation of cardiac tissue in microgravity-toward cardiac disease modeling, drug discovery and toxicity testing, and ultimately cell replacement therapy.

The Children's Heart Foundation

We would like to extend a warm welcome to Cherise Gunnerson, President of the Georgia Chapter for The Children's Heart Foundation. The Georgia Chapter has done a commendable job increasing awareness of CHD, as well as fundraising for research. In their first year alone they raised over $7,500.

I've heard it said that having a child with Congenital Heart Disease (CHD) is simply luck of the draw; however, I do not believe CHD's are a result of simply "bad luck."

I am a "Heart Mom." Two of my five children were born with a CHD, one is an angel and one is a survivor. My sister was also born with a CHD. As a "Heart Mom," I believe research is vital in finding a cure and in identifying the causes of CHD. I'm very excited about the lifesaving research currently underway locally and abroad that will increase the quality of life for the 40,000 children born with CHD every year around the world.

CHD is the number one birth defect in the world affecting approximately 1 in 100 births. Thanks to major advancements in the early diagnosis and treatment of CHD more children are living past their first birthday and well into adulthood. Scientists are also making discoveries connecting genetics and CHD giving us hope for our future generations.

In 2013, I founded The Children's Heart Foundation – Georgia chapter in hopes of connecting Georgia families and in support of the national organizations mission to fund the most innovative CHD research and the advancement of treatment and early diagnosis of CHD.

Please consider joining us in our efforts to support CHD research. For additional information on how you can get involved with The Children's Heart Foundation – Georgia chapter please email Cherise Gunnerson at CHFGA@ChildrensHeartFoundation.org or contact the center directly to help support our local research projects.

I would also like to invite you to join us in the first official Congenital Heart walk scheduled for Saturday, May 10, 2014 at Stone Mountain. To register, or support an existing team, please visit www.congenitalheartwalk.org

The Children's Heart Foundation Georgia Chapter is committed to bringing health, hope and happiness to children impacted by congenital heart defects. We are volunteers working to accomplish this goal by fundraising for CHD research, advocating for Georgia heart families, and promoting CHD awareness throughout the state.

Become a Center for Cardiovascular Research Member

Benefits of Membership

There are several benefits to membership in a Children's Research Center. These include:

• Eligible to have access to all Center shared resources and equipment (e.g., cores), at subsidized rates. This same benefit is available to all Emory Department of Pediatrics (DOP) faculty and Children's Medical Staff. (The project must be related to pediatric research.)

• Access to pilot project grants. Substantial resources will be available in these grants, and will be seen as a mechanism for leveraging pilot projects into full externally funded projects.

• Administrative support for program project, equipment, and other major research grant submissions.

- Numerous opportunities for interdisciplinary collaboration for grant submissions and publications, and critical inter- and intra-programmatic activities.

Categories

There are two broad categories of Center membership in the Children's Research Centers: **Primary Membership and Affiliate Membership**. In either category, extramural, peer-reviewed funding, research publications, committee membership in national research organizations, and value added to the specific Center's programmatic goals are considered in evaluating the application. At this time, membership is open to Emory University, Georgia Tech, and Morehouse School of Medicine faculty members or Children's Medical Staff. To read more about the membership categories, please click here.

Process of Membership

Membership applications should be submitted to the Director of the particular Center of interest. The membership process will be in two phases. First, Directors of the Children's Research Centers will review proposed members with their Steering Committees or similar Internal Advisory Boards, and submit names and affiliations to the Research Advisory Council of those investigators whom they deem acceptable for one of the levels of membership. Applicants are encouraged to meet with the Center Director. The Research Advisory Council will then review all members proposed by the Centers and be charged with a consistent policy of assignment as a Primary Member (full or provisional), or Affiliate Member.

Membership in a Center will be reviewed annually by the Center Director. Membership applications must be renewed every three years. Members will be required to submit a 4-page NIH biosketch (in new 2010 format) including research support information, and a paragraph describing their current research and interactions with the Center. Renewals will be reviewed first by the individual Center Directors, to guarantee that such members are actively involved in center programs and/or other activities; and then by the Research Advisory Council.

To apply for Center Membership, please click MEMBERSHIP APPLICATION