

American Heart Association and The Children's Heart Foundation Congenital Heart Defect Research Awards Second Round Recipients

Quick Facts

- Seven projects have been funded during the second round of the CHD Research Awards
- The grants total \$1,073,219
- Grant amounts range from \$40,000 to \$308,000
- Recipients are from Indiana, Ohio, South Carolina, Virginia, Washington state, two from Texas
- The total amount awarded through the CHD Research Awards since the program began in 2014 is \$1,877,035

Recipient Information

Please note: answers to the following questions have been provided by the award recipients. They do not represent the views or the science of the American Heart Association.

REAL-TIME PREDICTION OF ACUTE ARREST IN INFANTS WITH SINGLE VENTRICLE PHYSIOLOGY

Dr. Craig Rusin, Texas - Baylor College of Medicine

Award Amount - \$140,000

What is the major problem being addressed by this study?

Children with single ventricle congenital heart lesions account for 25-40% of all neonatal cardiac deaths. Between 35-50% of these kids will experience an unanticipated acute cardio-respiratory arrest event within the first months of life, and 15% will not survive. This study addresses the current inability to accurately detect the onset of acute cardio-respiratory arrest events in this population. We intend to validate a system which provides a 1-2 hour early warning notice to care team members of an imminent arrest, which would allow them to proactively respond to mitigate arrest events before they become life threatening, decreasing mortality and morbidity of these children.

What specific questions are you asking and how will you attempt to answer them?

We have developed an algorithm which can continuously assess the chance of a cardio-respiratory arrest event occurring in the next 1-2 hours in single ventricle children. Our study questions are simple: 1) How well does this algorithm work? 2) Can we improve the algorithm by using additional types of physiologic measurements? 3) How is the indication of risk generated by the algorithm related to other post-surgical outcomes? We intend to answer these questions by studying a large independent cohort of subjects at Texas Children's Hospital (one of the largest children's hospital in the world), in order to validate our algorithm, measure its performance, and correlate the results of the algorithm with patient outcomes.

What is the long-term biomedical significance of your work, particularly as it pertains to the cardiovascular area? What major therapeutic advance(s) do you anticipate that it will lead to?

This study directly impacts the mission of the AHA by creating a new clinical diagnostic tool which can be used to help prevent life-threatening cardio-respiratory arrest events in children with congenital heart defects. The predictive algorithm described in this study represents a fundamental shift in the way that these critically ill patients are monitored: a shift from reactive care to proactive care. We know that the sooner an intervention can be applied, the larger its protective effect. This translates into decreased length of stay, lower mortality and morbidity, as well as reduced cost of care for these children. The technologies and methodologies developed by this study are immediately applicable to other cardiac populations, both in the pediatric as well as adult populations.

INFORMING DEVELOPMENTAL SCREENING AND EVALUATION PROCEDURES FOR YOUNG INFANTS WITH COMPLEX CONGENITAL HEART DEFECTS

Dr. Jill Heathcock, Ohio – The Ohio State University Wexner Medical Center

Award Amount - \$148,319

What is the major problem being addressed by this study?

Babies with complex congenital heart disease (CCHD) have a heart defect that requires surgery soon after they are born. Surgeons have ways to rebuild or fix the hearts of these fragile babies allowing them to live. Now that the babies with CCHD

are surviving we know that some of them have motor or learning disabilities when they are in preschool or kindergarten. The major problem being addressed by the current study is to identify motor and cognitive disabilities in infancy, from birth to six months of age. We think that identifying disability in preschool or kindergarten is too late, and we want to do better and identify it earlier. When we identify disability earlier we can provide treatments such as physical or occupational therapy to help infants get better faster and thrive.

What specific questions are you asking and how will you attempt to answer them?

There are 3 things important to track when assessing how babies develop: motor and cognitive skills and brain development. We will measure the motor and cognitive skills of babies using clinical test that track milestones like crawling. We will test learning in the mobile paradigm, where a baby's leg is gently tethered to an overhead mobile so that when they kick the mobile moves, providing reinforcement and take pictures of the baby's brain with MRI. Since babies with CCHD have something wrong with their heart and their heart provides blood and oxygen to their brain, we also think it is important to track how their heart beats respond to learning activities and how their brain grows. We will test all of these things 3 times from birth to 6 months of age to accurately identify motor and co

What is the long-term biomedical significance of your work, particularly as it pertains to the cardiovascular area? What major therapeutic advance(s) do you anticipate that it will lead to?

It is our goal to comprehensively understand the development of learning and motor skills; how the heart beats; and how the brain develops in infants with CCDH from birth to six months of age. The results of this study have major implications to immediately advance screening and monitoring procedures, and could influence the timing of medical procedures. This project will identify disability much earlier than is currently done, thereby allowing appropriate intervention and recovery, lessening the expression of disability in one of our most fragile and vulnerable populations.

IDENTIFICATION OF GENETIC PREDICTORS OF SURVIVAL AND PATHOPHYSIOLOGIC MECHANISMS IN CONGENITAL HEART DISEASE PATIENTS

Dr. Daniel Seung Kim, Washington – University of Washington School of Medicine

Award Amount - \$40,000

What is the major problem being addressed by this study?

My research seeks to identify the genetic factors that underlie poor survival in children born with non-syndromic congenital heart disease. Despite surgical and clinical improvements over the past few decades, these infants consistently have high mortality rates (approximately 35% by 3 years after surgery). Identifying and possibly risk factors, such as which genetic pathways are involved, may allow new, targeted interventions to reduce mortality. At the same time, I seek identify specific infants at high risk of death, so that clinicians can take preventative measures in these children.

What specific questions are you asking and how will you attempt to answer them?

I have previously identified several genetic risk factors of mortality following surgery in these children with congenital heart disease. In this proposed work, I seek to build upon these results and validate them in an independent and large (~4000) cohort of children with congenital heart disease. Validation will provide compelling evidence that these genetic risk factors should be considered in the clinical evaluation of these high-risk patients and that targeting them may provide new, life-saving treatments. Moreover, I seek to identify the specific pathologic mechanisms that lead to death in these patients with a given genetic risk factor. Finally, I will identify whether there is an increase in healthcare resource utilization in these children with specific genetic risk factors.

What is the long-term biomedical significance of your work, particularly as it pertains to the cardiovascular area? What major therapeutic advance(s) do you anticipate that it will lead to?

Identification of novel genetic risk factors and validation of ones I have previously identified will provide clinicians with additional data that can be used to identify high-risk patients for more intensive follow-up and may lead to new treatments. This clinical intervention will likely decrease mortality by shifting healthcare resources to the patients most likely to suffer serious morbidity and possible mortality in the future. Moreover, identifying specific pathophysiologic mechanisms that each carrier of a genetic risk factor is most likely to suffer from will aid physicians in constructing teams of specialists better able to prevent organ-specific diseases that arise after surgery for congenital heart disease in this high-risk patient group.

HAND TRANSCRIPTION FACTORS IN CARDIAC OUTFLOW TRACT DEVELOPMENT AND CONGENITAL HEART DISEASE

Joshua Vincentz, Indiana - Indiana University-Purdue University Indianapolis

Award Amount - \$308,000

What is the major problem being addressed by this study?

The heart of an estimated 1 of every 100 newborns is affected by a potentially lethal birth defect. Of these defects, over half affect the region of the heart where blood exits the ventricles and enters the major blood vessels, called the outflow tract. The gene networks that orchestrate the development of the outflow tract are not well understood. Mutations in either of two genes that make proteins called HAND factors have been linked with cardiac birth defects. This study will thoroughly investigate how HAND factors regulate heart development in order to more broadly understand both how the outflow tract forms and what goes wrong when birth defects afflict the heart.

What specific questions are you asking and how will you attempt to answer them?

Mutations in either of two HAND factors are associated with cardiac birth defects. Within an individual cell, HAND factors work by turning on or off specific target genes, thereby controlling that cell's growth, movement, or identity. The two Hand factors are closely related, and may, in fact, target many of the same genes. Interestingly, both Hand factors are active in the developing outflow tract. Our group has generated various mouse genetic models with which to precisely study how Hand factor mutation affects outflow tract development. In addition to modeling heart defects, these mutant mice will enable us to identify target genes common to the two Hand factors. We then will assay whether reducing the amount of one Hand factor can correct the defects caused by an increase in another.

What is the long-term biomedical significance of your work, particularly as it pertains to the cardiovascular area? What major therapeutic advance(s) do you anticipate that it will lead to?

Currently, the only therapies available to correct birth defects within the heart are surgical. Both improved therapies and more sensitive methods to detect the genetic risk factors that lead to these defects require a complete understanding of the gene networks that control outflow tract development. Using the mouse models detailed in this proposal to both generate and correct outflow tract defects genetically will ultimately lead to two major therapeutic advances. First, these findings will identify novel genetic risk factors for cardiac birth defects. Second, these studies will identify genetic targets that will ultimately facilitate the development of drug therapies to correct these defects.

COAGULATION COMPLICATIONS OF CARDIOPULMONARY BYPASS (C-3PO STUDY)

Dr. Andrew Meyer, Texas – University of Texas Health Science Center San Antonio

Award Amount - \$154,000

What is the major problem being addressed by this study?

In North America, over 18,000 children and 800,000 adults each year need life-saving cardiopulmonary bypass surgery. Cardiopulmonary bypass, also known as the heart-lung machine, removes blood from the body, supplies it with oxygen, and returns it back to the body. Although the overall risk for this operation is low, the rate of post-operative clots that result in stroke or death is unacceptable. Therefore, we propose to study a new mechanism to explain the increase in risk of clots and subsequent stroke. This mechanism is the creation of small blood cell pieces (microparticles) generated by the heart lung machine used during surgery. Our research defines the potential of these pieces to promote clots.

What specific questions are you asking and how will you attempt to answer them?

Our previous studies document the generation of clot forming small blood cell pieces (microparticles) in a laboratory model of a heart-lung machine using human blood. This proposal seeks to confirm and extend these results in a clinical study of children and adults on cardiopulmonary bypass (heart-lung machine). Specifically, we hypothesize that prolonged time on a heart-lung machine will increase microparticle release that results in increased clot formation more in children than adults. We will then answer the question why children after cardiac surgery have a higher incidence of clot formation than adult patients. This information will help to power a larger multi-institutional trial to define the role of microparticles and possible interventions to decrease clots after cardiac surgery.

What is the long-term biomedical significance of your work, particularly as it pertains to the cardiovascular area? What major therapeutic advance(s) do you anticipate that it will lead to?

Overall, the potential impact of these planned studies is to progress research efforts to reduce the prevalence of life threatening coagulation complications after cardiopulmonary bypass surgery. We anticipate that our studies will establish microparticles as a sentinel marker for potential clot formation and to design clinical trials with novel therapies. Reducing the prevalence of coagulation complications during cardiopulmonary bypass will allow an increase in lifesaving heart surgery to improve all lives suffering from heart disease or stroke.

FREE-BREATHING CINE DENSE MRI OF DYSSYNCHRONY AND DELAYED ACTIVATION IN PEDIATRIC SINGLE VENTRICLE PATIENTS

Xiaoying Cai, Virginia – University of Virginia School of Medicine

Award Amount - \$51,900

What is the major problem being addressed by this study?

This proposal addresses the problem of how to assess and potentially improve treatment for patients who are born with single ventricle defects and who develop cardiac dysfunction, even after the reparative Fontan reconstruction operation. First, we propose to develop a free-breathing imaging method so that we can better image cardiac function in young subjects to quantify dyssynchronous contraction (dyssynchrony) and detect late-activating regions of the heart. Second, we propose to assess dyssynchrony and myocardial scar using the new imaging method along with the standard scar imaging protocol to investigate whether MRI can detect regions of the heart that are both late-activated and do not have scar. This study might demonstrate MRI as a powerful tool to optimize management and treatment.

What specific questions are you asking and how will you attempt to answer them?

We would like to know the severity and prevalence of cardiac dyssynchrony in single ventricle patients. First, we will develop a repeatable free-breathing strain imaging method using advanced MRI engineering. Next we will apply this technique to image single ventricle patients and quantify dyssynchrony. By using imaging both strain and scar using MRI, we will determine whether single ventricle patients have locations in their hearts that are both late activating and free of scar, as such regions would be optimal target locations for implementing advanced pacemaker devices to resynchronize the heart and improve cardiac function.

What is the long-term biomedical significance of your work, particularly as it pertains to the cardiovascular area? What major therapeutic advance(s) do you anticipate that it will lead to?

The successful completion of this work will provide improved imaging methods to quantify cardiac dyssynchrony in young subjects and potentially lead to better therapies for patients who have undergone surgical repair of congenital heart disease.

DESIGN OF FONTAN CAVOPULMONARY ASSIST USING A NOVEL COMBINED EXPERIMENTAL-COMPUTATIONAL TECHNOLOGY

Dr. Ethan Kung, South Carolina – Clemson University's College of Engineering, Computing and Applied Sciences

Award Amount - \$231,000

What is the major problem being addressed by this study?

No blood pump device has been designed to help restore the circulation of single-ventricle patients back into a normal two-ventricle configuration. The main obstacles to developing such a device are lack of understanding of how to achieve good patient outcomes, and lack of a good way to directly test the device before putting one into a patient. This research will develop an engineering technology to provide a benchtop testing environment which captures human in-vivo responses. We will then use this system to investigate a feasible surgical installation of a pump device for single-ventricle patients, and obtain a set of device operation criteria to help boost the development of such a device.

What specific questions are you asking and how will you attempt to answer them?

We would like to identify an optimal surgical configuration for a pulmonary blood pump device in a single-ventricle patient, and quantify the resulting cardiovascular improvements. We are also interested to obtain specific operation requirements of the device under various metabolic states and pathological conditions. We will develop and apply a new engineering technology to investigate the dynamic interactions and feedback between device behavior and a patient's changing cardiovascular physiology. This technology will involve benchtop experiments using a "simulated patient" with no risk to

any real patient. From these experiments, we hope to obtain critical information on how to properly design and install a pump device for single-ventricle patients.

What is the long-term biomedical significance of your work, particularly as it pertains to the cardiovascular area? What major therapeutic advance(s) do you anticipate that it will lead to?

A suitably designed pulmonary blood pump is the most promising therapeutic option for improving the quality and length of life for single-ventricle patients. Our goal is to aid the development process of such a device by providing a technology to realistically predict the device interactions with patient physiology, and use it to answer important clinical questions. A matured version of this technology also has the potential to transform the design and testing processes of a wide variety of cardiovascular devices and procedures, such as heart valves and bypass surgeries. A paradigm shift in patient management could be expected given the possibility to "try" a medical device implantation or surgical procedure for any specific patient before its actual deployment in the patient.