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THE LEADING EDGE
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Genetics of Congenital Heart Disease

Though the causes of congenital heart disease (CHD) are largely unknown, some researchers have suggested that there may be a genetic component underlying CHD. One laboratory at the USC CardioVascular Thoracic Institute (CVTI) at Keck Medical Center of USC aims to understand the genetic basis of CHD with the eventual goal of tailoring therapy to each patient's personal genetics. Among the ultimate questions that this laboratory is trying to answer are how do the genetics of CHD affect a patient's ability to respond to surgery and what other conditions (eg, neurological) are also associated with these genetic mutations.

Within this laboratory, the primary research project examining the genetic basis of CHD is the Congenital Heart Disease Genetic Network Study (CHD GENES). CHD GENES is funded by the National Heart, Lung and Blood Institute. The study is investigating the relationship between genetic factors, clinical features and outcomes in subjects with CHD.[1,2] CVTI is one of nine sites in the United States and United Kingdom participating in the consortium and is the only site in California.

For the CHD GENES protocol, clinicians collect medical history, cardiac diagnoses and blood samples from patients with CHD. Genomic DNA is then extracted from blood and analyzed in a variety of ways. A recent analysis from CHD GENES examined the genes in patients with CHD. The investigators found that children with severe CHD who had de novo mutations in chromatin-modifying enzymes were more likely to display concurrent neurodevelopmental diseases than patients with heart defects and no mutations, indicating that these mutations impair global developmental processes important in multiple organ systems.[3,4]

To understand the basis for these clinical genetic changes, CVTI investigators have launched a separate but related study

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CLINICAL TRIALS

CVTI Part of Distinguished Cardiothoracic Surgery Trials Network

In 2007, the National Heart, Lung and Blood Institute (NHLBI), National Institute of Neurologic Disorders and Stroke (NINDS) and Canadian Institutes for Health Research (CIHR) created the Cardiothoracic Surgical Trials Network (CTSN). "The mission of CTSN is to design, conduct and analyze multiple, collaborative clinical trials that evaluate surgical interventions, and related management approaches, for the treatment of cardiovascular disease in adult patients."[15]

Through the clinical trials organized by CTSN, leading cardiac surgeons, cardiologists and neurologists collaborate to evaluate current and novel therapies to treat patients with cardiovascular disease. The USC CardioVascular Thoracic Institute at Keck Medical Center of USC is proud

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MESSAGE FROM LEADERSHIP

Vaughn A. Starnes, MD

Hastings Distinguished Professor and
Chair, Department of Surgery
Keck School of Medicine of USC

Executive Director
USC CardioVascular Thoracic Institute

Dear Colleague,

The USC CardioVascular Thoracic Institute (CVTI) has built a reputation for clinical excellence, conducting groundbreaking clinical research and employing advanced medical technology. It is our mission to not only treat cardiovascular disease, but to prevent it and successfully rehabilitate those patients with a history of cardiovascular issues.

Our multidisciplinary team of physicians and staff offers advanced, patient-centered care to individuals whose health is threatened by cardiovascular disease, while our scientists are continuously pursuing research that will lead to more effective treatment and prevention therapies in the future.

This issue of The Leading Edge explores basic science and translational research in the field of cardiovascular disease. You will read about how researchers at one of our laboratories aim to understand the genetic basis of congenital heart disease. The CVTI at Keck Medicine of USC is one of nine sites in the United States and United Kingdom to participate in this research study – and the only site in California. This issue also explores cardiovascular development and regeneration in transgenic mouse models, as well as extracorporeal life support and clinical care trials.

Lastly, we are proud of our evolving cardiothoracic resident training laboratory. As we continue to train the next generation of cardiothoracic surgeons, we have incorporated cardiothoracic surgery simulation into the training curriculum and have introduced resident educational tools into the digital age. Our program is one of 27 in the United States that is accredited by the Accreditation Council for Graduate Medical Education to provide the I-6 resident training pathway (integrated pathway) and the only program in Southern California.

We look forward to many more exciting advances in medicine and research at the CVTI at Keck Medicine of USC – and we welcome the opportunity to partner with you in the care of your patients.

Cardiovascular Development and Regeneration in Transgenic Mouse Models

Through evolutionary forces on cardiovascular development, mammals lost the ability to regenerate myocardium. After a cardiac injury such as myocardial infarction (MI), a section of necrotic tissue alters the cardiac electrophysiology and mechanical performance. Currently, there is no way to treat or reverse the necrotic myocardium. Clinicians can only attempt to halt the spread of the infarct. Consequently, the patient is left with a permanent section of necrotic myocardium.

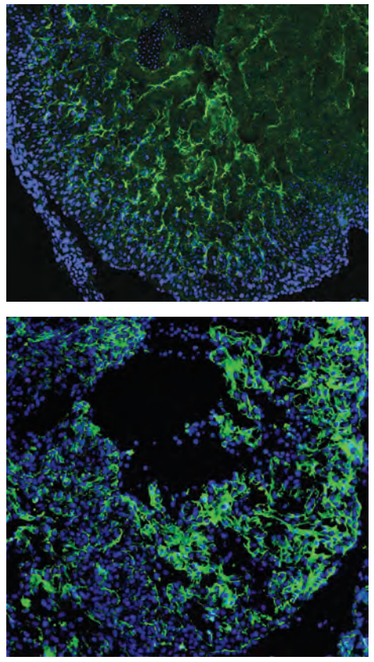
One possible solution to regenerate the myocardium after injury, such as MI, is using the developmental principles of fetal cardiogenesis. During the fetal and early newborn periods, mammals possess the ability to regenerate myocardium. The Cardiovascular Development laboratory at CVTI aims to find the cardiac physiological signals that were present during the fetal/newborn period and re-establish them to treat adults with myocardial injury.

One fetal cardiac signaling pathway that has been identified is Ephrin type-B receptor 4 and its ligand Ephrin-B2 (EphB4/EphrinB2). The Cardiovascular Development laboratory showed that EphB4/EphrinB2 proteins are crucial for developing new blood vessels and maintaining cardiomyocyte proliferation during development.[6]

In the mouse model used, EphB4/EphrinB2 were present in fetal myocardium and at post-natal day 1 (P1). At P3-4, EphrinB2 expression was no longer observed. The EphB4/EphrinB2 are highly conserved proteins and the same pathway exists in humans.

Ongoing experiments will examine if the presence of the EphB4/EphrinB2 signaling pathway can generate new, stable blood vessels and form new cardiomyocytes after MI. To accomplish these goals, the laboratory is using a transgenic mouse model to test systemic delivery of the protein products. It remains to be seen what the best mechanism is to deliver or stimulate these protein signals and if they will have the desired effect of myocardial regeneration in humans.

In the translational research phase of this project, investigators will examine samples of blood and myocardium from patients with MI to see if they show the same changes as were seen in mice when altering the EphB4/EphrinB2 pathway. If this research shows promise and can be translated to humans, possible delivery mechanisms of EphB4/EphrinB2 include protein-eluting stents, myocardial injections and systemic protein delivery. Other possible populations that this research could apply to are patients with cardiomyopathy, end-stage heart failure or peripartum cardiomyopathy.



The receptor protein EphB4 decorates the inner lining (endocardium) of the developing mammalian heart. The ligand protein EphrinB2 is expressed both in the endocardium as well as the muscle layer (myocardium) of the heart.

Transforming the Education of Cardiovascular Surgery Residents

Surgeons at CVTI have recognized the need to update and expand their modalities to train the next generation of cardiothoracic surgeons.[7] To accomplish this goal, CVTI has remodeled the resident training program, incorporated cardiothoracic surgery simulation and dedicated research time into the training curriculum and brought resident educational tools into the digital age.

Erin Nogle, USC Design Studio

Beating Heart Laboratory at the Surgical Skills Simulation and Education Center at the Keck School of Medicine of USC

CVTI is one of 27 programs in the United States that is accredited by the Accreditation Council for Graduate Medical Education (ACGME) to provide the I-6 resident training pathway and is the only program in Southern California. In the I-6 pathway, medical students apply directly to an integrated cardiothoracic surgery residency program, in contrast to both the Traditional and Fast-Track residency programs in which the medical student first completes a general surgery residency followed by a cardiothoracic surgery residency. The I-6 pathway is expected to produce highly competent cardiothoracic surgeons who are skilled and knowledgeable in topics not covered in the Traditional pathway, such as advanced imaging, perfusion and cardiology services.

The I-6 program is a six-year program and two students are accepted to the program at CVTI each year. According to the Thoracic Surgery Directors Association, the I-6 pathway aims to "provide a more comprehensive and rational total immersion in the diagnosis and management of all aspects of cardiovascular and thoracic diseases through multidisciplinary training."[8]

At CVTI, the early stages of the I-6 pathway consist of training in cardiac and thoracic surgery, acute care surgery, intensive care, cardiovascular anesthesia/perfusion, imaging, cardiology and vascular surgery. Senior residents become proficient in all aspects of complex cardiac and thoracic diseases including transplantation assist devices, minimally invasive and robotic surgery, as well as complex endovascular therapies. The I-6 pathway has recently incorporated a structured research year to familiarize trainees with the fundamentals of clinic and basic science research and ensure we continue producing thoracic surgery leaders.

In addition to the I-6 training pathway, CVTI has enhanced their resident training program with cardiothoracic surgery simulation. At Keck School of Medicine of USC, there is a virtual cardiothoracic surgery room where residents practice surgical procedures on inanimate, animate and cadaveric models. A pressurized cadaver model allows residents to dissect fresh tissue with artificially perfused vasculature.[9,10] Residents train to perform procedures, including placement of an intra-aortic balloon pump, coronary artery anastomosis, minimally invasive mitral valve replacement and temporary mechanical support.

Another pillar of the enhanced resident training program is the newly developed cardiothoracic surgery educational platform. In 2008, the director of resident education at CVTI became involved with the Joint Council of Thoracic Surgery Education to reshape the educational paradigm in cardiothoracic surgery residency. The director was one of the leaders developing a new platform to deliver all educational content to the residents electronically. From this platform, all of the educational content is accessible from a desktop computer, mobile device or an e-learning platform. With these enhancements to the training program, residents receive important early essential skills training and ultimately progress to become highly competent cardiothoracic surgeons.

Extracorporeal Life Support Increasingly Used for Hemodynamic Support

Historically, extracorporeal life support (ECLS) was used as an adjunct therapy for children facing cardiovascular and pulmonary failure. Recent advances in equipment and perfusion protocols for ECLS have expanded the therapy to be useful for adults. As the patient criteria for ECLS candidates have evolved, there has been an accompanying improvement in patient outcomes and increased survival.

Traditionally, patients who need acute hemodynamic support are treated with one or more therapies including intravenous inotropes and vasopressors, intra-aortic balloon pumps (IABP), percutaneous ventricular assist devices, advanced mechanical ventilatory support (eg, bi-level and airway pressure release), neuromuscular blockers and nitric oxide.

ECLS is considered when the patient is judged as having a 50 percent mortality risk, and ECLS is indicated in most circumstances when the patient has an 80 percent mortality risk without the therapy.[11] For patients receiving it for cardiac reasons, ECLS can be a bridge to recovery, transplant or implantable circulatory support depending on the patient's condition and status.[12] A randomized study of patients with acute respiratory distress failure showed that those receiving ECLS had improved survival compared to those receiving standard ventilatory support.[13]

A retrospective analysis of patients treated with ECLS at CVTI showed that patients received a median of six days of ECLS and were most often treated with veno-arterial extracorporeal membrane oxygenation (ECMO). Overall, 45 percent of patients treated with ECLS survived to be discharged from the hospital. Most patient deaths were attributed to infection, pre-ECLS neurological injury or failure to qualify for more permanent advanced therapies (eg, heart/lung transplant or durable VAD).[14]

Moving forward, investigators at CVTI are developing a risk assessment tool to help determine which patients are good candidates and would likely benefit from ECLS.

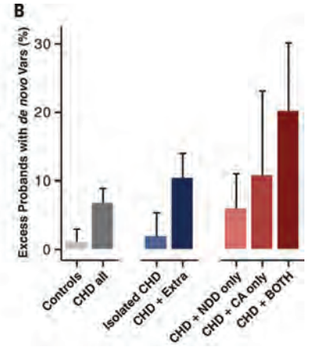
WHEN IS A PATIENT A CANDIDATE FOR ECLS?

- Patients with cardiogenic shock (after myocardial infarction or cardiac surgery); acute respiratory distress syndrome; cardiomyopathy; arrhythmias, massive hemoptysis; saddle pulmonary embolus.
- Patient exhibits severe hypoxia or hypercapnia despite maximal ventilator management.
- Patient has ongoing hemodynamic compromise despite 2+ inotropes or balloon pump or percutaneous VAD.
- Early referrals for ECLS can increase the chances for a positive outcome for the patient.

Genetics of Congenital Heart Disease

Continued from page 1

to examine how mutations in Tri-Methyl-Histone 3 Lysine 4 (H3K4me3), one chromatin-modifying enzyme, contributed to heart disease in the avian heart. In this study, researchers found that H3K4me3 was missing from the epicardial layer during early cardiac development. In addition, the presence of a functional H3K4me3 pathway was necessary to make the epicardial-to-mesenchymal transition (EMT).[5] One hypothesis is that the mutation in the H3K4me3 pathway leads to CHD by preventing EMT and subsequent cardiac development. Future studies along this line of experimentation may examine if drugs that modify methylation of H3K4 can impact CHD.



Burden of damaging de novo mutations in HHE genes among CHD cases with extra- cardiac phenotypes. Percent excess of individuals carrying damaging de novo mutations in HHE genes by indicated phenotype (±95% confidence interval). From "De novo mutations in congenital heart disease with neurodevelopmental and other congenital abnormalities." Reprinted with permission from AAAS.

CLINICAL TRIALS

Continued from page 1

to be one of only 10 institutions in the United States and Canada designated as a Core Clinical Center within CSTN.

CTSN has sponsored 10 past and current clinical trials. Two major trials were recently completed. A study with patients undergoing mitral-valve repair or replacement for severe ischemic mitral regurgitation showed no significant between-group difference in left ventricular reverse remodeling or survival at two years. Mitral regurgitation recurred more frequently in the repair group, resulting in more heart-failure–related adverse events and cardiovascular admissions.[16] A study of patients with atrial fibrillation who are managed by either a rate control or a rhythm control strategy showed that both treatments were associated with similar length of hospital stay, similar complication rates, and similar rates of persistent atrial fibrillation.[17]

Current interventional trials in CTSN will examine the efficacy and safety of embolic protection devices to reduce ischemic brain injury in patients undergoing surgical aortic valve replacement (AVR) [NCT02389894]; the benefit of concurrent tricuspid valve repair during mitral surgery [NCT02675244]; and stem cell injections during a VAD procedure.

A previous clinical trial with a small population examined the injection of stem cells into the myocardium during implantation of a left ventricular assist device (LVAD).[18] Results from this study of 30 patients demonstrated that patients receiving the mesenchymal precursor cells (MPCs) tolerated more temporary weans from the LVAD compared to the control group. Serious adverse event rates at 90 days and 1+ year were similar between the group receiving MPCs and

The follow-up to this study is a randomized, controlled, double blinded study of 120 patients to examine the injection of stem cells at the time of LVAD implantation [NCT02362646]. Investigators at CVTI have enrolled two patients in the current clinical trial and hope to finish enrollment by the end of 2016. CVTI is the only program in Southern California serving as a study site for the stem cell/LVAD study and one of only two in California.

For questions about the CTSN clinical trials that are being conducted at CVTI, please contact our research office at (323) 442-5849.

CASE STUDY

"Technically, I died three times." That is how John Nordblad summarizes his condition that concluded with a five-day ECLS treatment at Keck Medical Center of USC. Nordblad, an active 54-year-old with a prior myocardial infarction and placement of two coronary artery stents, was in generally good health when he had an acute MI in June 2015 while participating in a motorcycle race in Big Bear, California. Nordblad was transported to a local hospital, where he rapidly deteriorated into acute cardiogenic shock. The medical staff replaced the two existing coronary stents and placed a third stent in the circumflex artery. Several days after the procedure, Nordblad was extubated briefly but was re-intubated due to cardiorespiratory failure.

After it was apparent that the existing treatment was not sufficient and that Nordblad's condition was further deteriorating, he was transferred to Keck Hospital of USC. Upon arrival, the staff at Keck Hospital of USC determined that Nordblad was hemodynamically unstable and had severe myocardial hypokinesis. Despite maximal ventilatory support, he continued to have refractory hypoxemia. Pulmonary angiography revealed bilateral massive pulmonary emboli, which were treated with tissue plasminogen activator. After placement of an intra-aortic balloon pump failed to improve the hypoxemia, CVTI physicians decided to treat Nordblad with veno-arterial ECMO. Immediately after implementing ECMO, Nordblad's condition rapidly improved, with stabilized hemodynamics and oxygenation, and he was weaned off of ECMO after five days. Today, Nordblad is running his own full-time construction business and is comfortable doing the same physical activities as previously. He notes that the contributions of all the nurses and physicians at Keck Hospital of USC made a huge difference in his recovery.

John Nordblad with wife Susan Nordblad

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