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SCCOR Grant Supports Extensive LVAD Research

$17 million will fund multiple studies addressing the biology of long-term mechanical support and the major limitations of Left Ventricular Assist Devices (LVADs).

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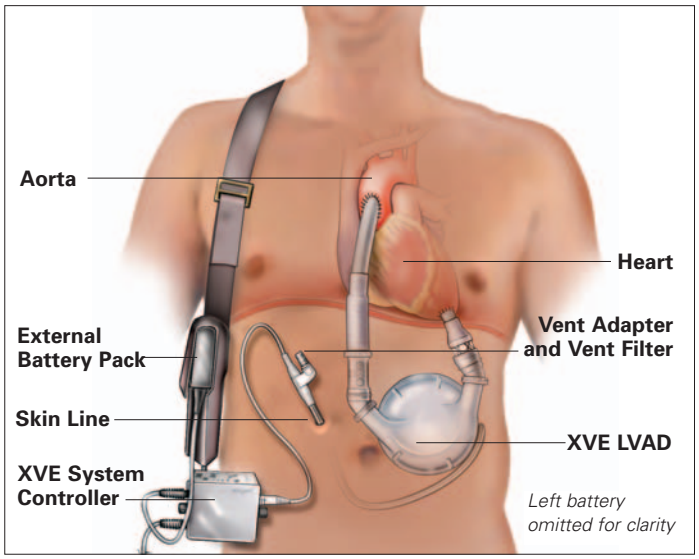

Having proven the benefits of Left Ventricular Assist Devices (LVADs) in prolonging the lives of non-transplantable end-stage heart failure patients, the landmark REMATCH trial, directed by Principal Investigator Eric A. Rose, MD and the International Center for Health Outcomes and Innovation Research (InCHOIR), resulted in the historic FDA approval and Centers for Medicare and Medicaid Services (CMS) reimbursement for the devices. Since CMS approval in 2003, more than 150 LVADs have been implanted as destination therapy and more than 500 as bridge-to-transplantation (BTT). With better reimbursement rates now in place, that number is expected to rise. Yet while implantation of mechanical circulatory support devices is becoming standard practice as BTT, long-term "destination" therapy remains problematic due to serious adverse effects. Its life-saving potential notwithstanding, implantation of LVADs remains an invasive, demanding mechanical therapy, with significant risks of infection, bleeding, neurological complications, and device failure.

Awarded to the Columbia University College of Physicians and Surgeons in March 2005, a $17 million NIH grant will fund multiple basic and clinical studies to address these problems, with the goal of transforming LVADs into a safer and more widely accepted therapy. "These improvements will benefit heart failure patients and make the therapy more cost-effective," according to Annetine C. Gelijns, PhD, and Alan J. Moskowitz, MD. This landmark project will include patients with advanced heart failure who receive LVADs as bridge-to-transplantation, destination therapy, and bridge to recovery.

The Specialized Centers of Clinically Oriented Research (SCCOR) is a program funded by the NHLBI to foster translational research in order to improve prevention, diagnosis, and treatment of particular diseases. When the Columbia investigators submitted their application in 2003, they received the highest score from among all applicants, and this grant represents the largest ever awarded in the field of mechanical circulatory support. "Because NewYork-Presbyterian/Columbia has such a strong program for heart failure and transplantation, it is natural that it would be a primary center for implantation of ventricular assist devices, and a central research institution in the field of mechanical circulatory support," says Mario C. Deng, MD.

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SCCOR Grant Supports Extensive LVAD Research

Realizing the potential of mechanical circulatory support devices will require overcoming a host of challenges, according to the NewYork-Presbyterian/Columbia team. "We encourage our collaborating physicians to refer patients early for evaluation of options, including mechanical circulatory support," says Dr. Deng.

When used as bridge-to-transplantation, usually 90 days on average, current pumps are reasonable," explains Deborah D. Ascheim, MD. "For this duration, they are very reliable, and the infection rate is low. For destination therapy, however, pumps must become more reliable and have lower risks." During each year of implantation, patients with LVADs as destination therapy may experience the following rates of serious adverse effects:

- 20-40% of patients suffer sepsis
- 56% experience a serious bleeding event requiring hospitalization
- 39% undergo neurologic complications such as stroke or TIA
- 39% experience infection of a single organ
- 25% suffer renal failure
- 14% endure a peripheral embolic event
- 12% develop a supraventricular arrhythmia

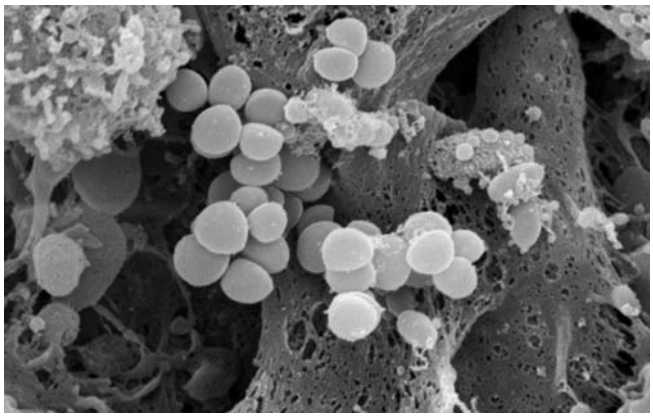
In addition to these events, the rate of LVAD malfunction increases over time, which is less relevant for the BTT population, but clearly important when the devices are used for destination therapy, according to Dr. Ascheim.

The SCCOR program will simultaneously investigate the most serious adverse events – infection, coagulopathy, and neurological events – and will seek to improve myocardial recovery with the goal of early removal of the device (avoiding long-term therapy). Seven other institutions, members of the network of heart failure centers of excellence that investigated the clinical values of destination LVAD therapy in the REMATCH trial, will participate as collaborating clinical sites. At the same time, additional collaboration with industry-sponsored trials will facilitate the development of the next generation of devices using continuous flow technologies. This technology will facilitate further miniaturization of the devices, expects Dr. Gelijns. According to Michael Parides, PhD, "The SCCOR program represents a critical opportunity to develop innovations that we hope will lead to significant improvements in device performance in the near future."

The following sections describe the three main research projects.

Infection Research

Staphylococcal infection is one of the leading causes of death among long-term LVAD recipients. Of all LVAD recipients, 20 – 40% develop infections at some time, ranging from driveline infections to sepsis. Under the direction of Frank Lowy, MD, and in collaboration with Drs. Yoshifumi Naka, Mario Deng and Kung-Ming Jan, the infection research project includes a series of complementary laboratory, clinical, and epidemiological studies



Staphylococci adhering to an explanted LVAD membrane.

designed to understand the process by which staphylococcal infections develop in LVAD patients.

One laboratory study will examine the way in which proteins on the surface of staphylococcal bacteria adhere to the inner membranes (blood contacting surfaces) of LVADs. This study will help explain why staphylococci are able to cause these life-threatening infections. By examining the membranes of devices after their removal from patients' bodies, the team is working to define the role that different proteins play in the adhesion process. "We have looked at twelve surface proteins so far," explains Dr. Lowy. "Three of these seem to be most likely responsible for adhesion to the LVAD membranes." Having done extensive research on explanted membranes, Dr. Lowy believes that clumping factor and fibronectin binding protein are the most likely culprits. He adds, "Moreover, the binding process changes over time, and we plan to find out why."

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Coagulation Research

Although the outer lining of LVADs is designed to mimic the natural endothelium, implantation of the device nevertheless causes activation of the body's coagulation pathways, frequently leading to serious bleeding episodes, thrombosis, and stroke. Researchers believe that immediately after bypass, the device stimulates intravascular coagulation: "Naturally protective clotting factors are rapidly consumed, and this creates an imbalance," describes Ann Marie Schmidt, MD. To date, physicians have wrestled with the question of whether to prescribe anticoagulant drugs (heparin or coumadin) to LVAD patients, weighing their presumed benefits against the risks of consumptive coagulation.

In SCCOR's coagulation project, investigators are seeking to develop an optimal anticoagulant that can both reduce thrombosis at the time of device implantation and prevent late bleeding events. Such a targeted agent would maintain intravascular anticoagulation while reducing extravascular bleeding by selectively blocking only the intrinsic pathway of the coagulation cascade.

Dr. Schmidt and colleagues have already proven that this goal can be achieved by selectively blocking Factor IX in the procoagulant pathway. The molecule they developed, Factor IXai, worked extremely well in earlier patient trials. Because Factor IXai is a large molecule, however, development as a clinical agent is too complex and expensive to permit competition with cheaper agents such as heparin. Another option had to be found.

In collaboration with Dr. Schmidt's laboratory, Transtech Pharma turned to the development of a small molecule inhibitor of Factor IX. The resulting product, called 889, has proven successful in phase 1 human trials. Like the large Factor IXai molecule that preceded it, this smaller version selectively blocks Factor IX in the clotting cascade while leaving Factor X unaffected. Moreover, 889 is inexpensive to produce and is even orally bioavailable.

"In the SCCOR protocol, we will test the hypothesis that blocking Factor IX will reduce the process of consumptive

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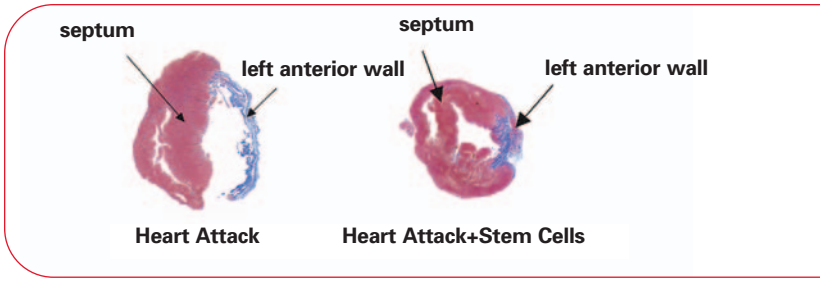
Cell Transplantation Research to Improve Myocardial Recovery

The goal of this project is to stimulate healing of the native heart so that LVAD implantation can potentially be used as a bridge to recovery rather than as a bridge to transplantation or left as long-term destination therapy. While some experts believe that unloading the heart with mechanical assistance may allow the heart to recover, in fact relatively few patients (less than 10%) experience sufficient myocardial recovery to permit explantation of the device. Yet if the heart could regain enough of its ability to contract, patients would be spared the adverse effects associated with long-term circulatory support or transplantation.



The left hand panel demonstrates a representative rat heart that has undergone an experimental heart attack. The red depicts viable heart tissue and the blue represents dead heart tissue that has been replaced by scar. In contrast, in the panel on the right the animal has received stem cells, resulting in far less dead heart tissue and translating into an improved heart function and prognosis for long term survival.

Led by Silviu Itescu, MD, the cell transplantation project will seek to find ways of regenerating the heart while the LVAD is in place to support heart function. His team will compare the efficacy of transplanting patients' own hematopoietic precursor cells, termed angioblasts, with mesenchymal precursor stem cells (MPCs). Both human angioblasts and human MPCs have been shown to avert heart failure in rodents by preventing the development of large scars after myocardial infarction.

"Both cell types were active in initial animal studies," says Dr. Itescu. "However, we think MPC precursors will be more

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SCCOR Grant Supports Extensive LVAD Research

Infection Research CONTINUED FROM P.2

A second laboratory study will examine the ability of staphylococcal bacteria to bind to host surfaces under different flow conditions. By identifying a) the staph aureus surface molecules and b) components of the LVAD membrane cellular matrix that mediate adhesion, Dr. Lowy's team hopes to be able to reduce adhesion of the bacteria to the device surface membrane.

In a third study, the researchers will study the ability of various staphylococcal proteins to mediate adherence to an implanted aortic LVAD patch in a mouse model of infection.

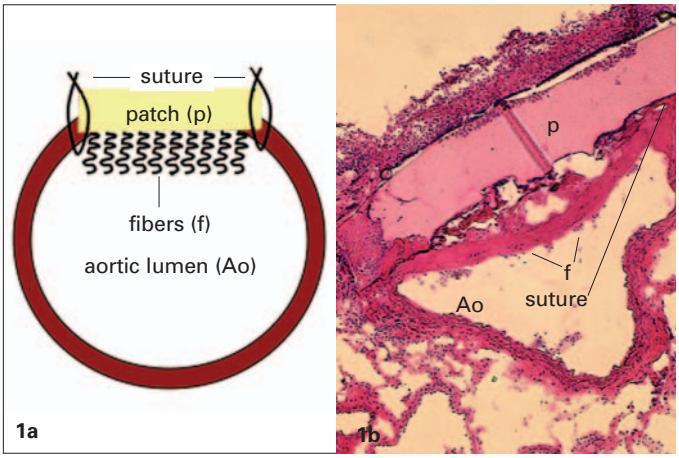

Figure 1a: Cross-section of mouse aorta with patch sutured into it. Figure 1b: Live cross-section of mouse aorta with patch. During the four-week period after implantation, endothelial cells cover the patch, mimicking the clinical situation.

They will inject protein expressed on the surface of a nonpathogenic bacterial species, and then determine if it enables the bacteria to infect the patch.

Clinically, Dr. Lowy's team will oversee a multicenter, randomized, double-blind, placebo-controlled trial of an anti-staphylococcus vaccine under development by Nabi Biopharmaceuticals. Evaluating the effect of the vaccine in reducing infection during LVAD implantation, this is the first anti-staph aureus vaccine to have progressed this far in research. The vaccine appeared promising in an earlier study among dialysis patients.

A second multicenter, randomized, double-blind, placebo-controlled clinical trial will test a topical ointment that eliminates nasal staph aureus. "People who carry staph aureus in the nose have a higher risk of developing infection after LVAD implantation," explains Dr. Lowy. "Our hypothesis is that if we eradicate nasal carriage prior to implantation, we can reduce the risk of infection."

Finally, a molecular epidemiological study will survey patients' normal bacterial skin flora to try to determine if bacteria already present are causing the infection, or if patients become colonized with new bacteria in the hospital during LVAD implantation.

Says Dr. Lowy, "We hope these studies will address some of the fundamental questions about the pathogenesis of these infections, and the clinical trials will provide new approaches that are non-anti-microbial based. Since there is so much bacterial resistance (due to antibiotic use), it is better to prevent than to treat infections later." ■

Cell Transplantation Research to Improve Myocardial Recovery CONTINUED FROM P.3

effective in human trials because they produce larger caliber arterioles and have a greater impact on functional cardiac recovery than angioblasts, which produce small-caliber capillaries." Additional theoretical advantages of using MPCs are direct regeneration of new heart muscle, and the potential for allogeneic use since they are not recognized by the immune system of unrelated individuals.

While angioblast isolation can be performed today using existing FDA-approved technologies, Dr. Itescu and colleagues are working to optimize the process of MPC isolation and culture to meet Good Manufacturing Process (GMP) standards in order to obtain FDA approval for this component. Consequently, the cell therapy clinical protocol will be staged sequentially to take into account the FDA approval process: the initial series of patients will receive the FDA-approved angioblasts, and on receipt of FDA approval for the MPC isolation and culture process, the subsequent series of patients will receive MPCs. Autologous cells will be obtained by bone marrow biopsy at the time of LVAD implantation, and either angioblasts (initially frozen) or culture-expanded MPC will be injected into the myocardium of the

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Leadership of the SCCOR Grant

Eric A. Rose, MD, who was Principal Investigator of the REMATCH trial, serves as Principal Investigator of the SCCOR grant. Dr. Rose is Associate Dean for Translational Research at Columbia University Medical Center. Co-Principal Investigators are Alan Moskowitz, MD, and Mario Deng, MD. Dr. Moskowitz directed the Clinical Coordinating Center for the REMATCH trial and is Co-Director of InCHOIR. Dr. Deng is Director of the Mechanical Circulatory Support Device (MCSD) Database of the International Society for Heart Lung Transplantation, and Director of Cardiac Transplantation Research at NewYork-Presbyterian/Columbia.

Leadership of individual projects

Coagulation research: Ann Marie Schmidt, MD and Les Miller, MD

Infection research: Frank Lowy, MD and William Holman, MD

Cell Transplantation and Myocardial Recovery: Eric A. Rose, MD and Silviu Itescu, MD

Animal Research Laboratory: Yoshifumi Naka, MD and Jonathan Chen, MD

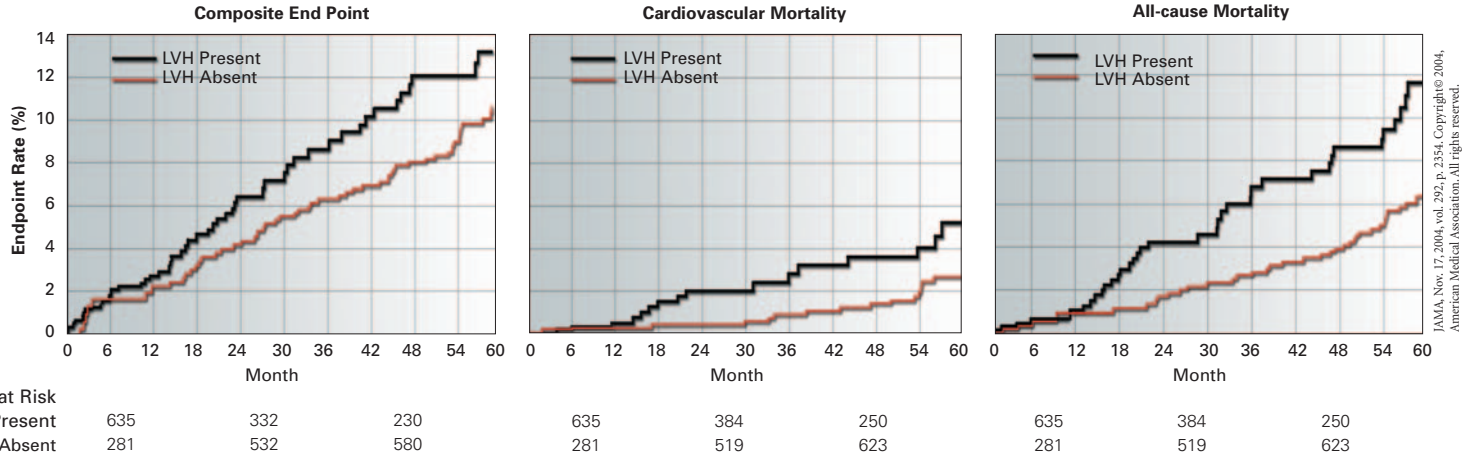
Clinical Materials: Daniel Fink, MD

Neurosciences: Ronald Lazar, MD

Clinical Trials, Data Management and Statistics: Annetine Gelijns, PhD, Deborah Ascheim, MD, and Michael Parides, PhD

Reducing Left Ventricular Hypertrophy

Weill Cornell researchers provide conclusive evidence that reducing left ventricular hypertrophy reduces fatal and non-fatal cardiac events.



JAMA, Nov. 17, 2004, vol. 292, p. 2354. Copyright© 2004, American Medical Association. All rights reserved.

Composite endpoint, cardiovascular death, and all-cause mortality stratified by time-varying presence of echocardiographic left ventricular hypertrophy.

It is well established that long-term increases in the mass of the heart muscle strongly predict myocardial infarction (MI), stroke, heart failure, atrial fibrillation, and other cardiac events. Until recently, however, there was no conclusive evidence that reversing or reducing this increased heart mass — termed left ventricular hypertrophy (LVH) — is clinically beneficial. In the absence of strong evidence that alterations in ventricular mass could directly benefit patient outcomes, LVH has not been considered a specific target for therapy, but has been used rather as a marker to identify patients at risk.

During the design phase of the *Losartan Intervention for Endpoint Reduction in Hypertension* (LIFE) study in 1995, Richard B. Devereux, MD, Peter M. Okin, MD and co-investigators hypothesized that reductions in ventricular mass during treatment for hypertension would provide a better predictor of patients' prognoses than reductions in blood pressure, and independent of treatment measures. As the study results show, their hypothesis proved true.

As reported in the *Journal of the American Medical Association* (JAMA) in November 2004, the LIFE study compared losartan and atenolol in reducing cardiac events (cardiovascular death, MI or stroke) among more than 9000 patients with hypertension and electrocardiographic LVH. Serial measurements of left ventricular mass were made by echocardiography and electrocardiography throughout the study period.

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During the past decade, Dr. Okin has been instrumental in the development of better electrocardiographic criteria to improve utility of the ECG. "We found that specific voltages in ECG leads were strongly and independently associated with the amount of heart muscle present," he explains. Having determined that two voltages and QRS duration were strong, measurable indices of left ventricular mass, he combined them to yield the improved ECG, today commonly called the "Cornell voltage duration product."

In the LIFE trial, a subset of patients underwent echocardiography (direct visualization of anatomy) and all patients underwent electrocardiography (measurements of QRS voltage) at regular intervals. Lower ventricular mass detected by both methods were associated with reduced morbidity and mortality in the study population. Measurements obtained by echocardiography proved significantly more effective, however, in detecting about 90% of cases of LVH (as compared with only about 50% detected by electrocardiography). Given the strength of these results, "we have gone directly back to weighing the heart muscle as our reference standard," explains Dr. Devereux.

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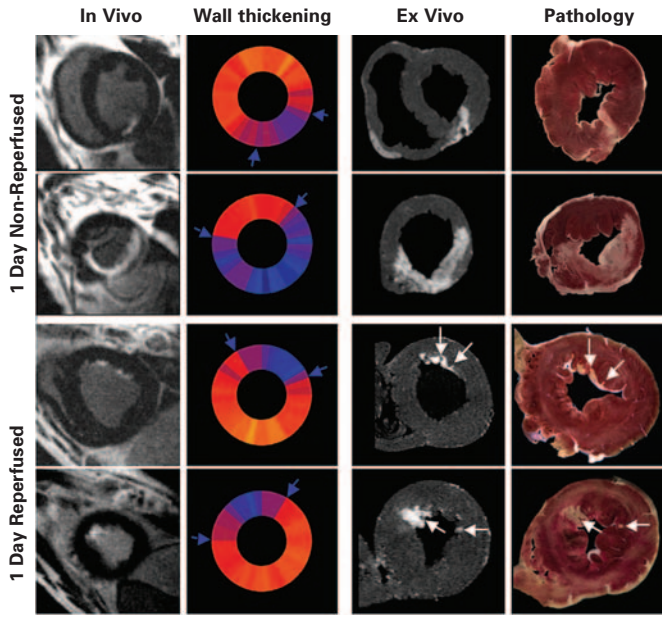
Advances in Cardiac MRI

Latest technology can distinguish reversible from irreversible injury after heart attack, and predict success of revascularization therapy.



In the above animal study, both in-vivo (column 1) and ex-vivo (column 3) magnetic resonance images demonstrate a close correlation between hyperenhanced (white) areas on MRI and infarct on pathology specimens (column 4). *Wall thickening scale:* orange = normal contractility; red = hypokinesis; blue = akinesis. In spite of many areas of abnormal wall thickening, substantial viability persisted.

If cardiac tissue remains viable after myocardial infarction (MI), revascularization through angioplasty or coronary artery bypass surgery can markedly benefit patients. If the heart muscle is unsalvageable, however, revascularization will not help. Until recently, limitations to the conventional tests have meant that in up to one third of cases, it was not possible to determine in advance whether therapy would be beneficial.

In just the last five years, however, advances in cardiac MRI have begun to revolutionize cardiac imaging, and may well establish a new gold standard in diagnosing heart disease and predicting response to therapy. Improvements in the technology, notably scanning speed and image resolution, have made it possible to now capture precise, extremely well-defined images of the beating heart. The result — unsurpassed diagnostic and prognostic information in a single, non-invasive test. For high-risk patients or in cases where the state of the heart muscle is questionable, this offers compelling advantages.

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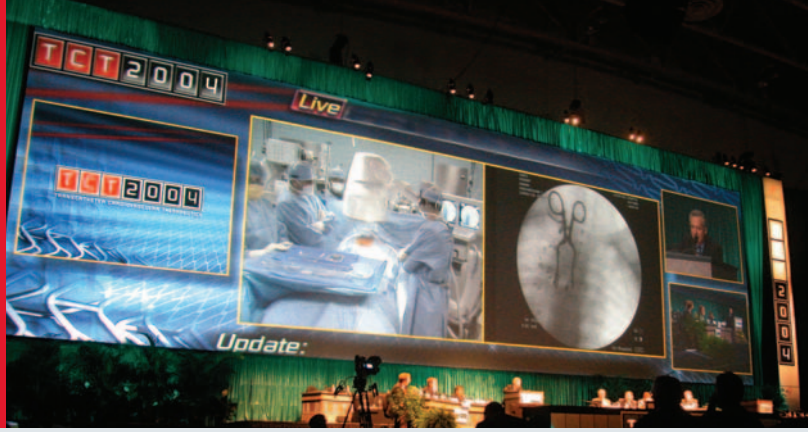
"Cardiac MRI technology blends high-resolution imaging of cardiac function with very detailed tissue characterization," says Jonathan W. Weinsaft, MD. "This is the first technology that shows the muscle of the heart in a way that provides sensitive definition of tissue changes." By detecting specific characteristics in the muscle condition, cardiac MRI has been shown to be useful in predicting therapeutic benefit for high risk patients being considered for coronary revascularization. By differentiating living from dead tissue, cardiac MRI provides the clearest measure of tissue viability available today. "Compared to other technologies, cardiac MRI is better able to predict how patients will fare after MI, and how well they will respond to angioplasty and other therapies," according to Dr. Weinsaft. For high-risk patients who might otherwise be considered ineligible for revascularization, but who in fact have viable tissue, the use of cardiac MRI could easily mean the difference between receiving a life-saving procedure or not.

Emerging research also suggests that cardiac MRI may be useful in identifying heart failure etiology for patients with suspected amyloidosis, hemachromatosis, idiopathic nonischemic cardiomyopathy, sarcoidosis, valvular heart disease, and otherwise unexplained causes of heart failure.

Despite the expense of the equipment, many physicians believe that cardiac MRI is a cost-saving tool because a single exam can predict both identify etiology and predict response to therapy. "In one exam, we can obtain information about cardiac function, about the left and right ventricle, valvular function, stenotic and regurgitant valves, flow or shunting in patients with congenital heart disease, ischemia and prior infarction in patients with coronary artery disease… One test provides information that would otherwise require a number of procedures," says Dr. Weinsaft. In addition to being non-invasive, cardiac MRI does not require the use of any radioactive tracers.

Because the technology is relatively new, and because it requires a high level of training and collaboration between academic divisions, Weill Cornell is one of only several dedicated cardiac MRI centers in the U.S. today. Having participated in numerous studies on the prognostic efficacy of cardiac MRI, Dr. Weinsaft has recently joined the faculty at Weill Cornell and is contributing to the center's clinical and research activities. "Weill Cornell offers a very diverse patient population, committed academic investigators, and an outstanding tradition of clinical research, all of which are essential components needed to make ongoing advances in this exciting area of non-invasive cardiovascular imaging," explains Dr. Weinsaft. ■

MRI Image: Raymond J. Kim, MD, Duke Cardiovascular Magnetic Resonance Center. "Relationship of MRI Delayed Contrast Enhancement to Irreversible Injury, Infarct Age, and Contractile Function." *Circulation* 1999;100:1992-2002.



Transcatheter Cardiovascular Therapeutics Symposium

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Transcatheter Cardiovascular Therapeutics (TCT), sponsored by the Cardiovascular Research Foundation® (an affiliate of NewYork-Presbyterian/Columbia) is a scientifically stimulating symposium for physicians and other specialists in interventional vascular therapy. Numerous groundbreaking innovations relevant to clinical practice will be introduced, beginning Sunday at 1:00 pm with how-to workshops emphasizing new device applications and techniques.

Highlights of the week-long symposium include:

Live Peripheral and Coronary Cases: 60 hours of live cases, transmitted from 25 nationally and internationally renowned institutes. Cases emphasize advanced techniques and complications management of complex coronary and peripheral intervention, in areas such as carotid and peripheral arterial intervention, structural heart disease, chronic total occlusions, and more. The Main Arena will focus on investigational devices, drugs, and strategies not yet approved by the FDA.

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Oral and Poster Abstracts: approximately 600 oral and poster abstracts will be presented, with 100 oral abstracts integrated into the main scientific sessions.

Scientific Symposia: stand-alone, 1½-day, cutting-edge didactic symposia such as Cardiovascular CT and MR Imaging, Peripheral and Neurovascular Intervention, Drug-Eluting Stents, and Structural Heart Disease.

Case Reviews With the Experts: small group environment during lunchtime sessions for angiographic case review and clinical decision-making.

Cardiovascular Nurse and Technologist Symposium: 1-day symposium featuring a new format of case review sessions with a multidisciplinary panel of nurses, technologists, physician assistants and physicians. Attended by close to 1,000 cardiac catheterization laboratory nurses, technologists, cardiovascular administrators and managers, research assistants, and other allied health care providers.

To learn more about TCT, please visit http://tct2005.com or call 866.695.5498 to register.

Coagulation Research CONTINUED FROM P.3

coagulopathy," says Dr. Schmidt. "This will be studied first in large animals, then in humans including patients with VADs."

Different LVADs may activate clotting to different degrees, according to Dr. Schmidt; evidence suggests that the Thoratec device may not activate clotting because of its particular endothelial-like surface. The choice of which device to employ during the study will be made based on further investigation into this issue. ■

Cell Transplantation Research to Improve Myocardial Recovery CONTINUED FROM P.4

native heart four weeks later. Follow-up of each group is expected to be approximately three months, with repeated assessment of the native heart function and histological examination of the explanted native heart at the time of transplantation.

Given the high cost of autologous cell processing, widespread use of cell therapy for the large numbers of patients suffering from cardiovascular disease will require development of more efficient and less expensive methodologies. The immunomodulatory properties of MPC make this type of cell therapy an ideal candidate for possible allogeneic use. Consequently, after obtaining FDA approval for MPC isolation and culture, Dr. Itescu and colleagues will evaluate the safety and efficacy of allogeneic MPC for cardiac regeneration. ■

Reducing Left Ventricular Hypertrophy

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While both drugs similarly reduced blood pressure, losartan therapy more effectively reduced both LVH and a host of cardiovascular events.

In an environment where physicians typically treat hypertension but not LVH, the strong correlation between reduced LVH and cardiovascular morbidity and mortality carries important implications. "Even if we effectively reduce blood pressure, we need to aggressively treat patients to reduce LVH," states Dr. Okin, Principal Investigator of the electrocardiographic analyses from the LIFE study.

According to Dr. Devereux, who was Vice-chair of the LIFE steering committee and Principal Investigator of an echocardiographic substudy, long-acting angiotensin receptor blockers, angiotensin-converting enzyme receptor blockers (ACE inhibitors) and calcium channel blockers appear better than beta-blockers and diuretics in reducing LVH. Adds Dr. Okin, "Regression of LVH appears to reduce the risk of congestive heart failure, atrial fibrillation, and diabetes. Interestingly, losartan is associated with a decreased risk of diabetes. Clearly, thorough study of losartan and other therapies is warranted." ■

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NewYork-Presbyterian Heart is comprised of physicians of Columbia University College of Physicians and Surgeons and Weill Medical College of Cornell University representing medical and surgical disciplines working together with other health professionals in a collaborative process.

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Faculty Highlights

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Widely esteemed for his technical skill, collegiality and humility, Jonathan M. Chen has chosen to apply his expertise in left ventricular assist devices and transplantation to the challenging world of congenital heart defects. His leadership at NewYork-Presbyterian/Columbia has propelled the pediatric cardiac transplant program to a new level of prominence, and as the new Director of pediatric cardiac surgery at NewYork-Presbyterian/Weill Cornell, Dr. Chen is now expanding this program with like success. With visionary perspective, his research and clinical efforts are forging a new era of applying mechanical assist devices in children; under special FDA approval, he is credited with having implanted the Berlin Heart VAD in the smallest child in the U.S.

In collaboration with Niloo M. Edwards, MD and Pamela A. Mazzeo, Dr. Chen is coeditor of *Cardiac Transplantation: The Columbia University Medical Center/ New York-Presbyterian Hospital Manual.*

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Considered a highly talented and "tireless" surgeon by his colleagues, Allan Stewart, MD thrives on the challenges of high-risk surgery and innovative research. His specialties: aortic dissection and aneurysm surgery, LVADs as bridge to recovery, cardiac transplantation, complex valve disease, and reoperative surgery. His accidental discovery of literature about anterior cerebral perfusion (ACP) led him to investigate the technique during his residency, and the success of those efforts ultimately led the NewYork-Presbyterian/ Columbia team to change its method of circulatory arrest to ACP with axillary cannulation during thoracic aortic surgery. Dr. Stewart's current research endeavors include cutting-edge work in gene therapy and heart failure, and the combination of LVADs and angiogenesis to create a bridge to recovery.

Recent publications include "Blocking Free Radical Production via Adenoviral Gene Transfer Decreases Cardiac Ischemia-Reperfusion Injury." *Molecular Therapy* 2000;2(5):470-5.

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