

## Angiogenesis: Four Approaches to Restoring Cardiac Function

Researchers at Cornell and Columbia are pursuing four different approaches to stimulate the regeneration of blood vessels, in attempts to reverse cardiovascular disease among the elderly and the most ill heart failure patients.

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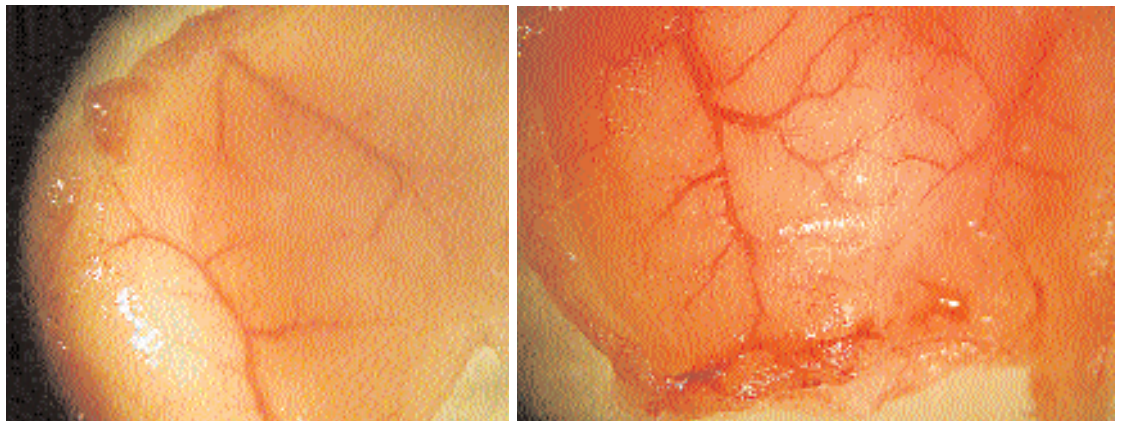
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Growth of new vascular branches in response to angiogenic growth factors: Left, vascular anatomy of mouse peritoneum, with control vehicle stimulation; Right, stimulated growth of interarterial vessels in the presence of slow-release angiogenic growth factors

Few fields have advanced as dramatically over the last two decades as cardiology and cardiothoracic surgery. Yet, for people whose blood vessels are unsuitable for angioplasty, endovascular stenting, brachytherapy, or bypass surgery — people with “malignant” heart disease — modern medicine offers no treatment options.

If only these failing hearts could grow new blood vessels.

“That is the hope and the dream of angiogenesis,” says Judah Z. Weinberger, MD, PhD, Director of Interventional Cardiology at CPMC and Associate Professor of Medicine and Pharmacology at Columbia University.

In 1971, surgeon Judah Folkman hypothesized that angiogenesis was a major factor in enabling malignant tumors to grow.

He was ridiculed at first by clinicians and basic scientists, but today his ideas are widely accepted and have fostered development of antiangiogenic therapies that are proving effective in reducing malignant tumors.

Inspired by the possibilities initiated by Folkman’s work, heart researchers today are working to stimulate, rather than block, angiogenesis. They face a prodigious task: the mechanisms that trigger blood vessel growth are complex, and they must be carefully controlled to avoid unwanted outcomes that can come with an oversupply of blood vessels, which is seen in such disorders as rheumatoid arthritis, psoriasis, and diabetes.

Despite the complexity, however, the research has shown highly promising results thus far, especially in these four approaches.

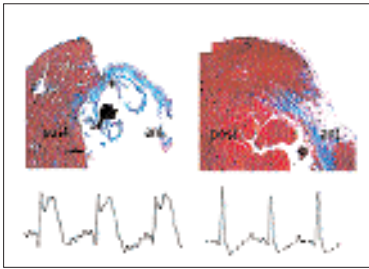
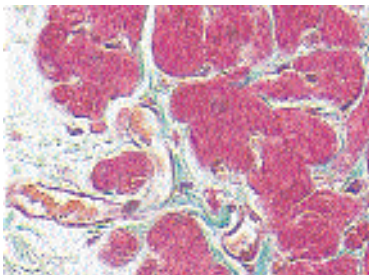
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## Four Approaches to Restoring Cardiac Function

### Dr. Silviu Itescu: Using Adult Stem Cells to Promote Angiogenesis

At Columbia, a team led by Dr. Silviu Itescu has identified the specific type of stem cells in adult human bone marrow that give rise to blood vessels and has developed a method of using these cells in order to prevent cardiomyocyte apoptosis, reduce remodeling, and improve cardiac function after a heart attack.

Essentially, Dr. Itescu's method stimulates new blood vessel growth within damaged or "at risk" cardiac tissue, thereby protecting and even causing regeneration of heart muscle. The team is now studying ways by which a variety



Above: New capillary formation adjacent to hypertrophied rat cardiac myocytes at the peri-infarct rim after intravenous injection of human adult bone marrow angioblasts

Below: Salvage of cardiac muscle and prevention of left ventricular remodeling and fibrous replacement in rat heart at 15 weeks after intravenous injection of human adult bone marrow angioblasts (right) compared with animal receiving saline (left)

of biological agents can further augment the cardiac regenerative capacity of adult bone marrow stem cells, including enhancing migration and targeting to the damaged heart.

In treating the sickest heart failure patients during the past decade, Dr. Itescu faced significant limitations with all therapeutic options. The severe shortage of donor hearts renders transplantation impossible for most patients, and mechanical devices (LVADs and artificial hearts) and xenotransplantation both produce significant immune responses that lead to immune deficiency and frequent infections.

Unsatisfied with these options, Dr. Itescu began searching for a new solution. His approach: to stimulate the growth of new blood vessels, thereby providing a pathway to deliver nutrients and blood flow, and restoring and maintaining function of the heart tissue itself.

In his preliminary investigations of bone marrow stem cells, Dr. Itescu achieved remarkable success in three short years. He published the first evidence, in *Nature Medicine* in April 2001, that certain bone marrow

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### Dr. Jay Edelberg: Restoring Endogenous Pathways to the Aging Heart

At Weill Cornell, Dr. Jay Edelberg is working to restore angiogenic capacity in the aging heart through both basic research in blood vessel growth factors and transplantation of bone marrow stem cells. His goal is to prevent and even reverse cardiovascular disease in the elderly, and to reduce morbidity and mortality after MI. He focuses specifically on the aging heart, because "that's where most cardiac disease occurs."

Dr. Edelberg's approach is twofold. On the one hand, his team is conducting basic research into the molecular and cellular pathways that govern angiogenesis and vascular function, and the basic causes of dysregulation in the older heart. Aging patients suffer a markedly decreased capacity to develop new blood vessels following MI; by understanding the biological reasons why angiogenesis is impaired, the researchers hope to develop targeted therapies to reverse such impairment.

Simultaneously, the team is also working to restore endogenous pathways to the aging heart via transplantation of adult bone marrow stem cells. Cornell research has shown that alterations in the migration of endothelial cells may contribute to the depressed angiogenic potential in the senescent heart. Systemic approaches such as restoring bone marrow capacity may prove to restore the body's natural ability to generate blood vessels and thereby protect the aging heart from infarction-induced damage.

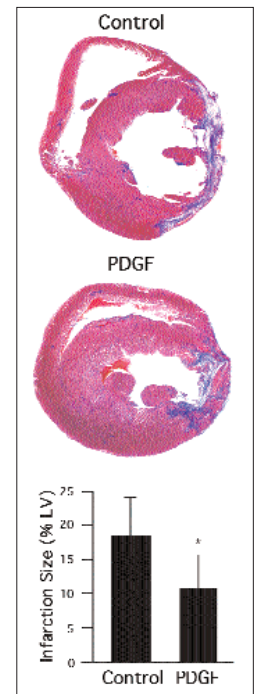
Aging cardiac endothelial cells exhibit different transport behavior from young ones, and Dr. Edelberg believes that restoring the cellular pathway

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The size of myocardial infarctions in aging rat hearts is reduced by injection of the cardiac muscle with platelet-derived growth factor (PDGF) as compared with saline (control). Adapted from: Edelberg et al. *Circulation* 2002, 105:608

## Dr. Judah Weinberger: Angiogenic Growth Factors

At Columbia, Dr. Judah Weinberger's group seeks to replicate the biological process of angiogenesis through the use of slow-released forms of angiogenic growth factors. "We are studying the ability of these factors to stimulate the growth of collaterals and new blood vessels," he says. "We see this process occurring naturally in the earliest stages of the life cycle, as the fetus and embryo grow new blood vessels during the development of the organism." Dr. Weinberger has recently identified and isolated genetic materials from bone marrow and muscle cells. "I am hopeful that this recent addition to our technical and cognitive armamentarium, or general approach, will help us in our understanding of the angiogenic process," he says. He predicts that it will be another year or two before he is ready to begin clinical trials that apply this research.

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### Summary of the 4 Approaches to Angiogenesis

Researcher	Approach	Ultimate Goal
Dr. Itescu	<ol style="list-style-type: none"> <li>1. Basic research into use of bone marrow stem cells and biologic agents to stimulate blood vessel growth and induce heart muscle regeneration</li> <li>2. Protocol study to establish the safety and efficacy of procedures to harvest and reinfuse adult stem cells for blood vessel growth and regeneration of heart muscle</li> </ol>	Stimulate growth of blood vessels and improve heart function by halting the remodeling process after a heart attack and inducing heart muscle regeneration after established heart failure
Dr. Edelberg	<ol style="list-style-type: none"> <li>1. Basic research into causes of angiogenesis</li> <li>2. Systemic bone marrow transplantation to restore endogenous pathways to the aging heart</li> </ol>	Restore angiogenic capacity to the aging heart
Dr. Weinberger	Use of slow-release forms of angiogenic growth factors to stimulate development of new blood vessels	Replicate the biological process of angiogenesis
Dr. Lee	Gene therapy in which VEGF is infused directly into heart via viral delivery	Perform "biologic bypass" to achieve angiogenesis in patients with malignant heart disease



Judah Z. Weinberger, MD, PhD is Director of Interventional Cardiology at Columbia Presbyterian Medical Center and Associate Professor of Medicine and Pharmacology at Columbia University College of Physicians & Surgeons.

## Dr. Leonard Lee: Gene Therapy for "Biologic Bypass"

At Weill Cornell, Dr. Leonard Lee, together with surgeon Todd K. Rosengart, MD, now at Evanston Northwestern Healthcare, and Ronald G. Crystal, MD, Professor and Chair, Genetic Medicine and Chief, Pulmonary and Critical Care Medicine at Weill Cornell Medical Center, hopes to reprogram the heart using gene therapy to perform what they call a "biologic bypass." Their group conducted a Phase I clinical safety trial with 21 human subjects in 1999, shuttling the genetic material, specifically vascular endothelial growth factor (VEGF), directly into the heart via the Ad<sub>GV</sub>VEGF121.10 adenovirus.

As reported in *Circulation* and *Annals of Surgery*, 15 of the 21 patients underwent conventional coronary bypass in addition to gene therapy, and 6 received gene therapy as the sole treatment. "At 6 months' post-treatment, these individuals showed no adverse effects," Dr. Lee says. "By all of our criteria, we found gene therapy to be very safe."

However, as the group was about to verify its results with a new trial, the FDA halted gene therapy research nationwide after the death of a research subject in an unrelated project at another university. That embargo has recently been lifted, and Drs. Lee, Rosengart, and Crystal are now ready to go ahead with an FDA-approved Phase I/Phase II safety and efficacy trial to promote angiogenesis using gene therapy, to be conducted at NewYork-Presbyterian and Evanston.



Ex-vivo coronary angiography following AdVEGF121 administration

### A new Phase I/II gene therapy study

Dr. Lee is seeking 100 patients to participate in a placebo-controlled Phase I/II study of on- and off-pump CABG (50 patients in each). Half of the study subjects will receive gene therapy adjunct to coronary bypass surgery, for circumflex distribution. The study will test safety and efficacy of treatment. VEGF will be injected directly into the heart via AdVEGF121 adenovirus.

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# Higher Blood Pressures During Bypass Surgery Reduce Stroke and MI

Cornell research shows that maintaining higher mean arterial pressures significantly reduces major postoperative complications, particularly among patients with advanced atherosclerosis.

As part of their continued efforts to understand the complex relationships among depressive symptoms, cognitive dysfunction, and surgical procedures, Cornell researchers Karl Krieger, MD and Mary Charlson, MD have studied the effects of maintaining higher mean arterial pressures during coronary bypass surgery since 1991. Their team

## Cognitive Sequelae and Postoperative Depression After CABG

High rates of neurocognitive dysfunction after CABG have attracted widespread concern during the last decade, but are not accurate, according to Cornell doctors Karl Krieger and Mary Charlson. Cornell research indicates that impairments in cognitive function (as measured by memory, fine motor coordination, and linguistic function) are widely over-reported due to varying definitions of cognitive deterioration. Dr. Charlson states that "Cognitive complications after bypass surgery are no more common than they are after hip or knee replacement surgery. And nobody believes that cognitive complications are a sequela of hip and knee replacement surgery."

Yet today, many patients avoid potentially life-saving cardiac surgery because of their belief in the high risks of postoperative cognitive dysfunction. Cardiologists need to be aware of the power of such myths among both patients and physicians, and simultaneously alert to signs of depression among their patients, which is common following CABG surgery and leads to patients perceiving cognitive deficits. Such deficits are potentially reversible once the depression is treated.

While cognitive sequelae among CABG patients are actually far less a problem than generally perceived, post-operative depression among CABG patients is both prevalent and widely undertreated. According to studies done at Cornell, 43% of patients exhibited significant depressive symptoms before surgery but only 23% showed significant postoperative depression.

Depression leads to lower scores on cognitive tests and is clearly associated with higher morbidity and mortality. Moreover, depression frequently manifests as cognitive dysfunction in elderly patients, adding fuel to the misconception that CABG is associated with a high risk of neurocognitive dysfunction.

arterial pressures dramatically reduced the rate of cardiac and neurologic complications, including stroke and myocardial infarctions, 6 months after surgery.

■ Among 248 non-emergent bypass patients, those randomized to high pressures (80 – 100 mm Hg) during coronary bypass had combined cardiovascular/neurological complication rates of 4.8%, as compared to 12.9% for those at lower pressures (50 – 60 mm Hg). At 6 months after coronary bypass, total mortality was 1.6% versus 4.0%, stroke was 2.4% versus 7.2%, and cardiac compli-

cations were 2.4% versus 4.8% for the high and low pressure groups, respectively.

■ Neurocognitive decline was comparable in both groups, approximately 11% for both low and high pressure.

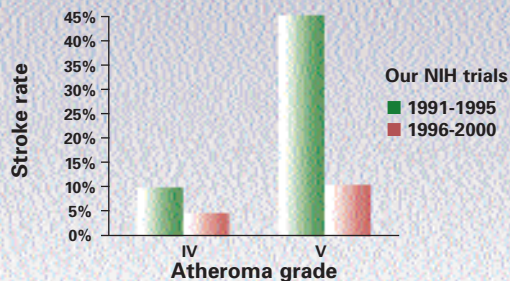
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### NEUROLOGIC COMPLICATIONS

Higher pressures have led to decreases in stroke in the highest risk patients



has studied over 600 patients during the last decade to test the effects of higher mean arterial pressures on 5 outcomes including cardiac/neurologic complications, neurocognitive sequelae, and quality of life.

Their first study, published in 1995, demonstrated that maintaining CABG patients on higher mean



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# Congenital Heart Disease in the Adult

As innovations have dramatically improved the prognosis of children with congenital heart disease, surviving adults now present unique problems as a result of both their anatomy and complications from their pediatric repairs.

It took vision in 1987 to recognize the need for a congenital heart specialist for the adult population. While the number of adult survivors of significant congenital heart problems was small, the development of successful pediatric cardiac surgery was beginning to vastly improve the prognosis for these patients. To Marlon Rosenbaum, MD, a specialist in both adult and pediatric heart disease, it seemed just a matter of time.

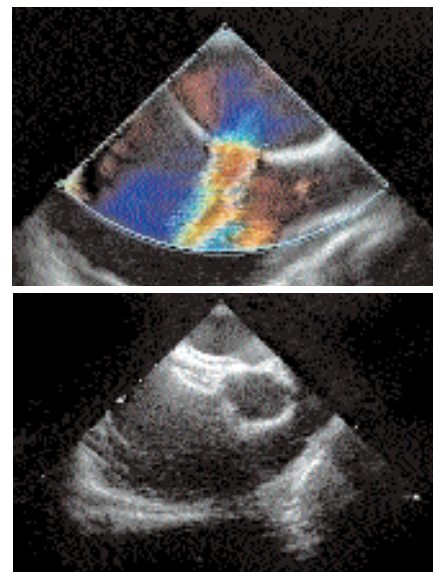
“Adult congenital heart disease did not exist as a subspecialty during the 1980s, but children were now surviving into adolescence and adulthood. We were beginning to see problems that had never been seen before,” recounts Dr. Rosenbaum, Director of the Schneeweiss Adult Congenital Heart Disease Center at Columbia and one of the few specialists in the United States who devotes full time to this field.

The unique needs of this patient population now demand the expertise of specialists who can place congenital defects and their repairs in the context of an adult patient. “The whole spectrum of pediatric cardiology is superimposed on the problems encountered by the adult cardiologist,” comments Dr. Rosenbaum. “Traditionally, pediatric cardiologists followed their adult patients because there were very few adult cardiologists familiar with their

anatomy and management. Today, adult congenital heart specialists can bridge the gap between pediatric and adult cardiology, and are often best suited to manage difficult adult-related problems such as complex arrhythmias and chronic heart failure.” These patients present with a broad range of problems, which may include the need to revise a childhood repair, the development of new lesions superimposed on an early repair, newly recognized congenital heart defects, complex arrhythmias, and pregnancy issues.

Dr. Rosenbaum, who coauthored *Congenital Heart Disease in the Adult* with Welton Gersony, MD in 2002, says that treatment of difficult cases may require a complex plan involving congenital heart surgeons, interventional cardiologists, electrophysiologists, and other specialists. “For example, our patients may have both hemodynamic problems and complex arrhythmias, and require both reoperation and sophisticated arrhythmia mapping with radiofrequency ablation.” At the same time, “the emergence of catheter-based interventions has an important place in the treatment of congenital heart defects, and in some cases, may be used in lieu of an operation,” says Dr. Rebecca Hahn, Director of Clinical Echocardiography at Weill Cornell and a specialist in both heart disease in pregnancy and adults with congenital heart disease.

According to Dr. Rosenbaum, “The reality is that we do not know exactly what problems these patients will face as they reach their 50s and 60s. Even for those of us who work in this area day to day, the field continues to evolve.” Dr. Rosenbaum and Dr.



Interventional catheterization procedures, such as percutaneous atrial septal defect (ASD) closure, represent an important part of the treatment options for adults with congenital heart disease,” says Dr. Rosenbaum. These images from a transesophageal echocardiogram demonstrate the successful closure of a newly recognized ASD in an adult. *Top:* flow is seen (in red) across the ASD. *Bottom:* following device insertion, the ASD has been closed, eliminating blood flow across the atrial septum.

Hahn concur that the lessons learned during follow-up of adults with congenital heart disease can provide feedback that is crucial for the pediatric cardiologist and surgeon. “For example,” states Dr. Rosenbaum, “late problems with the early surgical repair for D-transposition of the great arteries and single ventricle led to a change in the type of surgery performed for these lesions. This is a very dynamic field likely to pose new challenges not only as the initial survivors age, but as we are confronted by new problems from the subsequent innovations in pediatric repairs.”



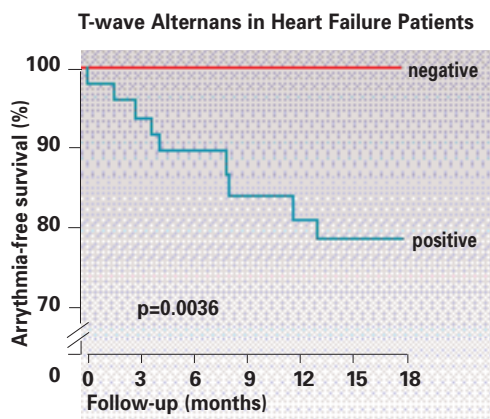
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# Predicting and Preventing Sudden Death

A noninvasive test of T-wave alternans is now available for predicting ventricular arrhythmias. It detects risk for sudden death signaled by subtle abnormalities in T-wave repolarization that predict life-threatening ventricular tachycardia, and fibrillation.

The ability to identify the risk of sudden death before it occurs has improved dramatically by an innovation that is both noninvasive and rela-



#### Numbers at risk

■ Negative	33	30	27	21	16	14	11
■ Positive	52	45	40	32	30	26	24

**Kaplan-Meier analysis of event-free survival for patients with congestive heart failure, stratified by positive or negative T-wave alternans test results.**

Adapted with permission from *The Lancet*, T. Klingenhoben et al, August 19, 2000, Vol 356, pp 651-652.

tively inexpensive. The new test, T-wave alternans, is FDA-approved and has the potential to play a significant role in reducing one of the most common types of cardiovascular mortality. This test is effective in identifying those with a propensity for life-threatening ventricular arrhythmias not previously

detectable by other noninvasive tests. After inception of the test of T-wave alternans at MIT, researchers there collaborated with Cambridge Heart and NewYork-Presbyterian Hospital researchers to study it, create the rules for its interpretation, and establish the protocol for its use.

T-wave alternans testing offers sensitivity and specificity far superior to other noninvasive tests proposed in the past, such as signal-averaged electrocardiography (ECG) or QT dispersion analyses. In a published prospective multicenter trial of 313 patients in sinus rhythm, T-wave alternans performed as well as cardiac electrophysiological (EPS) testing, an invasive and far more expensive test not routinely administered to patients with an intermediate risk of having ventricular arrhythmias (the group of patients from which the majority of sudden death events emerge).

“About half of cardiovascular mortality is the result of sudden death. The majority of sudden death is attributed to ventricular arrhythmias. These are huge numbers,” observed Hasan Garan, MD, an expert on heart rhythm disturbances. “Although we have had devices that can save lives in patients who experience the arrhythmias that cause sudden death, until now we had no reliable way of determining who was going to need them.”

T-wave alternans testing is based on the observation that very subtle microscopic fluctuations in the morphology of the T-wave on the ECG reveal abnormalities in repolarization. These abnormalities develop in advance of ventricular arrhythmias. With sophisticated signal-processing of the ECG, they can be detected when

the heart rate is accelerated with exercise. The exciting development is that T-wave alternans, although easily administered without invasive methodology, may even be superior to EPS for a number of patient populations at risk.

T-wave alternans testing is now FDA-approved, guidelines for its use are published, and coding for reimbursement has been established. As it gains use, the applications of T-wave alternans may evolve both as a result of experience with the test and through additional refinements in the software that underlies its accuracy. According to Daniel Bloomfield, MD, who made key contributions to its development, the ultimate utility of the tool may not be in clarifying the degree of risk in individuals already singled out by known ventricular arrhythmias, but in the far larger group of individuals with heart disease who are otherwise doing well but may be at increased risk for sudden cardiac death. The task heretofore has been like looking for a needle in a haystack.

“The opportunity to save lives by detecting risk of sudden death is much greater in primary prevention than in secondary prevention, and this is where T-wave alternans may take us,” Dr. Bloomfield suggested. “A noninvasive, highly sensitive screening tool for the intermediate risk population would be expected to go a long way in addressing a major public health problem.”



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## Dr. Itescu: Using Adult Stem Cells to Promote Angiogenesis

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cells (cells that express the c-Kit protein) can be manipulated to become angioplasts. When injected into the tails of rats with simulated heart attacks, these highly differentiated cells migrated directly to the area of heart damage, halted the remodeling process, and helped regenerate blood vessel tissue. The protective effect was clear: in this trial, the technique resulted in up to 40% improvement in heart function in the animals studied. This marked a major therapeutic achievement compared to the 10% improvement typically expected with current medical management.

Dr. Itescu's approach differs from that of other researchers who are working to stimulate the growth of heart tissue itself. Regenerated heart tissue is of limited value if the blood vessels supporting it are inadequate. Furthermore, the team's efforts thus far demonstrate that regeneration of blood vessels actually promotes the development of heart muscle cells too. "The capillary network must be able to

meet the increased demands of the post-infarction heart," Dr. Itescu explains.

"What we are doing is trying to enhance a naturally occurring process."

On the basis of his groundbreaking work, Dr. Itescu was awarded a 5-year NIH RO1 grant for over \$2 million in direct and indirect funding to begin examining the function of bone marrow stem cells from human heart disease patients. He has obtained ethics committee approval to begin a protocol trial testing the safety and potential efficacy of procedures to harvest and subsequently reinfuse adult bone marrow stem cells. This trial sets the stage for upcoming randomized clinical trials of the efficacy of progenitor cells in repairing the human heart.

In this 12-month trial, the researchers are collecting, processing, and re-infusing endothelial stem cells systemically in about 25 patients of various ages who have angina, who have suffered a heart attack, or who have heart failure. The administration of granulocyte stimulating factor (G-CSF) induces the migration of the cells from the bone marrow to the blood, where they are

obtained. The team then purifies, concentrates, and stains the cells with radioactive dye before reinfusion. Whereas in this study the stem cells will be reinfused systemically, in subsequent studies Dr. Itescu will evaluate whether injecting the cells directly into the heart or through a catheter might be more effective for certain clinical indications such as congestive heart failure. The initial trial is designed to evaluate the safety of this process so that it may be employed in subsequent efficacy trials using adult stem cells to restore cardiac function.

If the process works in humans, the ability to grow new blood vessels through infusions of adult stem cells carries enormous potential for reducing morbidity and mortality associated with cardiovascular disease. Dr. Itescu is confident that not only will the harvesting and delivery process prove safe, but that evidence of efficacy may even become apparent in this initial trial. Once safety is demonstrated, he will begin clinical efficacy trials in which the effects on the heart will be studied.

## Dr. Jay Edelberg: Restoring Endogenous Pathways to the Aging Heart

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might be a key factor in reversing angiogenic decline. Indeed, his work has shown already that young endothelial cells restore the cellular communication in aging animal hearts, resulting in improved heart function. For his work demonstrating this,

and to support his ongoing research in this area, Dr. Edelberg was awarded the prestigious \$450,000 Beeson Award in 2001.

Dr. Edelberg's delivery system is via systemic bone marrow transplantation. "Whether using cytokines or stem cell approaches, the key is to address the fundamental changes in the aging heart as a way to develop long-lasting targeted

therapies," he states. "One way is by restoring bone marrow stem cell capacity." At this time, Dr. Edelberg is working with animal subjects. If his research demonstrates efficacy, it could lead to human trials of therapy aimed at promoting the growth of cardiac blood vessels. This would represent a significant potential to reduce the incidence of cardiovascular disease among aging patients.

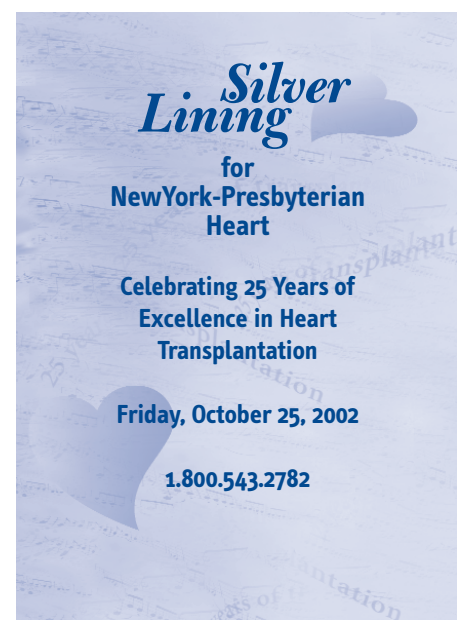
## Higher Blood Pressures

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To further investigate the compelling 1995 results, Drs. Krieger and Charlson conducted a second NIH-funded study in which patients were randomized to either 80 mm Hg or a customized pressure (based on patients' preoperative blood pressure). This study, to be published this year, underscored the 1995 findings, demonstrating that high pressures clearly benefit all CABG patients, and in particular, high-risk patients with grade IV or V atheroma. The improvement in stroke rates achieved by maintaining higher mean

arterial pressures is striking among such patients especially vulnerable to hypoperfusion injury. While patients with grade V aortic atheroma had stroke rates of 67% when maintained at conventional pressures during the first study, stroke incidence dropped to 20% when maintained at higher pressures. Furthermore, 6-month complication rates for grade V atheroma patients dropped from 45% in the 1995 study to 11% in the 2000 study.

As a result of the dramatic improvements demonstrated by the team's research, Cornell physicians now maintain higher pressures during all CABG surgeries.



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## Robotic Cardiac Surgery at the Columbia Weill Cornell Heart Institute: A Progress Report

- ▶ New York-Presbyterian surgeons and researchers are helping to develop innovations such as the **4-armed robot**. The newly added 4th arm enhances surgeons' dexterity during cardiac surgery, assisting with difficult tasks without the bulk of human hands.
- ▶ **A closed-chest procedure for atrial fibrillation** will soon be tested by Dr. Michael Argenziano, who developed the procedure.
- ▶ Use of the surgical robot is opening **new possibilities in thoracic surgery** such as removal of pericardial cysts, placement of pacemaker leads for biventricular congestive heart failure, Nissen fundoplication for reflux disease, Heller myotomy for achalasia, and removal of other thoracic tumors.

**The Columbia Weill Cornell Heart Institute** is a service line management model designed to provide financial, operational, and clinical direction to promote the growth and development of cardiology and cardiovascular surgical activities. The Heart Institute is comprised of physicians of Columbia University College of Physicians & Surgeons and Weill Medical College of Cornell University representing medical and surgical disciplines working together with other health professionals in a collaborative process.

## Faculty Highlights



**Niloo M. Edwards, MD, FACS** *Director, Cardiac Transplantation, New York-Presbyterian Hospital, Director, Geriatric Cardiac Surgery, Columbia Presbyterian Medical Center, Assistant Professor of Surgery, Columbia University College of Physicians & Surgeons*

Dr. Niloo M. Edwards is an expert in cardiac transplantation with a special interest in geriatric cardiac patients. Dr. Edwards founded the interdisciplinary American Geriatric Experience (AGE) program at Columbia to address elderly patients' unique needs. He also developed a special program to match high-risk heart patients with high-risk donors, increasing the number of heart transplants.

Dr. Edwards completed his training at Columbia and at the University of Rochester, Strong Memorial. Recent publications include "Mechanical Support for the Failing Cardiac Allograft: A Single Center Experience," *Circulation*, October 23, 2001; v. 104: 17-II-759, and "Effects of a Selective Nitric Oxide Synthase-2 Inhibitor in the Prevention of Acute Cardiac Allograft Rejection," presented at the annual meeting of the International Society for Heart and Lung Transplantation, Washington DC, April 2002.

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**S. Chiu Wong, MD** *Director, Cardiac Catheterization Laboratory, Weill Medical College of Cornell University*

An expert in invasive and interventional cardiology, Dr. Wong is a leader in developing procedures to fight coronary artery disease and restenosis. Under his direction, the Weill Cornell cardiac catheterization laboratory research team made significant contributions to the GAMMA I, II, IV and START trials, which examined the use of GAMMA and beta rays and led to FDA approval of intravascular radiation treatments for in-stent restenosis.

Dr. Wong is currently the local PI of several drug-eluting stent trials, including the SIRIUS (Rapapume loaded), ACHIEVE and TAXUS (taxol-loaded) trials.

After his training at Columbia and St. Lukes/Roosevelt Hospital Center in New York, Dr. Wong received advanced training in stent technology in 1991 at the Scripps Clinic and Research Foundation.

Recent publications include "Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting." *New England Journal of Medicine* 2001;344:250-6.

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