

# NEW YORK-PRESBYTERIAN Transplant

Affiliated with COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS and SURGEONS and WEILL MEDICAL COLLEGE OF CORNELL UNIVERSITY

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## Liver: Living Donor Safety

Columbia and Weill Cornell researchers at NewYork-Presbyterian Hospital are entering the second phase of the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL), a multicenter, 7-year clinical trial looking at the safety and efficacy of living donor liver transplantation.

According to Jean C. Emond, MD, co-chair of the NIH-funded study, about 15% to 20% of the more than 500 living donor transplantations performed at the 9 centers during the remaining 5 years of the trial will take place at NewYork-Presbyterian Hospital. The patients selected for living donation will be emotionally or genetically related to the patient in need of transplantation, said Robert S. Brown, Jr, MD, MPH.

A report on the retrospective data collected during the opening stage of A2ALL was presented at the annual meeting of the American Association for the Study of Liver Diseases in November, according to Dr. Brown. The report was the first to demonstrate in a multicenter trial that living-donor transplants decrease mortality, primarily by shortening the average time patients spend waiting for an organ. These findings are drawn from data on a retrospective cohort of some 2,000 persons at the 9 A2ALL centers. The cohort includes donors, potential donors, and recipients who received living donations, as well as those who received livers from deceased donors. It also includes recipients who died before receiving a transplantation. Data show that 20% of patients on the

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## Research Seeks To Enhance Outcomes in Lung Transplants

The Lung Transplant Program at NewYork-Presbyterian Hospital/Columbia University Medical Center, which has achieved lung transplant success rates far exceeding national averages, has embarked on a number of investigations that could further enhance patient care and prevent graft rejection.

While patient care remains a top priority, research is now a key focus for program leaders. In collaboration with academic medical centers throughout the United States, the Lung Transplant Program is participating in a variety of studies involving genetics, outcomes, and immunosuppression.

"We spent several years building a good clinical base, and now the research base is just starting to build," said Joshua R. Sonett, MD. "Translational research is starting to percolate and that is going to be a real benefit to the patients."

Outstanding success rates over the past several years have helped the Lung Transplant Program achieve Medicare



Photo courtesy of COC/Dr. Edwin P. Ewing, Jr.

Gross pathology of lung showing centrilobular emphysema. Researchers are seeking to improve outcomes in lung transplantation.

certification. Today, Medicare-eligible patients are covered for preoperative evaluation, surgery, and postoperative care.

Over the past 3 years, more than 80 lung transplants have been successfully performed. The 6-month survival rate was 96%, and the 1-year survival rate was 92%. By comparison, the national average for 1-year survival is roughly 78% to 80%. These outcomes are particularly significant because of the high-

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For More Information visit:  
[www.nytransplant.org](http://www.nytransplant.org)

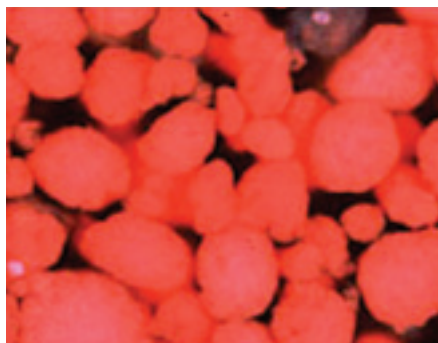
## Grants Support Groundbreaking Research in Islet Cell Transplantation

**W**ith the support of grants from the National Institutes of Health (NIH) and the Juvenile Diabetes Research Foundation (JDRF), Columbia and Weill Cornell researchers at NewYork-Presbyterian Hospital are carrying out both basic and clinical research designed to bring patients with severe type 1 diabetes closer to the ultimate goal of insulin-free existence.

Awarded to NewYork-Presbyterian Hospital/Columbia University Medical Center, the NIH grant has been used to create the Islet Cell Resource Center (ICRC). One of 10 such facilities in the country, the ICRC will provide resources for researchers working to improve techniques for isolating islet cells and find new ways to boost the scarce supply of islets nationwide. The JDRF grant, awarded to NewYork-Presbyterian Hospital/Weill Cornell Medical Center, is providing part of the funding for an ambitious new research effort to advance the relatively recent work in islet cell transplantation.

"If you look now at centers around the world, the insulin-free rate at 1 year is about 58%," said Kevan Herold, MD. "But the procedure isn't perfect. The long-term survival of the islets needs to be improved. We still need 2 donors for each recipient. It would be better if we could either do 1 donor to 1 recipient, or have 1 donor where we would expand the islet mass before we transplanted it so that we could still do 1 donor for 1 recipient. However, in spite of the existing difficulties with the procedure, these achievements have opened up the relatively new field of cellular therapy in which needed cells, rather than whole organs, can be replaced."

As part of the clinical effort, a great



Courtesy of the Islet Cell Research Center

**A scan of islets after isolation. Researchers at NewYork-Presbyterian Hospital are hoping to improve the identification of "good" islets for transplantation into patients with type 1 diabetes.**

deal of research is ongoing at both centers of NewYork-Presbyterian Hospital to facilitate clinical islet transplantation. "One of the difficulties is to identify 'good' islets," commented Mark Hardy, MD. Dr. Hardy, along with his collaborator, Paul Harris, MD, has spearheaded a study of genes expressed by isolated human islets and is working to improve initial visualization of transplanted islets with positron emission tomography in experimental models. "If we can produce better islets and more of them, we should be able to make rapid progress to treat diabetic patients more effectively in the future," said Dr. Hardy.

Part of the research at NewYork-Presbyterian/Weill Cornell involves the use of molecular diagnostic techniques to monitor patients for possible islet rejection. "Right now, when we do an islet transplant, we don't really know when the islet is failing or when it's going to fail," said Manikkam Suthanthiran, MD. "So we are bringing our background in the molecular diagnosis of transplant rejection to monitor the health of the

islet. We get blood or urine from the patient and look at a variety of genes to better manage these patients."

Under the ramped-up programs, both centers of NewYork-Presbyterian Hospital have already performed islet transplantations. The first islet transplant, performed on a patient with a previous kidney transplant in the New York metropolitan region, was performed at the ICRC at NewYork-Presbyterian/Columbia in January 2003. Surgeons at the ICRC, which officially opened in early 2002, prepared for the first procedure by isolating and harvesting "happy" (or healthy) islet cells and perfecting transplantation procedures. Having accomplished these goals, they are now looking toward the future.

"Our immediate goal is to get 3 patients insulin-free by next summer," said Dr. Herold.

The Columbia research team is currently working on a protocol investigating the transplantation of islet cells into 10 patients with kidney transplants. The advantage of enrolling kidney transplant patients, Dr. Herold said, is that they are already on immunosuppressant drugs to prevent rejection. Dr. Hardy, who together with Dr. Herold initiated the effort at the ICRC, feels that the use of islets in patients who already have transplanted kidneys may protect the new kidneys from the development of diabetes. In October, Weill Cornell surgeons performed the first solitary islet transplantation in the New York-New Jersey-Connecticut area, according to Dr. Suthanthiran. In contrast to NewYork-Presbyterian/Columbia, NewYork-Presbyterian/Weill Cornell will enroll patients with type 1 diabetes whose own kidneys are still functioning and who are not on immunosuppressants but have significant problems in managing their diabetes despite intensive insulin therapy.

Much of the effort at the 2 medical centers will build on the so-called Edmonton protocol, which was used at the University of Alberta, Canada, to reduce insulin dependence in a high percentage of patients with type 1 diabetes who received islet transplants. The paper that marked a sea change in the field was originally published in the *New England Journal of Medicine*

(2000;343:230–238). Since then, nearly 200 islet cell transplantations have been performed worldwide.

Both Columbia and Weill Cornell researchers are also focusing on reducing the number of pancreases needed to extract the islets used for transplantation. “Nowadays, when you use the Edmonton protocol, you usually need 2 or 3 pancreases for any given patient,” said Dr. Suthanthiran. “One of our goals is to do a transplantation using a single pancreas.”

To reach that goal, Weill Cornell researchers at NewYork-Presbyterian Hospital are conducting parallel experiments in mice. “We have identified a factor called transforming growth factor-beta that may suppress the immune response sufficiently so that islets from 1 pancreas will be enough,” said Dr. Suthanthiran. “In fact, in mice we are able to reverse diabetes with this factor. That’s in mice—not yet in humans.” Because of this work, he added, transplant patients may eventually require immunosuppressants for a very short period and then be drug-free.

Although geographically separate, the 2 programs share plans, information, and ideas. “There is an active collaboration between the 2 groups,” said Dr. Suthanthiran. “Our plan is to further develop this relationship and work as a team together.”

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**Mark Hardy, MD**, is Surgical Director, Islet Transplantation Program at NewYork-Presbyterian Hospital/Columbia University Medical Center, and is Auchincloss Professor of Surgery at Columbia University College of Physicians and Surgeons. E-mail: mah1@columbia.edu.

---

**Kevan Herold, MD**, is Medical Director, Islet Transplantation Program at NewYork-Presbyterian Hospital/Columbia University Medical Center, and is Associate Professor of Medicine at Columbia University College of Physicians and Surgeons. E-mail: kh318@columbia.edu.

---

**Manikkam Suthanthiran, MD**, is Chief, Nephrology and Transplant Medicine at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, and is Stanton Griffis Distinguished Professor of Medicine at Weill Medical College of Cornell University. E-mail: msuthan@med.cornell.edu.

## NewYork-Presbyterian Transplant Editorial Board

---

### Linda Addonizio, MD

**Medical Director, Pediatric Cardiac Transplant Program**

*Morgan Stanley Children’s Hospital of NewYork-Presbyterian/Columbia*

**Professor of Pediatrics**

*Columbia University College of Physicians and Surgeons  
lja1@columbia.edu*

---

### Selim Arcasoy, MD, FCCP, FACP

**Medical Director, Lung Transplantation Program**

*NewYork-Presbyterian/Columbia*

**Associate Professor of Clinical Medicine**

*Columbia University College of Physicians and Surgeons  
sa2059@columbia.edu*

---

### Robert S. Brown, Jr, MD, MPH

**Medical Director, Center for Liver Disease and Transplantation**

*NewYork-Presbyterian/Columbia*

**Associate Professor of Clinical Medicine and Pediatrics**

*Columbia University College of Physicians and Surgeons  
rb464@columbia.edu*

---

### David Cohen, MD

**Medical Director, Renal Transplant Program**

*NewYork-Presbyterian/Columbia*

**Associate Professor of Clinical Medicine**

*Columbia University College of Physicians and Surgeons  
djc5@columbia.edu*

---

### Jean C. Emond, MD

**Vice Chairman and Chief, Transplantation Services**

*NewYork-Presbyterian/Columbia*

**Thomas S. Zimmer Professor of Surgery**

*Columbia University College of Physicians and Surgeons  
je111@columbia.edu*

---

### Mark Hardy, MD

**Director, Center for Liver Disease and Transplantation**

*NewYork-Presbyterian/Columbia*

**Auchincloss Professor of Surgery**

*Columbia University College of Physicians and Surgeons  
mah1@columbia.edu*

---

### Sandip Kapur, MD

**Surgical Director, Kidney/Pancreas/Islet Cell Transplantation**

*NewYork-Presbyterian/Weill Cornell*

**Assistant Professor of Surgery**

*Weill Medical College of Cornell University*

**Adjunct Assistant Professor of Surgery**

*Columbia University College of Physicians and Surgeons  
sak2009@med.cornell.edu*

---

### Milan Kinkhabwala, MD

**Surgical Director, Liver and Pancreas Transplant Programs**

*NewYork-Presbyterian/Weill Cornell*

**Associate Professor of Surgery**

*Weill Medical College of Cornell University  
mik2005@med.cornell.edu*

---

### Donna Mancini, MD

**Medical Director, Cardiac Transplantation Program and Heart Failure Center**

*NewYork-Presbyterian/Columbia*

**Associate Professor of Medicine**

*Columbia University College of Physicians and Surgeons  
dmm31@columbia.edu*

---

### Yoshifumi Naka, MD

**Director, Mechanical Circulatory Support Program**

*NewYork-Presbyterian/Columbia*

**Herbert Irving Assistant Professor of Surgery**

*Columbia University College of Physicians and Surgeons  
yn33@columbia.edu*

---

### Stuart D. Saal, MD

**Medical Director, Kidney Transplantation**

*The Rogosin Institute at*

*NewYork-Presbyterian/Weill Cornell*

**Professor of Clinical Medicine and Surgery**

*Weill Medical College of Cornell University  
saals@mail.rockefeller.edu*

---

### Michael Schilsky, MD

**Medical Director, Center for Liver Disease and Transplantation**

*NewYork-Presbyterian/Weill Cornell*

**Associate Professor of Clinical Medicine**

*Weill Medical College of Cornell University  
mls2003@med.cornell.edu*

---

### David Serur, MD

**Medical Director, Kidney/Pancreas Transplantation**

*The Rogosin Institute at*

*NewYork-Presbyterian/Weill Cornell*

**Assistant Professor of Medicine**

*Weill Medical College of Cornell University  
dserur@med.cornell.edu*

---

### Joshua R. Sonett, MD

**Surgical Director, Lung Transplantation Program**

*NewYork-Presbyterian/Columbia*

**Associate Professor of Clinical Surgery, Division of**

**Cardiothoracic Surgery**

*Columbia University College of Physicians and Surgeons  
js2106@columbia.edu*

---

### William Stubenbord, MD

**Chief, Division of Transplantation**

*NewYork-Presbyterian/Weill Cornell*

**Professor of Surgery**

*Weill Medical College of Cornell University  
wrs2003@med.cornell.edu*

---

### Manikkam Suthanthiran, MD

**Chief, Nephrology and Transplant Medicine**

*NewYork-Presbyterian/Weill Cornell*

**Stanton Griffis Distinguished Professor of Medicine**

*Weill Medical College of Cornell University  
msuthan@med.cornell.edu*

---

### John Wang, MD

**Associate Attending Physician**

*NewYork-Presbyterian/Weill Cornell*

**Associate Professor of Clinical Medicine and Surgery**

*Weill Medical College of Cornell University  
Wangjo@mail.rockefeller.edu*

## Living Donors Bring New Life To Kidney Transplantation

Today, the use of living donors is revolutionizing kidney transplantation, providing viable organs for patients in need. Roughly half of the kidneys used in US transplantations come from living donors, but at NewYork-Presbyterian Hospital, a leader in organ transplantation, the percentage is much higher: According to Stuart D. Saal, MD, roughly 6 to 8 of every 10 kidney transplantations performed at the Hospital use kidneys from living donors.

“Living organ donation is the most rapidly growing area in renal transplantation,” said David Cohen, MD.

Several factors have contributed to this growth. Current transplantation procedures have improved safety for donors and overall success rates for transplant recipients. Practices that once limited living donors to genetically related family members have been relaxed, and new

advances in surgical approaches have reduced discomfort and length of hospital stay for donors. Finally, advances in medical management have led to the successful transplantation of organs from donors to recipients previously considered incompatible.

This news couldn’t have come at a better time for patients in dire need of functioning kidneys. While the need for donated kidneys has increased sharply in recent years, the number of kidneys harvested from deceased donors has remained flat. More than 60,000 patients are currently on the waiting list nationally; in the New York area, the wait for a cadaveric kidney averages 7 years.

The new kidney exchange program at NewYork-Presbyterian Hospital seeks to expand the pool of living donors by taking an incompatible donor–recipient pair and then searching among other incompatible pairs for

cross-match and blood-type compatibility between willing donors and recipients from different families. If the donor and recipient in a pair both agree to donate and receive kidneys from strangers, and they are candidates for surgery, the transplants are performed at the same time in adjoining operating rooms. Recently, surgeons and physicians at NewYork-Presbyterian Hospital/Columbia University Medical Center performed the first successful kidney swap in the New York area. The Hospital matched an incompatible brother–sister pair with a woman and her stepmother.

According to Lloyd Ratner, MD, in the past, an incompatible blood type in a donor or antibodies against the transplant antigens of the donor in a recipient were “absolute contraindications to transplantation.” However, plasmapheresis can now be used to filter out antibodies to certain blood types and transplant antigens.

Although plasmapheresis can improve outcomes in challenging transplantations, Dr. Ratner said, recipients who undergo the procedure so that they can receive a transplant require a greater degree of immunosuppression and have a higher complication rate. The subsequent surgical procedures are also more expensive. “So if we can do the swap rather than utilize plasmapheresis, it is better for everyone involved,” Dr. Ratner said.

Currently, the number of exchange kidney transplants remains small, but it could eventually become much larger, according to David Serur, MD, if the concept is expanded geographically.

“What some people have talked about are regional lists of recipients that don’t have compatible donors,” Dr. Serur said. “Some people mention national lists. It’s foreseeable that someone from upstate New York could come down here and donate. And likewise someone from here might go somewhere else.”

One reason the waiting list is growing so rapidly is the increasing number of older recipients with failing kidneys who are now considered eligible for transplants. Age 70 used to be an automatic cutoff point.

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Sandip Kapur, MD, checks organs in storage prior to transplantation. New technology has made more patients—particularly older patients—eligible for transplant.

# Studies of New Devices and Procedures Aim To Raise Standard of Care in Heart Transplantation

A series of investigations under way at NewYork-Presbyterian Hospital may advance the standard of care for patients who require cardiac transplantation.

Surgeons and cardiologists in the Heart Transplantation Program at NewYork-Presbyterian Hospital/Columbia University Medical Center have a long history of applying advanced clinical and basic research in clinical practice. Now, this bench-to-bedside approach has expanded to include evaluation of novel immunosuppression regimens, refinement of life-sustaining left ventricular assist devices (LVADs) and development of microarray-based molecular testing to identify patients at risk of allograft rejection—an innovation that could obviate the need for invasive biopsy in many patients.

“NewYork-Presbyterian/Columbia remains one of the largest centers for heart transplant in the country, and is recognized throughout the world as a leading center,” said Donna Mancini, MD. “We have a team of physicians with special expertise that are dedicated to care of these patients before, during, and following transplants.”

According to Dr. Mancini, the Heart Transplantation Program has taken a leading role in “pushing the envelope” to include patients who in the past would not have been candidates for the procedure. For example, the program now accepts patients with cardiac amyloidosis, a disorder caused by the buildup of amyloid fibril protein in the heart. Today, many of these patients can undergo heart transplantation successfully when the procedure is combined with bone marrow transplantation.

NewYork-Presbyterian/Columbia was the main coordinating center for the Randomized Evaluation of Mechanical Assistance Therapy for Congestive Heart Failure (REMATCH) trial—the landmark clinical trial showing for the first time the ability of LVADs to improve survival in patients with end-stage heart failure—and continues to be

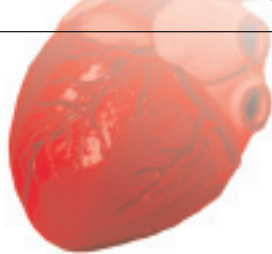
one of the largest LVAD centers in the country. This study has shown that LVADs may be useful as long-term therapy for heart failure, rather than a temporary bridge to transplantation.

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**“NewYork-Presbyterian/Columbia remains one of the largest centers for heart transplant in the country, and is recognized throughout the world as a leading center. We have a team of physicians with special expertise that are dedicated to care of these patients before, during, and following transplants.”**

—Donna Mancini, MD

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“We have an extensive and reliable history of research and clinical activity in this area, which is why we are leading this field,” said Yoshifumi Naka, MD.

Innovative new pumps that are smaller, quieter and more durable than earlier-generation devices are the subject of investigations already under way or scheduled to begin soon. One such device is the MicroMed DeBakey VAD, an axial flow device that weighs less than 4 oz and is one tenth the size of other

LVADs. NewYork-Presbyterian/Columbia is leading a major trial of this device as a bridge to transplantation. It is hoped that using this LVAD as a “destination therapy” will extend survival and improve quality of life in patients for whom transplantation is not an option.

“Rotary or axial flow VADs have potential advantages over other LVAD technologies,” Dr. Naka said. “They are much smaller, so patients may have less invasive surgery through a smaller incision, allowing for a quicker recovery. The pump is almost noiseless, which is a quality-of-life benefit, and the small percutaneous drive line results in fewer infections.”

The successful management of patients who undergo cardiac transplantation depends on careful monitoring for cardiac allograft rejection and dysfunction. Invasive endomyocardial biopsy is currently the gold standard for this surveillance. However, new research suggests management could be improved with microarray-based molecular testing. The use of peripheral leukocyte expression profiling assays in these patients has been evaluated in the Cardiac Allograft Rejection Gene Expression Observational (CARGO) study.

“We believe that gene array profiling of peripheral white blood cells has the potential to reduce and ultimately to replace routine biopsy, as the cardiac transplantation field accepts this new method,” said lead investigator Mario C. Deng, MD.

Results to date show that molecular testing can accurately distinguish acute rejection from the quiescent state. Dr. Deng and colleagues were able to identify more than 60% of biopsy-based encounters as quiescent using a clinical management algorithm combining clinical, graft function and assay data. The next step is to conduct a direct randomized comparison of molecular testing with biopsy. NewYork-Presbyterian/Columbia is 1 of 2 leading institutions in a research study designed to evaluate

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## Kidney

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“Not anymore,” said Sandip Kapur, MD. “We’ve transplanted close to a dozen people this past year that were 70 or over. But they look and feel more like 50. How can you deny them a transplant, particularly since we’ve gotten so good with immunosuppression and with our operation that many of them are able to withstand it just fine?”

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**David Cohen, MD**, is Medical Director, Renal Transplant Program at NewYork-Presbyterian

Hospital/Columbia University Medical Center, and is Associate Professor of Clinical Medicine at Columbia University College of Physicians and Surgeons.

E-mail: [djc5@columbia.edu](mailto:djc5@columbia.edu).

---

**Sandip Kapur, MD**, is Surgical Director, Kidney/Pancreas/Islet Cell Transplantation at New York-Presbyterian Hospital/Weill Cornell Medical Center, and is Assistant Professor of Surgery at Weill Medical College of Cornell University, and is Adjunct Assistant Professor of Surgery at Columbia University College of Physicians and Surgeons. E-mail: [sak2009@med.cornell.edu](mailto:sak2009@med.cornell.edu).

---

**Lloyd Ratner, MD**, is Director, Renal and Pancreatic Transplantation at NewYork-Presbyterian Hospital/Columbia University Medical Center, and is Assistant Professor of Surgery at Columbia University College of Physicians and Surgeons. E-mail: [lr2182@columbia.edu](mailto:lr2182@columbia.edu).

---

**Stuart D. Saal, MD**, is Medical Director, Kidney Transplantation, The Rogosin Institute at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, and is Professor of Clinical Medicine and Surgery at Weill Medical College of Cornell University. E-mail: [saals@mail.rockefeller.edu](mailto:saals@mail.rockefeller.edu).

---

**David Serur, MD**, is Medical Director, Kidney/Pancreas Transplantation, The Rogosin Institute at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, and is Assistant Professor of Medicine at Weill Medical College of Cornell University. E-mail: [serurd@mail.rockefeller.edu](mailto:serurd@mail.rockefeller.edu)

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## Heart

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whether molecular testing provides equivalent health outcomes while improving both quality of life and cost-effectiveness. This study, currently undergoing IRB review, is known as IMAGE (Invasive Monitoring Attenuation by Gene Expression).

“Noninvasive monitoring has the potential to improve quality of life, and would clearly provide the potential to fine-tune immunosuppressive medication regimens,” said Dr. Deng. This promising novel approach is currently expanding to major international heart transplant centers (CARGO 2) and to lung transplant rejection monitoring.

Other projects under way hold promise for patients undergoing heart transplant or LVAD implantation. Columbia researcher Simon W. Maybaum, MD, for example, is evaluating the incidence of recovery after placement of an LVAD device. In addition, he is looking at the use of the  $\beta_2$  agonist clenbuterol to improve the frequency of myocardial recovery and

exercise performance in these patients.

Columbia researchers are evaluating a powerful new immunosuppressant drug called everolimus. Similar to sirolimus, everolimus inhibits vascular smooth muscle cell proliferation, which in heart transplants may decrease incidence of serious postprocedural complications, including cardiac allograft vasculopathy.

However, transplant is just one area of focus. Columbia researchers are also looking at new procedures for heart failure such as biventricular pacing, and new treatments including the use of tolvaptan, a vasopressin antagonist, which may improve prognosis in these patients.

“Our hope is that we will continue to provide care at a high level, while developing therapies that not only treat heart failure, but may cure it,” Dr. Mancini said.

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**Mario C. Deng, MD**, is Director, Cardiac Transplantation Research at NewYork-Presbyterian Hospital/Columbia University Medical Center, and is Assistant Professor of Medicine at Columbia University College of

Physicians and Surgeons. E-mail: [md785@columbia.edu](mailto:md785@columbia.edu).

---

**Donna Mancini, MD**, is Medical Director, Cardiac Transplant Program and Heart Failure Center at NewYork-Presbyterian Hospital/Columbia University Medical Center, and is Associate Professor of Medicine at Columbia University College of Physicians and Surgeons. E-mail: [dmm31@columbia.edu](mailto:dmm31@columbia.edu).

---

**Simon W. Maybaum, MD**, is Attending Cardiologist, Cardiac Transplant Program and Heart Failure Center at NewYork-Presbyterian Hospital/Columbia University Medical Center, and is Assistant Professor of Medicine at Columbia University College of Physicians and Surgeons. E-mail: [swm17@columbia.edu](mailto:swm17@columbia.edu).

---

**Yoshifumi Naka, MD**, is Director, Mechanical Circulatory Support Program and Assistant Attending Surgeon at NewYork-Presbyterian Hospital/Columbia University Medical Center, and is Herbert Irving Assistant Professor of Surgery at Columbia University College of Physicians and Surgeons. E-mail: [yn33@columbia.edu](mailto:yn33@columbia.edu).

## Liver

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waiting list die before receiving a liver.

“That’s the benefit of live donations—you lower pretransplant mortality,” Dr. Brown said. “The fact that patients only receive half a liver doesn’t seem to affect the posttransplant outcome.”

In the remaining 5 years of A2ALL, investigators will evaluate a prospective cohort of approximately 1,000 patients and their paired living donors as candidates for transplantation. Only about 500 of the evaluations are expected to result in transplantations. The entire cohort will be studied on an intent-to-treat basis in order to identify the risks of living donation, as well as the factors that influence outcomes for both live donors and recipients. The study is being carried out under a grant from the National Institute of Diabetes and Digestive and Kidney Diseases.

“There are thousands of people waiting for livers, but only about 25% can be transplanted by waiting for livers from deceased donors,” Dr. Emond said. As a result, the number of living donor liver transplants has grown rapidly in the United States since the procedure was introduced in 1997. At NewYork-Presbyterian Hospital, a leader in the field, about one third of the livers are transplanted from living donors.

Availability of living donors is vital because there is currently no artificial liver support system comparable to renal dialysis in patients with failing kidneys. Transplantation remains the only option for patients with end-stage liver disease.

The risk faced by living donors who donate to adults remains uncertain,

whereas the use of living donors in pediatric transplantations is well established. Since the pediatric patient needs a smaller piece of liver (only the liver’s smaller left lobe is taken from the donor liver and transplanted into pediatric recipients), the operation is less risky for the donor. In contrast, adult transplant patients require the larger right lobe from the living donor, which comprises 50% to 60% of the liver mass. The procedure is feasible because both the donor and recipient livers can regenerate to full size following transplantation.

Controversy over the safety of living donation to adults “came to the fore after the death of a donor at another New York hospital in 2001,” Dr. Emond said. The media attention led New York State to develop the first regulatory guidelines for this procedure. The NIH sponsored a consensus conference in Washington, DC, which led to the formation of A2ALL, which looks at how donors fared over both the short and the long term.

“No one has clarified the risk to the donor,” Dr. Emond said. Nor, he added, has there been a formal study to clarify the fate of patients “who choose to have a living donation from a family member rather than wait for a deceased donor.”

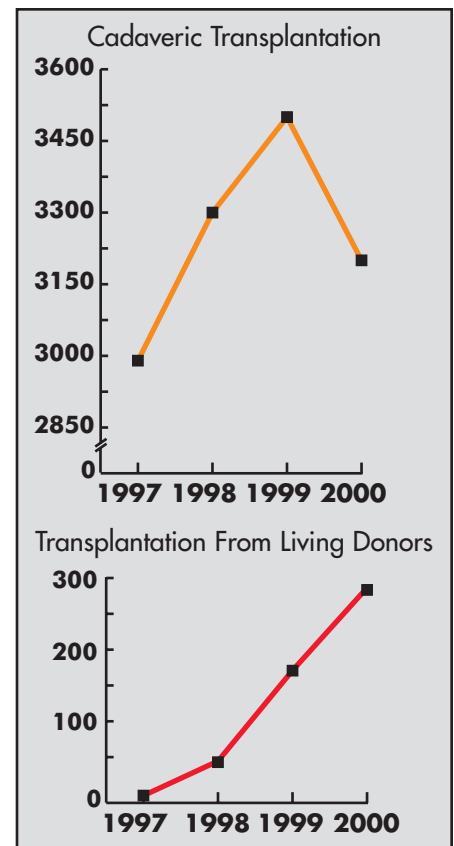
“We’re taking healthy people and exposing them to a procedure with risk, albeit small, for a benefit in another individual,” added Dr. Brown. “We have an obligation to study it and understand it.”

**Robert S. Brown, Jr, MD, MPH,** is Medical Director, Center for Liver Disease and Transplantation at NewYork-Presbyterian Hospital/ Columbia University Medical Center,

important research projects that will further improve patient care.”

These successes have set the stage for cutting-edge investigations in genetics, outcomes research, and posttransplant immunosuppression regimens. Investigations that are under way or planned include the following:

**Gene expression.** In 2 protocols, investigators will measure gene expression profiles in peripheral blood in an effort to



**Figure. Donor sources for liver transplantation nationally, by year.**

Source: Brown RS Jr, Russo MW, Lai M, et al. A survey of liver transplantation from living adult donors in the United States. *N Engl J Med.* 2003;348:818-825.

and is Associate Professor of Clinical Medicine and Pediatrics at Columbia University College of Physicians and Surgeons. E-mail: rb464@columbia.edu.

**Jean C. Emond, MD,** is Vice Chairman and Chief of Transplantation Services at NewYork-Presbyterian Hospital/ Columbia University Medical Center, and is Thomas S. Zimmer Professor of Surgery at Columbia University College of Physicians and Surgeons. E-mail: je111@columbia.edu.

## Lung

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risk patient base, according to Selim Arcasoy, MD.

“What accounts for the improvement is a significant enhancement of bedside patient care from a dedicated, multi-disciplinary team, and the development of protocol-based patient management,” Dr. Arcasoy said. “We are developing

diagnose transplant rejection without the need for an invasive procedure.

According to Dr. Arcasoy, the goals are to determine early which patients may reject the lung transplant and to understand the mechanisms for rejection, so patients can be treated more effectively.

**Outcomes.** Columbia researchers at NewYork-Presbyterian Hospital are looking at genetic factors, both in lung

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donors and recipients, that may determine the posttransplant clinical course. Another investigation is focused on whether certain factors, such as performance on an exercise test, might be determinants of favorable outcomes in the period immediately following transplant.

"We are hoping to find ways to determine which patients are sick or getting sicker, so that they will be placed on the waiting list sooner," said Dr. Arcasoy. "When a new priority-based system comes into play, as is expected to happen next year, such research will be instrumental in finding ways to prioritize patients for lung transplantation."

**Immunosuppression.** Ongoing studies are evaluating the potential of new post-transplant immunosuppression regimens. In particular, investigators are comparing 2 tacrolimus-based combination regimens (tacrolimus/sirolimus-

/prednisone vs tacrolimus/azathioprine/prednisone) in lung transplantation patients.

Transplant volume has increased dramatically in the past few years, from 11 cases in 2001 to 26 in 2003. It is expected that by the end of 2004, as many as 30 to 35 patients will have received lung transplants. But transplantation is just one of several therapeutic options that the Lung Transplant Program offers patients. Several medical and surgical therapies for advanced lung disease are available within the program, including lung volume reduction surgery, advanced minimally invasive surgery, and robotic techniques.

Patients also may be recommended for novel therapy protocols, either directly through the Lung Transplant Program, or through other programs within NewYork-Presbyterian/Columbia, including the Cystic Fibrosis Center, Pulmonary Fibrosis Program, and Pulmonary Hypertension Program.

"What sets our program apart is that

we will do whatever it takes to allow our patients to live as long as possible, and that may not include transplant," Dr. Sonett said. "Whatever is in the best interest of our patients is in our best interest as well."

**Selim Arcasoy, MD**, is Medical Director, Lung Transplantation Program at NewYork-Presbyterian Hospital/Columbia University Medical Center, and is Associate Professor of Clinical Medicine, Department of Medicine, Pulmonary, Allergy and Critical Care Division at Columbia University College of Physicians and Surgeons. E-mail: sa2059@columbia.edu.

**Joshua R. Sonett, MD**, is Surgical Director, Lung Transplantation Program at NewYork-Presbyterian Hospital/Columbia University Medical Center, and is Associate Professor of Clinical Surgery, Division of Cardiothoracic Surgery, Department of Surgery at Columbia University College of Physicians and Surgeons. E-mail: Js2106@columbia.edu.

**SERVICE LINE ADMINISTRATOR: Bruce Gantt, 627 West 165th Street, New York, NY 10032, 212.305.0009** E-mail: brg9003@nyp.org

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NewYork-Presbyterian Hospital  
425 East 61st Street  
New York, NY 10021

**Important news from the NewYork-Presbyterian Transplant Institute, at the forefront of heart, lung, liver, kidney, and pancreas transplantation, and clinical research to advance transplant surgery and organ health.**

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