Transplant Immunology: The Science Behind Organ Transplantation

The Columbia Center for Translational Immunology leads research using hematopoietic cell transplantation for induction of tolerance

Patients receiving treatment at the renowned organ transplant programs at NewYork-Presbyterian Hospital/Columbia University Medical Center may be unaware that just beyond their treatment rooms, a one-of-a-kind research powerhouse is quietly at work conducting some of the most vital studies underway in transplant immunology today.

The multidisciplinary Columbia Center for Translational Immunology (CCTI), established in 2010 under the leadership of Megan Sykes, MD, Director, is performing a host of cutting-edge studies. The work aims to increase understanding of immunologic diseases and directly translate that knowledge to the development of new or improved clinical therapies for transplant patients at NYU/Columbia and beyond.

Of these areas of study, one area holds particular importance for patients undergoing organ transplantation: hematopoietic cell transplantation (HCT). Hematopoietic cells are cells (including bone marrow cells) that develop into blood cells; transplantation of these cells from a healthy donor, the most widely used form of cellular therapy today, is the only known cure for certain blood cancers (leukemia, lymphoma, myeloma) and is performed in approximately 60,000 patients each year for that purpose. But HCT also has the potential to reverse the autoimmune process responsible for diseases such as type 1 diabetes—and to induce tolerance in patients who receive organ transplants.

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What is “Tolerance”?

When a patient receives a heart, lung, liver, kidney, or pancreas from an organ donor (living or deceased), the patient’s immune system will recognize the foreign tissue and mobilize to reject the organ unless he or she takes medications that suppress the immune system’s natural processes. These medications, known as immunosuppressants, are a lifelong requirement after organ transplantation. While these drugs allow people to tolerate the presence of foreign organs, they also increase patients’ risk of contracting infections, and infections and are associated with other undesirable side effects. The ability to induce tolerance to a transplanted organ, allowing it to thrive in the body without requiring these life-long immunosuppressants, would signify a dramatic improvement in quality of life for patients undergoing organ transplantation. For many in the field, induction is considered the “holy grail.”

During the last decade, Dr. Sykes’ research in HCT (begun while she was Associate Director of the Transplantation Biology Research Center at Massachusetts General Hospital) has produced notable results toward that goal. In one protocol, out of ten patients studied, seven have achieved long term tolerance, so far lasting three to ten years. Although several other U.S. hospitals have subsequently attempted similar protocols, this has been the most successful and long-lasting tolerance demonstrated to date.

To achieve these results, Dr. Sykes’ team first administered drugs known as a “conditioning regimen” to reduce both the immune function and the numbers of the patients’ own bone marrow cells. Next, they performed bone marrow and kidney transplants from living unrelated donors. A short course of immunosuppressant medications was administered immediately after transplantation, and then tapered down and stopped altogether.

According to Dr. Sykes, it was remarkable that tolerance was successful even when the donor’s most potent transplantation antigens were mismatched to the recipient’s. Most bone marrow transplants normally require a match between the donor’s and recipient’s human leukocyte antigen (HLA) system, part of the immune system which encodes the most potent antigens. Performing bone marrow transplants across the HLA barrier usually results in serious, systemic rejection known as graft versus host disease (GVHD). Using the protocol mentioned above, however, they achieved significant success without GVHD even across HLA barriers. “These are exciting results showing that we can achieve robust tolerance,” says Dr. Sykes.

Dr. Sykes’ team continues to test multiple protocols in an effort to strengthen tolerance even further, first in animal models to evaluate safety and efficacy. These protocols aim to achieve the following goals in stages:

• inducing tolerance with HLA-identical patients with kidney failure due to malignant disease (such as multiple myeloma);
• reliably performing transplants without GVHD in HLA-mismatched patients;
• using a large animal model to achieve more durable bone marrow engraftment and hence more reliable tolerance;
• achieving tolerance of pancreatic islet cells—to be studied in animal models and eventually in patients with combined islet and bone marrow transplants;
• achieving tolerance of liver transplants by combining liver and bone marrow transplantation;
• eventually, expanding tolerance studies to lung and heart transplantation.

Markus Mapara, MD, PhD, Director of the Blood and Marrow Transplantation (BMT) Program at Columbia University Medical Center, will collaborate with CCTI to develop novel hematopoietic cell transplant protocols beginning in 2013. According to Dr. Sykes, “The establishment of the BMT program is a key step in allowing NYP/Columbia to take a leadership role in these promising new applications of hematopoietic cell transplantation.” CCTI and the BMT program will further collaborate with leaders of the NYP/Columbia kidney and liver transplant programs, including Drs. Lloyd Ratner, David Cohen, Waichi Wong, Jean Emond and Tomoaki Kato.

To learn more about CCTI, please visit: www.cumc.columbia.edu/ccti
**Advances in Breast Surgery: Intraductal Papillomectomy**

Division of Breast Surgery to offer scarless, endoscopic procedure to detect intraductal papillomas

Patients at NewYork-Presbyterian Hospital/ Columbia University Medical Center will soon benefit from yet another in a long string of advances: intraductal diagnosis, and eventually, treatment of breast papillomas. Intraductal papillomas are benign lesions within the milk ducts that account for 40% of cases of pathologic nipple discharge in women aged 20-40.

The development of intraductal approaches to diagnosis and treatment represents one of the most important advances in breast disease treatment in the past decade. Intraductal techniques allow surgeons to perform evaluations through the nipple using very fine micro-endoscopes without surgery and without general anesthesia. This minimally invasive approach has been proven highly successful in the detection of papillomas. **Sheldon M. Feldman, MD**, Chief, Breast Surgery Section, is considered the most experienced breast endoscopist in the U.S., having researched and used minimally invasive techniques for ten years.

Now, NYP/Columbia is poised to become the only facility in the U.S. to offer scarless endoscopic papillomectomy for diagnosis of pathologic nipple discharge. This unprecedented advance will be made possible in large part by the presence of **Fatih Levent Balci, MD**, a postdoctoral research scientist who also has extensive expertise in endoscopic ductoscopy. In his native Turkey, Dr. Balci and colleagues determined that the intraductal approach could be successfully used not only for the diagnosis of intraductal lesions, but also to remove single papillomas. In his 2009 paper published in Onkologie, “Scarless Endoscopic Papillomectomy of the Breast,” Dr. Balci’s team found that the technique had 95% therapeutic efficacy in patients with pathologic nipple discharge due to papillomas. “Using this procedure, we can remove single papillomas in an office with a local anesthetic cream,” Dr. Balci says.

Despite its value in treating papillomas, endoscopic papillomectomy is currently restricted to diagnostic purposes in the U.S., as the super-fine micro-endoscope needed for removal of papillomas has not yet received FDA approval in this country. That technology is currently available in Turkey, permitting endoscopic removal of papillomas in patients there. Dr. Balci and Dr. Feldman have submitted applications for approval of the necessary catheter so that NYP/Columbia can begin using intraductal ductoscopy for both detection and removal of breast papillomas at this hospital. That process is likely to take several months, according to Dr. Balci.

In addition to its role in detecting and removing papillomas, Dr. Balci points to yet another potentially groundbreaking role of intraductal endoscopy: Detection of ductal carcinoma in situ (DCIS), a non-invasive form of breast cancer in the milk ducts. Although studies have yet to confirm his group’s early findings, Dr. Balci’s team has been able to detect DCIS using intraductal endoscopy during its research in Okmeydani Teaching and Research Hospital, Istanbul, Turkey, from 2004 to 2009. “DCIS does not always appear on conventional imaging such as MRI or mammography, but early results of our study indicate that DCIS can be detected during ductoscopy. The ability to detect breast cancer before our conventional imaging models find it would be an enormously valuable advance.” Moreover, Dr. Balci explains it would be possible to easily extract just the isolated duct using ductoscopy and microductectomy. “Extracting just the isolated duct should give women the best cosmetic result, with no deformity of the breast,” he says.

Dr. Feldman concludes, “By assembling a robust team with expertise in mammary ductoscopy and ductoscopic minimally invasive procedures, we are well poised to advance diagnosis and treatment of breast cancer.”

To learn more, visit: breastmd.org
Pediatric Cardiac Surgery

STS report confirms hospital's outstanding surgical outcomes

About one in 125 newborns is affected by a heart defect at birth, making congenital heart defects a leading cause of death in infancy. Over 35 identified defects span the range from mild and treatable to complex and life-threatening. Yet today, the vast majority of infants born with heart defects – even those with severe disease – are successfully treated and can expect to live healthy and active lives, thanks to the expertise of programs such as NewYork-Presbyterian Morgan Stanley Children’s Hospital of New York (MSCHONY) and Komansky Children’s Center.

Of all the centers that treat children with heart disease in New York State, MSCHONY far surpasses all others in terms of patient volume. The most recent national evaluation also confirms the program’s performance not just in terms of volume, but in clinical excellence: despite treating many patients with the most severe and complex conditions, the pediatric cardiac surgery program at NYP/Columbia has achieved outcomes superior to every other New York hospital performing the same surgeries. In addition to its top position in New York, MSCHONY’s outcomes also surpass the national rates in virtually every procedure. Overall, the center continues to rank in the top four centers nationally.

The most recent report, the Congenital Heart Surgery Database of the Society of Thoracic Surgeons (STS), lists the most frequent procedures performed in newborns and infants, and compares NYPH’s results against national outcomes from January 2008 to December 2011 (four full years). The STS database is considered the gold standard in terms of quality assessment in Congenital Heart Surgery. In all but two procedures, NYPH’s outcomes are significantly better than the national average, as measured by mortality.

For example, the national mortality rate for newborns undergoing the Norwood procedure (for hypoplastic left heart syndrome or other single ventricle disorders) is 16.7%, while at NYP/Columbia, the mortality rate is 12.9%. The mortality rates for arterial switch or arterial switch with ventricular septal defect (VSD) repair, and surgeries for aortopulmonary shunt, aortic arch repair, and interrupted aortic arch repair, are 3%, 6.7%, 4.4%, and 5.4% respectively across the nation. In comparison, the mortality rates for each of those procedures at NYPH is 0. For totally anomalous pulmonary venous connection (TAPVC) repair, the hospital’s mortality rate is just 3.8%, compared to 14.1% nationally. Overall, the non-risk adjusted mortality rate for all procedures is 2.4% at NYP compared to 3.3% nationally – but when adjusted for the higher risk of many of its patients, NYPH’s mortality rate improves even further.

To learn more about the Pediatric Surgery Program, please visit: www.childrensnyp.org

### Outcomes in Pediatric Cardiac Surgery

January 2008 – December 2011

<table>
<thead>
<tr>
<th>Most Frequent Procedures (Neonates)</th>
<th>Number of Procedures</th>
<th>Mortality at NYPH</th>
<th>STS Mortality (National)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norwood Procedure</td>
<td>85</td>
<td>12.9%</td>
<td>16.7%</td>
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<tr>
<td>Arterial Switch or Arterial Switch/Ventricular Septal Defect Repair</td>
<td>76</td>
<td>0%</td>
<td>3%</td>
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<tr>
<td>Coarctation Repair</td>
<td>38</td>
<td>2.6%</td>
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<td>Aortopulmonary Shunt</td>
<td>33</td>
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<td>6.7%</td>
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<tr>
<td>Aortic Arch Repair</td>
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<td>4.4%</td>
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<td>TAPVC Repair</td>
<td>26</td>
<td>3.8%</td>
<td>14.1%</td>
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<td>Interrupted Aortic Arch Repair</td>
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<td>5.4%</td>
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<tr>
<th>Most Frequent Procedures (Infants)</th>
<th>Number of Procedures</th>
<th>Mortality at NYPH</th>
<th>STS Mortality (National)</th>
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<tbody>
<tr>
<td>Ventricular Septal Defect Repair</td>
<td>97</td>
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<td>0.6%</td>
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<tr>
<td>Tetralogy of Fallot Repair</td>
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<td>Bidirectional Glenn</td>
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<td>Complete Atroventricular Canal</td>
<td>55</td>
<td>0%</td>
<td>2.2%</td>
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<tr>
<td>Heart Transplant</td>
<td>87</td>
<td>0%</td>
<td>3.1%</td>
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