Tissue Engineering and Regenerative Medicine: Progress toward alleviating donor organ shortages

Research advances in the MassGeneral Hospital for Children (MGH/C) Center for Regenerative Medicine have brought the field closer to engineering entire living organs that are free of immunosuppression challenges and that can be used to replace organs in end-stage failure. As researchers work toward that goal, says Joseph P. Vacanti, MD, deputy director of the Center for Regenerative Medicine and surgeon in chief at MGH/C, interim steps will produce living structures made from the patient’s own cells that can replace damaged or diseased tissue. Already, many of these interim products have been incorporated into clinical practice and hundreds more are in the pipeline.

Developing organ structures with polymers

Dr. Vacanti began working in the field of tissue engineering 25 years ago, when the field was in its infancy. Throughout the 1980s, he experimented with methods for growing cells on a palette of biogradable polymers, eventually focusing on the importance of a three-dimensional scaffold for solid organ formation. The addition of stem cells to the field of regenerative medicine further advanced the value of Dr. Vacanti’s work. Biodegradable scaffolds, he notes, provided a critical structure for tissue-specific cell seeding and guided tissue development. Normal healing processes replace the scaffolding as it degrades.

Currently Dr. Vacanti’s lab focuses on finding the right combination of synthetic polymer, cellular components, growth factors and modifications to the strength, flexibility and surface features of the matrix to create functional hearts, lungs and kidneys. Throughout the field of regenerative medicine, virtually every structure in the human body is under study. To become functional, says Dr. Vacanti, these components must be placed in a bioreactor that exposes them to tissue-specific mechanical forces, such as pressure and flow for blood vessels and compression and tension for cartilage and bone.

In addition to generating progress toward whole organs or tissues, knowledge and designs from the Vacanti Lab have resulted in assist devices that perform the mechanical function of organs but do not contain cells. These devices have been used in animal models for lung, liver and kidney. Once available clinically, they will provide bridge therapy for patients awaiting transplantation or destination therapy for patients who are not candidates for transplantation.

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Natural matrices using cadaveric organs

Harald Ott, MD, in the Center for Regenerative Medicine, has worked with Dr. Vacanti to expand on the value of matrices in a different direction by developing organ profusion decellularization, a technology to remove all cells from a cadaveric organ. The remaining collagen matrix is then infused with new adult-derived stem cells in a process that is identical to that used with the synthetic matrices. This method of reseeding and engraftment with native cells potentially eliminates the need for life-long immunosuppression in transplant patients, a particularly critical issue in pediatric transplantation since children undergoing organ transplant face a lifetime of immunosuppressive medications.

Dr. Ott’s initial work was in the heart. Following early animal studies that involved parts of recellularized hearts, Dr. Ott is working with the New England Organ Bank and the Mass General Transplant Center in an attempt to upscale the process of scaffold generation to human hearts. Additionally, his lab is attempting to isolate human cardiomyocytes, cells critical to heart function. The lab is also applying the technique in the lung which, says Dr. Ott, has an advantage over heart regeneration in that it does not need to provide active mechanical work. Instead, it provides gas exchange through a membrane that can be accessed on both sides to facilitate cell seeding. To date, Drs. Ott and Vacanti have reported the ability of transplanted regenerated lungs to function in vivo in animal models for a period of up to 10 days. Failure appears due to the need for cell subpopulations required for mucociliary clearing. Dr. Ott is collaborating with the Rajagopal Lab at Mass General to try to reconstitute mucociliary clearance. Additional efforts include applying the same approaches in the pancreas, kidney, and liver.

Since the results of this work were published in 2008, interest in using decellularized cadaveric organs as a platform for organ development has exploded. While the goal of providing these new organs in the clinic is still years away, says Dr. Ott, the work will produce intermediary steps of more immediate value to patients, including the creation of “patches” that can be used to replace damaged portions of hearts, lungs, airways, or other organs.

Successfully bringing together all of the factors necessary to create clinically viable living tissue and organs requires the resources of MGH/C and its collaborative relationship with MIT, which provide researchers in the Center for Regenerative Medicine with access to experts in surgical science, chemical engineering, cellular and molecular biology, and technology development. Equally as critical, says Dr. Vacanti, is the expertise of specialists in the Mass General Transplant Center, who provide insight into the most current understanding of biology of the inflammatory response.

“Even though these living organs will be made from stem cells of the patient who needs the organ,” explains Joren C. Madsen, MD, DPHL, director of the Mass General Transplant Center and section chief of Cardiac Surgery, “the structure itself is not of the patient’s tissues.” As a result, transplant specialists and immunologists need to participate in living organ development to address potential immunological effects. As the field of tissue engineering and regenerative medicine matures, MGH/C clinical researchers remain committed to continuing their leadership role in overcoming the remaining biological and engineering challenges. Each step of the way, says Dr. Vacanti, brings medicine closer to the goal of providing patients in need with biological substitutes that restore, maintain or improve tissue function for patients.

Since the results of this work were published in 2008, interest in using decellularized cadaveric organs as a platform for organ development has increased dramatically.
New Medical Genetics Chief Focuses on Expansion and Lifelong Genetic Services

While the traditional purview of medical genetics was inherited birth defects, says David Sweetser, MD, PhD, MassGeneral Hospital for Children’s (MGH/C) new chief of Medical Genetics, the field now encompasses inborn errors of metabolism that lead to abnormalities in children and adults. While some of these disorders are detected and managed from birth, others may not be diagnosed until they become problematic in adulthood. Identifying these disorders early — or even identifying the risk during pregnancy counseling — could help protect individuals and families from some of the long-term effects.

“We are one of the few programs in the country that can offer genetic services throughout the lifespan, from prenatal counseling and newborns and into adulthood,” says Dr. Sweetser. This comprehensive range of services facilitates care and also leads to improved understanding of the clinical symptoms and management of underlying genetic mutations. Individuals with a connective tissue disorder called Marfan syndrome, for example, are at high risk for aortic rupture. Following these patients with serial ultrasounds allows for identification of the optimal time for a surgical graft.

Under Dr. Sweetser’s leadership, the division will increase the scope of its services. These efforts include consultations with other specialists concerned about the possibility of a genetic cause for their abnormalities, prenatal genetic counseling, genetic counseling and screening of family members, and multidisciplinary clinics for patients with rare or more common syndromes, as well as a clinic for adult patients with Down syndrome. The division is expanding geographically as well, with a new clinic at Mass General/North Shore Center for Outpatient Care in Danvers, MA. In collaboration with Massachusetts Eye and Ear Infirmary, the division has created a new sensory-neuro hearing loss multidisciplinary clinic for patients with hearing loss attributable to genetic causes, and a new partnership with Shriner’s Hospital will focus on genetic components of inherited skeletal dysplasias and abnormalities of bone metabolism. Dr. Sweetser is recruiting new clinicians and scientists to reduce wait time for appointments and to uncover new genetic mutations that may point the way to new targeted therapies.

Dr. Sweetser’s research focuses on the genetic basis of cancer with the goal of finding novel targeted therapies. His lab identified a new class of tumor suppressor genes involved in leukemia that may be implicated in many more malignancies. The lab also screens new compounds in model systems, and has published findings relating to the ability of COX2 inhibitors to reduce risk for colorectal, breast and prostate cancer. Additionally, he is working with colleagues at the Broad Institute and in local academic hospitals to determine what aspects of whole genome sequencing are appropriate in the clinical setting.

Dr. Sweetser received his MD and PhD from Washington University School of Medicine (Missouri), and completed a residency in pediatrics at St. Louis Children’s Hospital. He has also done fellowships in medical genetics at Washington University and at University of Washington School of Medicine (Washington), as well as a fellowship in pediatric hematology/oncology at University of Washington. A Harvard Medical School assistant professor of pediatrics, he joined the staff at MGH/C in 2005.
At MassGeneral Hospital for Children (MGHfC), performance measurement is viewed as an opportunity to improve in meaningful areas of patient care. According to Esther Israel, MD, director of Inpatient Quality and Safety at MGHfC and associate unit chief of Pediatric Gastroenterology and Nutrition, quality and safety aren’t about collecting and reporting data. They’re an opportunity to define and respond to indicators of quality that provide patients, families and colleagues with the assurance that care is safe, efficient and effective.

Initiatives at MGHfC focus on the six aims defined by the Institute of Medicine for achieving quality in pediatric care: Safety, effectiveness, efficiency and equality, as well as timely and family-centered care. Individual projects, identified by members of the care team from day-to-day experience on the floor, and by the Quality and Safety Team using input from patient experience surveys, safety report forms available on the inpatient units and other data sources, build on MGHfC’s long history of service-wide and unit-based committees and projects relating to quality and safety. Improvements, says Kristen Solemina, MPH, quality and safety manager for MGHfC, can range from the small and quickly accomplished to larger-scale initiatives that are tackled by teams of nurse managers, physicians, residents, child life specialists, parent volunteers and other staff. “The quality and safety mindset is integrated into our daily processes,” says Solemina. “Everyone involved in the treatment of our patients is always thinking about how to do things better and provide the highest quality of care.”

Efforts in improving family-centered care include involving families with the management of the patient’s disease. Five years ago, MGHfC moved to bedside rounding. Rather than standing outside the patient’s room to discuss the case, the team gathers around the patient and family to discuss the treatment plan and include them in the process. A second initiative aimed at improving family-centered care helps ensure parents are kept updated during the pediatric intensive care unit (PICU) admissions process.

A MGHfC child life specialist uses distraction techniques to reduce needle insertion pain.
“Having your child admitted to intensive care is incredibly stressful for parents,” says Phoebe Yaeger, MD, PICU physician, who leads the project. “Our goal is to do what we can to alleviate that stress by connecting regularly with the parents to let them know how their child is doing.”

Needle insertion pain and distress for children undergoing IV insertion and phlebotomy is an issue recently identified by inpatient comments. One of the current Quality initiatives focuses on improving the management of needle insertions. Representatives from nursing, pain management and Child Life have joined forces with Dr. Israel to create a brochure and teaching module on reducing needle insertion pain and distress. The materials, based on extensive literature review, input from Mass General clinical experts and review of national best practices, include using a local anesthetic to numb the injection site, distraction techniques and holding techniques. Information is disseminated to nurses, physicians, and other practitioners in the hospital. A separate handout has been developed for parents.

But beyond these specific projects, Dr. Israel says, is the need for meaningful measures of whether good care is being provided. The Quality and Safety Team is working with each of the subspecialties individually and with national groups to define and measure quality. At the national level, MGHfC is participating in the Value in Pediatrics (VIP) project, a national collaborative aimed at benchmarking the care of inpatients with bronchiolitis and creating national care standards. The group analyzes length of stay, age, readmission, variable costs, and bronchodilator and steroid administration data for all bronchiolitis admissions with the goal of defining treatment guidelines that reduce readmissions nationally.

Within MGHfC, efforts are underway to establish baseline values for a high-quality pediatric colonoscopy. The team is now establishing baseline values that include the frequency with which pre-procedure steps are documented, the quality of the preparation, and whether the procedure was intended to reach the ileum and, if so, whether it did. This initiative improves documentation for referring physicians as well as ensuring the best quality diagnostic procedure.

According to Dr. Israel, these efforts and participation in other national organizations allow service areas within MGHfC, such as the PICU and newborn intensive care unit, to measure quality of care and medical outcomes and to compare performance to similar organizations. “Using this information, we can identify and celebrate our successes,” says Dr. Israel. “We can also help support the care team in their number one passion: Providing the best possible care for children.”

“Everyone involved in the treatment of patients is always thinking about how to do things better and provide the highest quality of care.”

Kristen Solemina, MPH

For more information about quality and safety initiatives at MGHfC, please visit massgeneralforchildren.org/qualityandsafety
As a comprehensive service within Mass General, MassGeneral Hospital for Children’s (MGHfC) transplant program provides multidisciplinary care for infants, children and adolescents before, during and after organ transplantation, including seamless transition to adult care at the appropriate time. This care, performed by a team of experts that includes pediatric specialists such as hepatologists, nephrologists, urologists, gastroenterologists, surgeons, psychiatrists, infectious disease specialists, nutritionists and social workers, as well as surgeons from Mass General’s Transplant Center. This care team is informed by the most current understanding of the disease’s process, diagnostic procedures, treatment options and psycho-social repercussions related to late-stage organ disease in infants and children.

“Patients referred to our pediatric specialists receive the full complement of medical care beginning with initial contact and extending throughout their lifetime,” says Uzma Shah, MD, medical director of the Liver Transplant Program and director of the Hepatobiliary and Pancreatic Program. “For those children requiring organ transplantation, we work in conjunction with the transplant surgeons to ensure high-quality, well-coordinated, patient- and family-focused care before, during and after surgery.”

This fully integrated relationship with Mass General’s adult transplant program is a benefit to patients as they age. It also provides important benefits for parent-to-child organ donations. Unique among New England’s pediatric organ transplant programs, MGHfC can offer surgical and medical care to both donor and recipient, allowing families to stay together during this challenging time.

Case review: liver transplant

In 2004, a pediatric gastroenterologist at Dartmouth-Hitchcock Medical Center in Lebanon, New Hampshire, referred a 5-month-old girl, “S,” with congenital biliary atresia to MGHfC. According to Martin Hertl, MD, surgical director of the Liver Transplant Program, the child had undergone a hepatoportoenterostomy, or Kasai procedure, to connect her small intestine directly to the liver at a New York Hospital, but the procedure had failed. Weighing only 5.4 kg, S was gaining water weight at a rate of one pound per week. Her pediatric end stage liver disease (PELD) score, which uses lab values and growth parameters to assess the risk or probability of death within three months if the patient does not receive a transplant, was 24 out of a 6-40 range.

On April 15, when Dr. Hertl first met his new patient, she had diarrhea and symptoms of an upper respiratory infection (URI). Following a consult with MGHfC pediatric infectious disease specialists, the baby was admitted to MGHfC for transplantation evaluation and URI treatment. While she was released two days later, she was on the operating table in just over a month.

This is fast, Dr. Hertl says, but evaluation can be done within a day if needed—a particular advantage in children who have overdosed on Tylenol. “Under one roof,” he says, “we can do everything required for transplantation preparation and evaluation and operate the next morning.”

Both parents were willing to donate to their child, but the father, “M,” was the preferred donor. On May 12, Dr. Hertl and his team removed S’s liver while, in the next surgical suite, a separate transplant team removed segments 2 and 3 of M’s liver and delivered them to Dr. Hertl, who successfully placed them in S’s body. Six days after surgery, S suffered hepatic vein thrombosis, caused by failure of a vein in the piece of liver received from her father. This complication necessitated a second transplant, this time of a hepatic vein received from a blood-group compatible cadaveric donor. This procedure was also done at MGHfC. S’s recovery was further slowed by duodenal perforation and candida peritonitis, which were managed by members of the multidisciplinary care team. In late July, S returned home to her parents, returning to MGHfC only briefly for treatment for viral gastroenteritis. Now a happy 7-year-old, S is seen annually in the MGHfC transplant clinic where she is followed by a team of specialists at each visit. Between visits, her care is managed by her pediatrician at Dartmouth-Hitchcock.
**Case review: kidney transplant**

In a case covered extensively by the *Boston Herald* earlier this year, Dicken Ko, MD, director of Renal Transplant Program and surgical director of the Kidney Transplant Program, and other members of the multidisciplinary pediatric organ transplant team, removed a kidney from 39-year-old Tara Johnson and placed it in her 2-and-a-half-year-old son, Andrew.

Andrew's condition, a blockage in his urinary tract, was diagnosed during a 19-week ultrasound. Andrew was not expected to survive, but the blockage improved, leaving Andrew's kidneys badly damaged. MGH/C pediatric nephrologist, Avram Traum, MD, medical director of Renal Transplant Program, began caring for Andrew the day he was born, including the 11 days the infant spent in the neonatal intensive care unit and during a surgery to fully relieve the blockage Andrew underwent when he was 3 days of age. Following discharge, Andrew was seen weekly by MGH/C transplantation specialists and underwent nightly dialysis beginning at 10 months of age while his organ transplant team waited for his body to be large enough to receive an adult kidney. Finally, in March, after assistance from the MGH/C nutritional team to help Andrew reach the goal weight of 10 kg, Andrew was ready.

“This is a rare operation,” says Dr. Ko. “Only about 140 kidney transplants done annually involve an adult kidney placed in a child under 5. In all of New England, there are probably only 30 of these procedures done each year.” Both parents were willing to donate but Tara’s evaluation, performed at the Mass General Transplant Center, showed her to be the preferred donor. Her procedure was done laparoscopically in a room that adjoined the surgical suite where Andrew awaited his new kidney. The kidney, says Dr. Ko, began working almost immediately.

To date, Andrew has experienced no serious complications, and continues to grow and develop. He will be followed by his care team and, following adolescence, will likely require another transplant.

**Easing the complexity of care**

One overarching goal for the MGH/C transplant program, says Dr. Traum, is to ease the complexity of care for patients and family members, both in the time leading up to and during the procedure and in follow-up care. “Having the same doctor before, during and after transplant is reassuring for families,” Dr. Traum says. This goal is further demonstrated in the seamless transition of pediatric care to adult care. According to Mass General transplant surgeon Heidi Yeh, MD, “These patients and their family members see the same specialists, in the same space, and all the doctors already know one another and communicate on a regular basis.” In addition to the ability to prevent or treat any medical issues that arise, this continuous care leads to solutions for post-transplant challenges such as compliance with medication. For example, the team is working on a text messaging application that will send reminders when it’s time to take medications. If no response is received, a second reminder is delivered. All activity is logged so that members of the care team can check compliance. This application will help middle adolescents learn to accept responsibility for their medications.

Reducing complexity helps community pediatricians as well by providing a single point of access for questions with the ongoing management of their transplant patients or for referrals to adult specialists such as dermatologists and OB/GYNs experienced in the care of transplant patients. “The complexity of care involved in organ transplantation requires a wide variety of specialists who communicate effectively, even in a critical situation,” says Dr. Traum. “Our goal at MGH/C is to provide this level of expertise to patients, families and referring physicians in a single visit or with a single phone call.”

**For more information about the MGH/C Transplant Program, please visit massgeneralforchildren.org/transplant**
Pediatric cardiologist Oscar J. Benavidez, Jr., MD, began his appointment as chief of pediatric cardiology at MassGeneral Hospital for Children (MGHfC) in April 2011. Dr. Benavidez received his medical degree at Harvard Medical School and completed a residency and fellowship at Children’s Hospital Boston. He is an assistant professor at Harvard Medical School. His primary areas of focus span a large age spectrum from fetal to adolescent care.

Clinics are currently available in Boston, at MGHfC at Newton-Wellesley Hospital and at the Mass General/North Shore Center for Outpatient Care in Danvers, MA. The combined strength of expertise in noninvasive imaging and collaborations with obstetricians, neonatologists and pediatricians will provide patients with improved diagnostic accuracy and earlier identification of heart problems, leading to more effective delivery planning and pediatric care.

Deeper collaboration with Massachusetts General Hospital adult congenital cardiologists and related specialists, Dr. Benavidez says, can help improve patient care by providing in-depth skill with the full range of imaging equipment used in the clinic and operating room.

Research aims for the division include identifying risk factors that affect optimal outcomes in congenital heart surgery in both the pediatric and adult population and uncovering new strategies for improving the sensitivity of the obstetrical screen for a fetal diagnosis of congenital heart disease.

For more information, call 888-644-3241