2013 was a historic year for vascularized composite allograft transplantation. In July, the U.S. government published a final decision in the Federal Register recognizing vascularized composite allografts as organs. As a result, effective July 3, 2014, allografts for face, hand and similar composite tissue transplants are for the first time allowed to be shared through the nationwide Organ Procurement and Transplantation Network (OPTN) system. This facilitates patient listing and graft procurement and promises an increase in the number of vascularized composite allotransplants performed.

That means more patients stand to benefit from the tremendous progress made over the past decade in addressing technical, logistical and social challenges in face and upper-extremity transplants and other types of reconstructive transplantation.

Cleveland Clinic has played a lead role in that progress, most notably by performing the first near-total face transplant in the U.S. in December 2008. Its Center for Reconstructive Transplantation continues to be a leading contributor to clinical and scientific progress in this field on the worldwide level.

Areas of expertise

Reconstructive transplantation is reserved for patients in whom conventional plastic and reconstructive surgery is unable to produce acceptable results. Potential patients are those who’ve suffered massive loss of complex combinations of tissue — including skin, subcutaneous tissue, neurovascular tissue, bone, muscle, fascia and cartilage — for whom prostheses are unavailable or insufficient for restoring physical integrity and function. The goal is to restore patients’ natural function, quality of life and ability to live independently.

Cleveland Clinic’s Center for Reconstructive Transplantation team consists of plastic and reconstructive surgeons as well as specialists in otolaryngology, neurology, transplant surgery, infectious disease, immunology, endocrinology, urology, anesthesiology and bioethics. This multidisciplinary team offers expertise in several key types of composite tissue transplantation:

**Face** — Face transplant requires exquisitely balanced attention to both form and function across parallel surgeries involving two teams of surgeons: one to remove...
The federal government’s recognition of vascular composite allografts as organs means these allografts have been eligible for sharing through the Organ Procurement and Transplantation Network (OPTN) system as of July 2014.

In response, the United Network for Organ Sharing, which operates the nationwide OPTN system, formed a committee to develop national standards and policies for vascular composite allotransplantation.

Renowned transplant surgeon John Fung, MD, PhD (photo at right), Chairman of Cleveland Clinic’s Digestive Disease Institute, was one of 12 physicians appointed to the 18-member committee.

In addition to creating a national registry for vascular composite allotransplants, the committee’s charge has included:

- Developing national standards and processes for donor consent and recovery
- Developing a system to prioritize candidates for available composite tissue allografts
- Establishing institutional standards for centers that perform vascular composite allotransplants

Wide research reach

Cleveland Clinic is likewise setting standards in scientific research in microsurgery and reconstructive transplantation. A few priority areas are profiled below.

**Tolerance induction.** A major focus of Cleveland Clinic research efforts is the induction of tolerance in composite tissue transplantation. Because of the diversity of tissues involved, composite tissue allografts are associated with more intense
rejection compared with vascularized organ grafts such as kidneys or livers. While several experimental designs of tolerance induction have been reported, side effects restrict their use to carefully selected applications.

Cleveland Clinic’s recent approaches to inducing tolerance center on the pivotal role of T cells in allograft rejection. These include exciting efforts to evaluate the role of marrow-derived stem and progenitor cells in tolerance induction following vascularized bone marrow transplantation. Cleveland Clinic staff published two important contributions related to tolerance induction in 2013, as profiled in two of the study summaries in the “future of transplantation” sidebar above.

Face transplant. In 2013 members of the Center for Reconstructive Transplantation reported results of a pathology review conducted four years after they performed the nation’s first near-total face transplant. This paper (Am J Transplant. 2013;13:2750-2764), one of the most comprehensive reports of its kind in the literature, demonstrated the need to correlate pathologic with clinical findings to monitor for rejection and the shortcomings of using histopathology as a sole monitor.

Another patient is now listed for face transplant at Cleveland Clinic, and the Center for Reconstructive Transplantation holds a Department of Defense-funded AFIRM grant (Armed Forces Institute of Regenerative Medicine) to study the clinical care of this patient (see sidebar).

Nerve regeneration. In addition to evaluating surgical techniques for enhancing nerve regeneration, Cleveland Clinic researchers are studying the effects of cyclosporin A on nerve degeneration and the effects of enhancing factors (e.g., DHEA and VEGF 165) on nerve regeneration in normal and diabetic rats.

Effective topical immunosuppression in an animal model of face transplant

Topical immunosuppression is an enticing anti-rejection strategy that may be uniquely well suited to composite tissue transplantation. In a rat model of face allotransplantation, Cleveland Clinic researchers found topical immunosuppression with tacrolimus and clobetasol to be effective in treating episodes of acute rejection (Transplantation. 2013;95:1197-1203). The best outcomes were achieved when these topical therapies were used after systemic immunosuppression. These findings support the utility of combined topical and systemic immunosuppression as an appealing potential therapeutic approach in vascularized composite tissue transplantation.

Novel model of composite vascularized sternal bone marrow transplant

In an experimental study in rats (Microsurgery. 2013;33:43-50), Cleveland Clinic investigators introduced a new model of vascularized sternal bone marrow transplant that can be applied to augment hematopoietic activity for chimerism induction after transplantation. The allografts remained unchanged after transplantation and did not develop rejection. This model can likely be used to study the correlation between the number of transplanted bone marrow cells and the level of chimerism in inducing donor-specific tolerance. It may also help illuminate differences in tolerance development between cellular and solid organ transplantation.

New vascularized cervical lymph node transplantation model

In the first published report of a vascularized lymph node flap model in the head and neck region of the rat (Ann Plast Surg. 2013;71:671-674), Cleveland Clinic researchers described a novel flap model with a greater number of lymph nodes than previously described. This model can be used for various transplant-related applications, including studies on the mechanism of immunologic tolerance and rejection.

LEADERSHIP IN AFIRM EFFORTS FOR SEVERELY WOUNDED WARRIORS

Together with more than a dozen other premier U.S. institutions, Cleveland Clinic is helping lead collaborative work within the Armed Forces Institute of Regenerative Medicine (AFIRM) to develop innovative therapies for wounded men and women in the armed services.

Reconstructive transplantation is an integral part of this activity, and Cleveland Clinic is one of only two centers in the country screening patients for reconstructive face transplantation, and one of just four centers screening for reconstructive arm and hand transplantation.

The Center for Reconstructive Transplantation has also received a Department of Defense-funded AFIRM grant to study the clinical care of a patient currently listed for face transplantation at Cleveland Clinic.
In addition to its distinctive vascularized composite tissue transplant program, Cleveland Clinic has long used bone and nonvascularized tissue segments in all types of surgical reconstruction — as well as corneal grafts in various corneal transplantation procedures.

PETER WILLIAMS: BACK ON HIS FEET AFTER BONE TRANSPLANT FOR LIMB SALVAGE FOLLOWING OSTEOSARCOMA

"I wasn’t that scared because the doctors put together a plan really fast." So says 13-year-old Peter Williams of Cleveland Heights, Ohio, about the limb salvage surgery he recently underwent at Cleveland Clinic.

After an afternoon spent playing touch football with friends in 2012, Peter began experiencing pain in his leg and started limping. Diagnosed with osteosarcoma in his proximal tibia, Peter soon underwent surgery to remove the tumor and place a tibial allograft/allograft-prosthetic composite to salvage his leg.

The procedure involved two free flaps and close collaboration between Cleveland Clinic orthopaedic and plastic surgeons as well as pediatric oncologists. Peter is now disease-free and resumed walking four months after his surgery.