



Reconstructive Transplant Research Program

VISION

Unlocking the full potential of reconstructive transplantation

MISSION

Developing innovative reconstructive transplant solutions to optimize the restoration of form, function, appearance, and psychosocial health for catastrophically injured Service members, Veterans, and American civilians

PROGRAM HISTORY

Many factors related to weaponry, personal protection, and trauma care during Operations Enduring Freedom and Iraqi Freedom resulted in greater survival of those sustaining increasingly severe combat injuries, particularly injuries to the face and extremities. These types of injuries often involve damage to and/or loss of multiple tissue types (i.e., composite tissues), including skin, muscle, bone, nerve, and vasculature. Congress recognized the importance of vascularized composite allotransplantation (VCA) as an alternative to prosthetics and traditional reconstructive procedures for restoring function and sensation to the recipient and thus initiated the Reconstructive Transplant Research Program (RTRP) in fiscal year 2012 (FY12). The RTRP supports research of exceptional scientific merit that has the potential to make a significant impact on improving the function, wellness, and overall quality of life for injured military Service members and Veterans, their caregivers and family members, and the American public. To our knowledge, the RTRP is currently the only funding program solely dedicated to supporting VCA research and has thus far supported investigators from nearly half of the 27 VCA transplant centers in the United States approved by the Organ Procurement and Transplantation Network. The RTRP has received \$81 million (M) in appropriations through FY18.

RESEARCH INVESTMENT

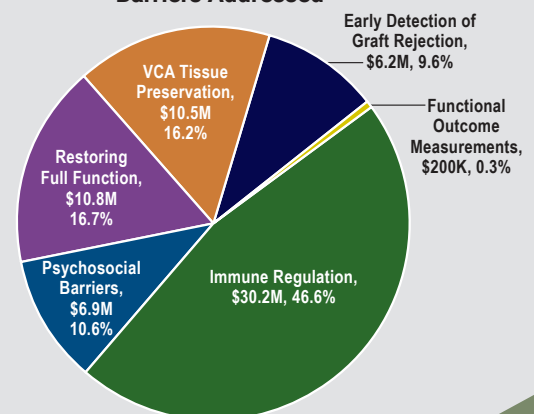
The RTRP has focused its investment on several key barriers to realizing the full potential of reconstructive transplantation. Although the specific program focus areas may vary somewhat from year to year, the overarching key barriers they address remain unchanged:

- Sub-optimal regulation of the immune system after VCA
- Limited preservation capability for VCA tissues
- Psychosocial challenges associated with VCA
- Lack of sensitive non-invasive early detection methods of graft rejection
- Incomplete recovery of full function after VCA
- Lack of appropriate functional outcome measurements for VCA

Through FY17, the RTRP has devoted nearly half of its investment to VCA-related immune regulation, which remains the single largest hurdle to more widespread practice and acceptance of this life-changing surgical procedure.

The overall goal is to reduce the risks of VCA-associated immunotherapy, and RTRP-funded researchers are addressing this from various perspectives, including a better understanding of the mechanisms of VCA immunogenicity, the development of novel approaches for immune tolerance, and a reduction in the toxicity of standard immunosuppression. The RTRP is also investing in research to overcome the other key barriers to reconstructive transplantation, as seen in Figure 1.

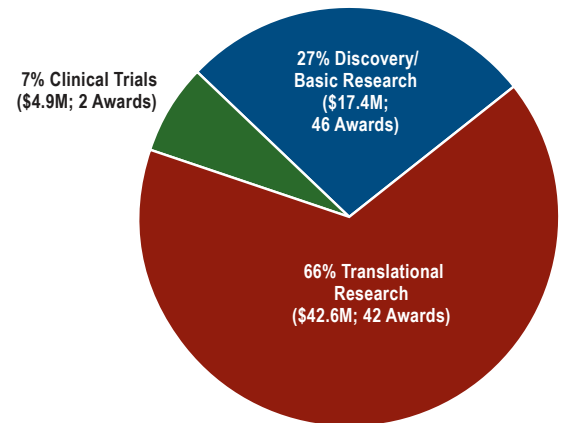
Figure 1. RTRP Investment by Barriers Addressed



RESEARCH PORTFOLIO

The RTRP's research portfolio includes projects across the research spectrum, from early discovery and basic research through to translational studies and clinical trials. Reconstructive transplantation is still a young and relatively small field, and there are many unknowns. To promote innovative ideas with the potential to open new avenues of research, the RTRP has offered award mechanisms that are specifically designed to support small projects that explore untested, high-risk/potentially high-reward research. The development of promising ideas is supported through mechanisms designed for larger projects in the basic research phase through to translational research. The RTRP is especially interested in advancing promising preclinical findings into medical knowledge and materiel products that facilitate the restoration of form, function, appearance, and psychosocial health to the catastrophically injured. As the science matures, the RTRP will have greater opportunities for investing in clinical trials. The RTRP's investment across the research spectrum is shown in Figure 2.

Figure 2. RTRP Investment Across the Research Spectrum



RESEARCH ACCOMPLISHMENTS

- RTRP investigators at Brigham and Women's Hospital have identified matrix metalloprotease 3 as a potential diagnostic marker discriminating no rejection from non-severe and severe rejection in face transplant recipients using a non-invasive blood assay.
- A team of investigators at the Children's Hospital of Philadelphia have demonstrated the utility of administering an IL-2/anti-IL-2 monoclonal antibody complex for increasing the number of graft protective T-regulatory cells and prolonging allograft survival in an animal model.
- RTRP investigators at the University of Pennsylvania are adapting a class of drugs that has been shown to increase the tolerance of solid organs to cold storage for use in VCA preservation. The team has shown that the drug inhibitors, which target histone deacetylases, can lead to significantly less tissue injury when administered prior to limb ischemia in a mouse model.
- Supported by RTRP funding, investigators at the University of California, Los Angeles, are seeking to understand the effect of immune suppression on nerve regeneration and to identify new drugs that may increase the rate of nerve regeneration to improve functional outcomes after VCA. The team has demonstrated a potential role of the immunosuppressant cyclosporinA to increase the rate of axon growth.
- Investigators at the University of Pittsburgh have designed and developed microparticles that release factors for the recruitment and expansion of allograft protective T regulatory cells. These formulations have been demonstrated to lead to greater than 200 days of graft survival in an animal hind limb transplantation model and to confer systemic donor specific tolerance.

ONGOING RTRP-FUNDED RESEARCH

- The RTRP is supporting an ongoing clinical trial at Brigham and Women's Hospital that is exploring the efficacy of low-dose IL-2 for enabling the minimization of immunosuppression therapy in face transplant recipients.
- Investigators at Temple University are developing a training program for Organ Procurement Organization request staff that is specifically targeted to improving communication about VCA donation in the hope that it will ultimately lead to an increase in VCA donor offers.
- Investigators at the University of Delaware are testing the hypothesis that direct replenishment of cellular cytosolic energy stores will increase allograft tolerance to cold ischemia and prolong cold storage time.
- Collaborators from Johns Hopkins University and the National Cancer Institute are developing a novel drug delivery platform that combines two innovative technologies (protease-sensitive peptide hydrogels and drug-loaded lipid nanoparticles) for the localized regulation of alloreactivity and the promotion of VCA survival.