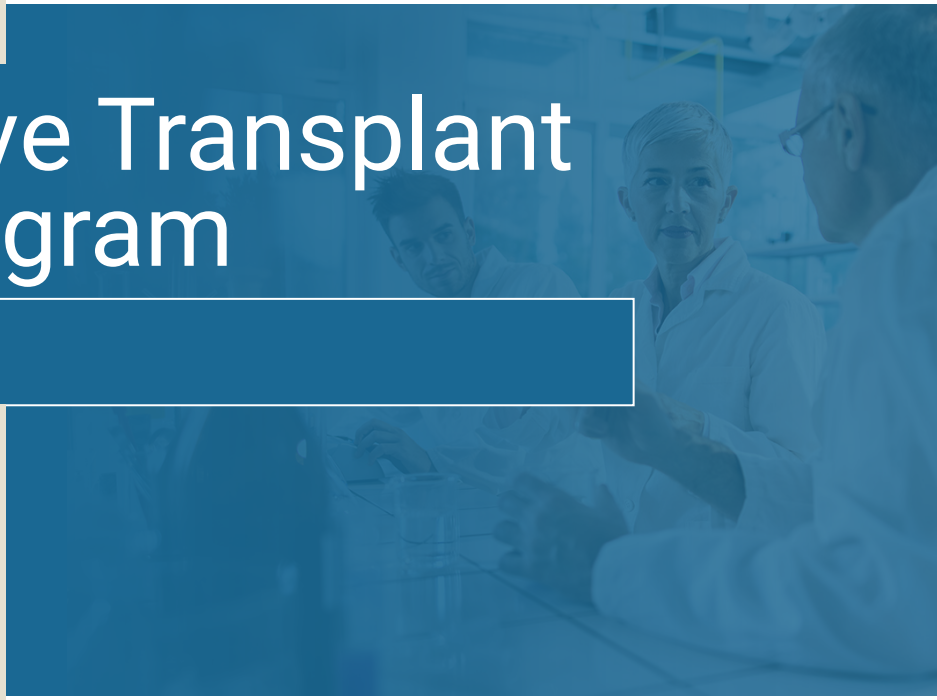
CDMRP
Department of Defense

Reconstructive Transplant Research Program

Strategic Plan



INTRODUCTION

The Congressionally Directed Medical Research Programs (CDMRP) represents a unique partnership among the U.S. Congress, the military, and the public to fund innovative and impactful medical research in targeted program areas. In 2015, an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine was assembled to evaluate the CDMRP's two-tier review process and its coordination of research priorities with the National Institutes of Health (NIH) and the Department of Veterans Affairs (VA). As part of their final report,[1] the committee recommended that each CDMRP program "… develop a strategic plan that identifies and evaluates research foci, benchmarks for success, and investment opportunities for 3–5 years into the future," and that these strategic plans "should specify the mission of the program, coordination activities with other organizations, research priorities, how those priorities will be addressed by future award mechanisms, how research outcomes will be tracked, and how outcomes will inform future research initiatives."

In accordance with these recommendations, the CDMRP's Reconstructive Transplant Research Program (RTRP) assessed the status of the field during their FY18 Vision Setting meeting, along with the most critical needs of its stakeholders, and developed the strategy described herein. This Strategic Plan is intended to be a dynamic document that adjusts with the ever-changing research landscape and will be reviewed annually and revised accordingly. Continued funding of the RTRP is subject to annual Congressional appropriations and is not guaranteed.

RTRP BACKGROUND AND OVERVIEW

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 for restoring function and sensation to the recipient, as well as the need for research to advance the science and medical capabilities for transplanting and maintaining these complex composite tissues. Thus, Congress initiated the RTRP in fiscal year 2012 (FY12) to provide support for 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. The RTRP challenges the scientific community to design innovative research that will foster new directions for and address neglected issues in the field of reconstructive transplantation, specifically focused on VCA research.

VISION: Unlocking the full potential of reconstructive transplantation

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

FUNDING HISTORY

The RTRP was established in FY12 with a $15 million (M) appropriation from Congress. Since then, a total of $81M has been received. Funding opportunities through FY17 have resulted in 75 research projects, representing 90 separate awards (Figure 1). Several RTRP award mechanisms have utilized the Multiple Principal Investigator (PI) Option, which provides an opportunity for up to four PIs to partner on a single project; each partner receives a separate award.

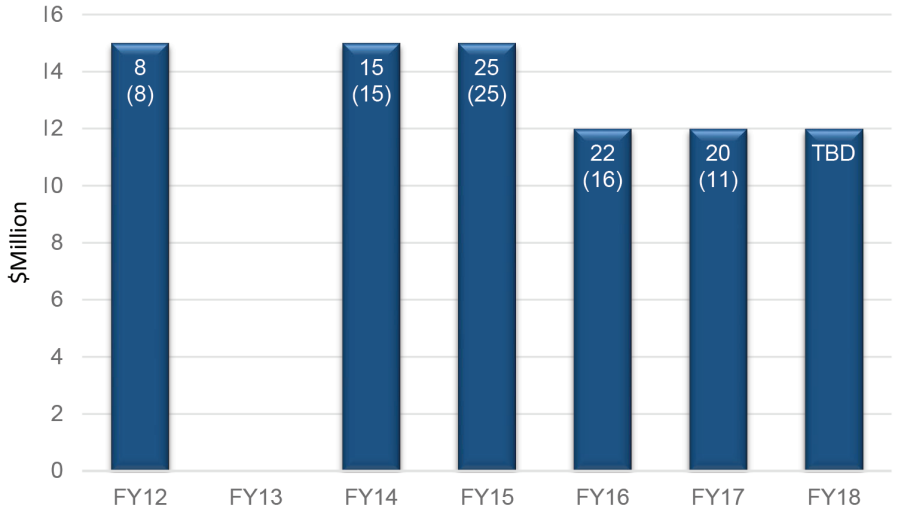


Figure 1: RTRP Annual Appropriations and Number of Awards (Projects)

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. Through FY17, the RTRP has funded 46 early discovery/basic research awards (41 projects) for a total of $17.4M; 42 translational awards (32 projects) for a total of $42.6M, and 2 clinical trial awards (2 projects) for a total of $4.9M. Roughly one quarter of the RTRP budget is focused on early discovery and basic research projects, as innovation is needed to drive the field forward. It is expected that some of these projects will continue successfully in the future as translational and clinical projects that can ultimately impact patients' lives. Approximately two-thirds of the RTRP budget has been devoted to translational studies and another 7% to clinical trials.

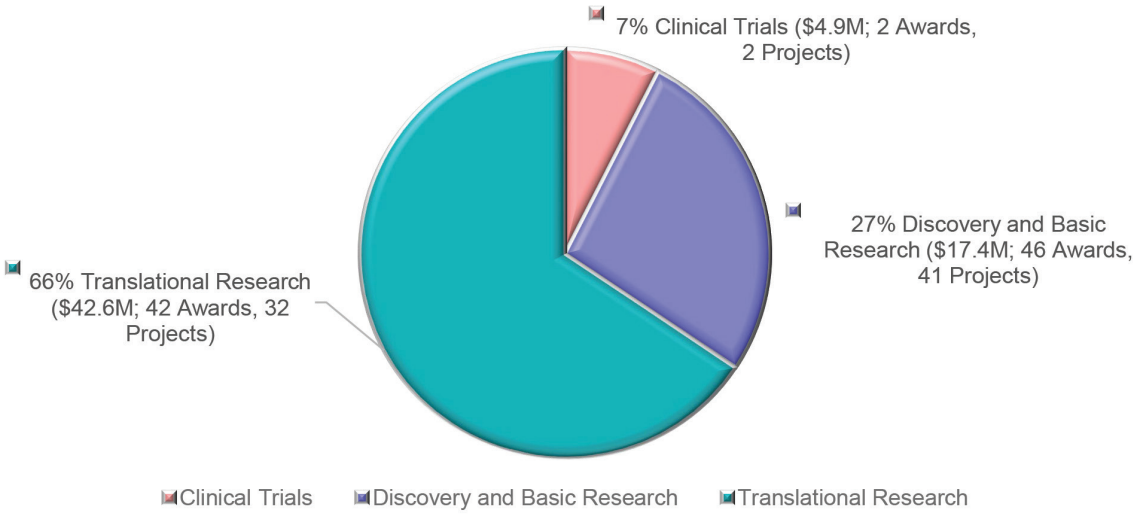


Figure 2: RTRP Awards Across the Research Continuum FY12- FY17

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:

- Ineffective 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

RTRP investment through FY17 to address these barriers is shown in Figure 3. The RTRP has devoted nearly half of its investment to VCA-related immune regulation (46.6%, $30.2M), which remains the single largest hurdle to more widespread practice and acceptance of this life-changing procedure. The overall goal is to reduce the risks of VCA-associated immunotherapy, and RTRP-funded investigators are addressing this from various perspectives, including efforts to gain 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 identified key barriers to reconstructive transplantation. An investment of $10.5M addresses the need for better tissue preservation capability and represents 16.2% of the portfolio. The need to restore full function after VCA represents 16.7% of the RTRP investment at $10.8M. Addressing psychosocial challenges represents 10.6% of the RTRP investment at $6.9M, with the need for sensitive non-invasive graft monitoring following shortly behind at 9.6% ($6.2M). One project has been funded to address the need for appropriate VCA functional outcome measurements (0.3%, $0.2M). It should be noted that a number of projects address multiple barriers in a single project; however, for clarity and simplicity, only the primary focus of the projects is represented in this figure. Therefore, representation of each barrier within the RTRP portfolio is actually higher than shown here.

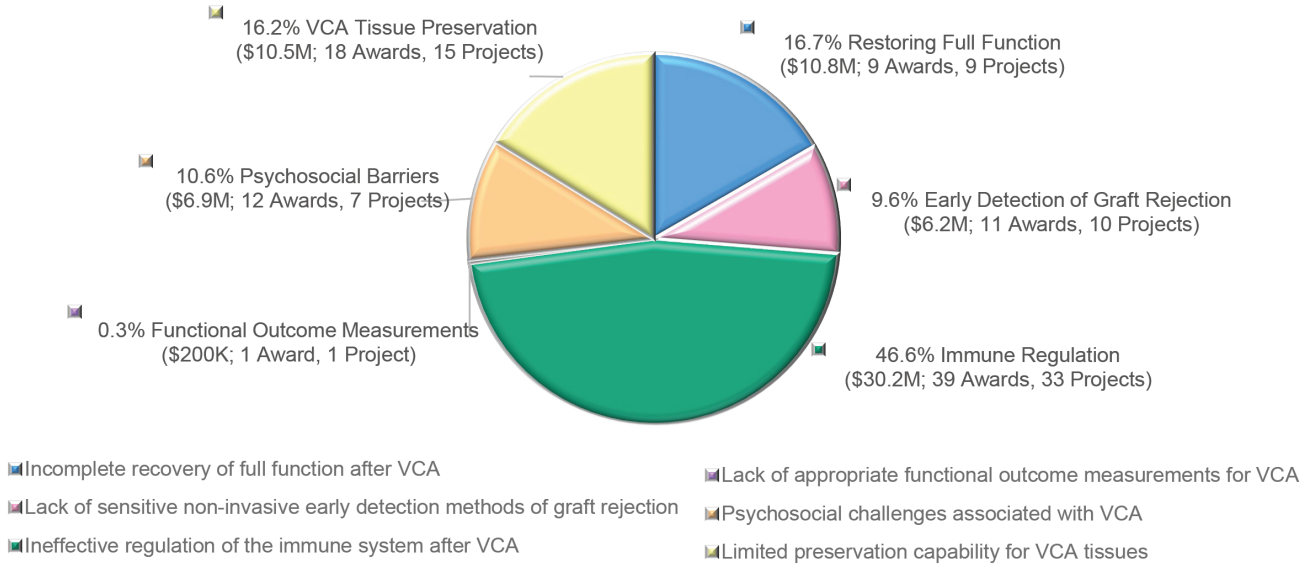


Figure 3: RTRP Investments by Barrier FY12-FY17

RESEARCH ACCOMPLISHMENTS

Although the RTRP is still a young program with its earliest awards only just now starting to close, there are a number of projects with promising results:

- Drs. Eduardo Rodriguez and Daniel Ceradini are conducting a clinical trial in which they will develop "personalized" face transplant techniques to improve the functional, aesthetic, and immunologic outcomes of patients who receive facial VCAs. A personalized surgery will be designed for each patient, who will receive an allograft containing significant pieces of vascularized bone from the donor's facial skeleton. The investigators hypothesize that, by transplanting fragments of bone along with critical ligaments of the face, the architecture of the face will be preserved. As a result, the recipient may experience improvements in the way the face looks and functions. This personalized reconstructive approach was used to successfully perform the most comprehensive face transplant reported to date.
- Drs. Leonardo Riella and Bohdan Pomahac hypothesize that novel biomarkers of allograft rejection could enable timelier clinical interventions and minimize the exposure of VCA recipients to anti-rejection medications. The investigators are using cutting-edge techniques and a unique biobank of samples collected from face transplant recipients to identify potential biomarkers of rejection. Their results suggest that molecular diagnostic tools may complement existing clinical, serological, and histological examinations for the diagnosis of allograft rejection in the context of VCA. Novel biomarkers identified in this study could lead to improved graft monitoring and new therapeutic targets for treating rejection, which could maximize the quality of life for VCA recipients.

- Dr. Wayne Hancock is exploring the protective anti-rejection effects of T-regulatory cells (Tregs) following VCA. Tregs expressing the transcription factor, Foxp3 (Foxp3+ Tregs), are key to immune tolerance and depend on the interleukin-2 (IL-2) signaling molecule for survival. IL-2/anti-IL-2 monoclonal antibody complex (IL-2C) was shown to increase the number of Foxp3+ Tregs 10-fold in naïve mice, and when administered before or after forelimb transplantation in a mouse model of VCA, allograft survival was significantly prolonged from 7 days in control mice treated with saline alone to more than 21 days ($p<0.001$). An added benefit was achieved with the combination of pre-transplant IL-2C therapy with post-transplant rapamycin administration, which led to greater than 50 days VCA survival ($p<0.001$).
- Dr. Matthew Levine is investigating ways to improve preservation of tissue grafts through the use of drug inhibitors targeting histone deacetylases (HDACs). HDACs regulate gene expression by modulating gene accessibility, and inhibition of these proteins has been shown to increase the tolerance of kidney transplants to cold storage in mouse models. Now Dr. Levine is translating this approach to mouse models of ischemia injury in VCA tissues. Results show that pretreatment of mouse limbs with HDAC inhibitors 16 hours prior, and again 30 minutes prior to ischemia, significantly reduced tissue injury compared to control mice ($p<0.05$). This protective effect was even greater when the HDAC-6 specific inhibitor, Tubastatin A, was used ($p<0.01$).
- Dr. Samantha Butler is researching how immunosuppression affects nerve regeneration and reinnervation in a mouse model of nerve transection. Following nerve transection, mice were treated with one of three different immunosuppressants (FK506, cyclosporine A [CsA], or rapamycin) and assessed for nerve regeneration by immunofluorescence using markers for neurofilament and GAP43. After 7 days of recovery post-nerve transection, robust nerve regeneration was observed in all groups, though CsA showed the most promise with higher levels of GAP43 expression beyond the lesion site, indicating active axon growth. Staining for cofilin, a protein which leads to an increased rate of axon growth, showed higher levels in mice treated with CsA, further supporting a role for CsA in promoting nerve regeneration.

RESEARCH AND FUNDING ENVIRONMENT

The VCA field is unique because it crosses many related fields, but has the added complexity of needing to integrate them. For example, there are many similarities between VCA and organ transplantation, including the requirement for lifelong immunosuppression and patient compliance. VCA is more complicated, however, because, unlike the general homogeneity of tissues in a kidney or liver, a VCA transplant includes many different types of tissue (e.g., nerve, muscle, bone, skin, and vasculature). Thus, the gaps and complications in one related field (e.g., nerve regeneration) are compounded by the gaps and complications in other related fields (e.g., bone and muscle regeneration). The RTRP closely monitors the advancements in these related fields.

The RTRP is currently the only funding program dedicated solely to VCA research. Funding opportunities are otherwise available through the related fields of solid organ transplantation, solid organ and tissue preservation, solid organ transplant immunology, or regenerative medicine for individual tissue components (nerve, muscle, bone, skin, and vasculature).

Within the NIH, regenerative medicine has been an emerging topic in areas such as tissue engineering and cell therapies. As part of the 21st Century Cures Act, the NIH, in coordination with the Food and Drug Administration (FDA), received $30M for regenerative medicine studies using adult stem cells. Overall, the NIH committed an average of 1.9% of its budget to regenerative medicine research in FY17. The VA does not support VCA research, but they do support research related to kidney and heart transplants, as well as transplant immunology. The Department of Defense (DoD) Clinical and Rehabilitative Research Program has funded a number of VCA-related efforts and currently has over $55M invested in active research projects addressing the key barriers in the field. The Armed Forces Institute of Regenerative Medicine is an interagency collaboration between the Army, Navy, Air Force, and NIH that has funded a variety of regenerative medicine projects, including VCA. The RTRP coordinates with all of these funders and stakeholders to avoid duplication of research resources and to help target research efforts toward the most critical gaps and barriers.

STATE OF THE SCIENCE

Immunotherapy: The immune system plays a critical role in defending the body from foreign invaders, which include a wide variety of pathogens such as bacteria, viruses, fungi, and many others. Transplanted tissues are also recognized by the immune system as foreign invaders. Transplantation typically triggers a cascade of cellular interactions that can lead to rejection of the new graft. To minimize graft rejection, patients must endure a life-long regimen of drugs to suppress the immune system. Immunosuppression is often initiated at the time of transplant using a drug to deplete the T cell population (e.g., antithymocyte globulin).[2] Subsequently, immunosuppression is commonly maintained using the triple therapy of a calcineurin inhibitor (e.g., tacrolimus), mycophenolate mofetil, and steroids. Levels of immunosuppression may be increased to treat episodes of rejection and decreased during periods of immune stability. While immunosuppression has made tissue transplantation possible, it is associated with severe side effects, such as increased risk for infection, cancer, kidney toxicity, diabetes, atherosclerosis, and hypertension. Since VCA includes many different tissue types, higher levels of immunosuppression are typically required for successful engraftment and maintenance than

the levels used to manage solid organ transplants; therefore, the risk to VCA recipients is often increased. Alternative methods for modulating the immune response are critically needed.

Tissue Preservation: Donor tissues for transplantation deteriorate rapidly after harvest and are typically preserved during transplantation by storage in a cold solution. Cooling of donor tissue using this technique allows only 4-8 hours before tissue becomes unsuitable for transplantation due to damage caused by lack of blood flow and oxygenation (ischemia). Donor tissue cannot be frozen prior to transplantation because ice formation can damage the cells, and rewarming the tissue to restore blood flow (reperfusion) causes further injury. Together, these caveats restrict the feasible distance between a potential donor and recipient, further limiting the donor pool that is already challenged by strict requirements for anatomical and immunological matching. Development of new strategies that extend tissue viability up to 24 hours is critical to increasing the potential donor pool and would allow VCA to become a more widely available procedure for wounded Service members, Veterans, and civilians.

Psychosocial Factors: There are a number of psychosocial factors associated with VCA, and they touch everyone associated with this life-enhancing procedure. Patients who are candidates for VCA must understand and consider the benefits and risks of receiving a transplant, as well as weigh the potential improvement in their quality of life against the difficult path of physical therapy and life-long immunosuppression before them. Family members of the VCA candidate must understand and consider that their loved one will require near-constant assistance with even the simplest of daily tasks, and they must be emotionally and physically prepared to provide assistance throughout the process. Physicians must assess both the candidate and the candidate's family for their psychological fortitude to handle the VCA transplant process and the likelihood that they will comply with the strenuous rehabilitation process and the immunosuppression regimen. The high cost of the procedure and the immunosuppression medications, as well as lack of insurance coverage, is another concern. Other psychosocial factors relate to concerns, fears, and barriers experienced by families/authorized parties of deceased loved ones regarding VCA donation. Despite the importance and impact of these factors on the capacity of VCA as a solution to the catastrophically injured, very little research has been initiated to study them to date.

STRATEGIC DIRECTION

With consideration of the current state of the science in the VCA field, and given the limited funding opportunities available outside of the DoD, the RTRP will continue to lead the effort toward unlocking the full potential of reconstructive transplantation. The ultimate goal is to return injured Service members to duty and restore their quality of life.

STRATEGIC GOALS/PRIORITIES

The RTRP Programmatic Panel identified three goals/priorities that are critical to moving the VCA field forward and making VCA a viable option for Service members, Veterans, and the general public:

Reduce the risks of VCA-associated immunotherapy

- Define the mechanisms of VCA immunogenicity
- Determine the extent to which VCA tissue preservation technology impacts VCA immune response
- Develop novel approaches for immune tolerance
- Reduce the toxicity of standard immunosuppression
- Identify key similarities and differences between immunosuppression associated with VCA and solid organ transplant
- Identify and/or validate new peripheral biomarkers for early acute and chronic rejection

- Revolutionize ex vivo VCA tissue preservation strategies to extend the timeline between procurement and transplantation
- Identify near- and long-term functional, quality-of-life, and psychosocial outcomes in VCA and their influencing factors
  - Identify criteria for optimizing successful patient selection and outcomes
  - Develop quality-of-life measures
  - Identify factors that influence psychological adjustment and a return to full participation in community life
  - Standardize transparent outcomes data for VCA recipients (multi-institutional)
  - Identify factors influencing donor registration and authorization
  - Identify factors impacting a patient's decision to pursue VCA

INVESTMENT STRATEGY

To achieve these strategic goals/priorities, the RTRP will solicit research proposals that address these topics through the following funding opportunities across the research continuum:

- **Concept Award:** Since reconstructive transplantation research is a young field with few funding opportunities, there are a lot of unknowns awaiting discovery. The Concept Award supports the exploration of highly innovative new concepts or untested theories and will be offered in an effort to facilitate an influx of new ideas and reveal potential new avenues of research.
- **Investigator-Initiated Research Award:** This broad award mechanism may be used to fund basic through translational research, including preclinical studies in animal models and human anatomical substances, as well as correlative studies associated with existing clinical trials. Clinical trials are not permitted under this award mechanism.
- **Qualitative Research Award:** This award mechanism is designed to address the psychosocial components of the RTRP goals/priorities and is intended to help researchers and clinicians better understand the experiences of individuals involved in the reconstructive transplant process (e.g., those considering or who have already received reconstructive transplant surgery and/or the reality of lifelong immunosuppression; caregivers; potential donors and their families; and clinicians).

This investment strategy will be re-evaluated and updated as necessary during the program's annual Vision Setting meeting.

MEASURING PROGRESS

Progress toward the RTRP goals/priorities will be measured in the near term based on making successful investments into those areas that are important to its strategy. Indicators of success in the medium to long term will be measured based on the outcomes of RTRP-funded research, including contributions to the scientific community and the impact on the lives touched by reconstructive transplantation. The RTRP may adjust the program's goals and priorities periodically based on these outcomes and other contributions in the field.

NEAR-TERM OUTCOMES (1-3 YEARS)

- Investments in each strategic goal/priority
- Investments in projects exploring highly innovative new concepts or untested theories
- Investments in basic through translational research to progress promising outcomes toward advanced development and clinical use
- Investments in qualitative research to advance the understanding of psychosocial components of reconstructive transplantation
- Successful progress of currently funded RTRP research efforts

MEDIUM- TO LONG-TERM OUTCOMES (3-5+ YEARS)

- Contributions to the scientific community (presentations, publications, patents, etc.)
- Progression of promising regenerative medicine products toward advanced development:
    - Investigational New Drug/Investigational Device Exemption submissions to the FDA and clearances
    - Follow-on funding
    - New collaborations with industry and venture capital firms, etc.
    - Funded research leading to clinical studies or clinical trials

REFERENCES

1. *Evaluation of the Congressionally Directed Medical Research Programs Review Process*. 2016. The National Academies of Sciences, Engineering, and Medicine. The National Academies Press. Washington, DC.
2. Kueckelhaus M, et. al. Vascularized composite allotransplantation: current standards and novel approaches to prevent acute rejection and chronic allograft deterioration. Transpl Int, 2016 29(6):655-662.