Avascularized Composite Allotransplantation (VCA) Research

The Emerging Field

Background

Organ transplantation is a proven therapy for the treatment of end stage solid organ failure involving, but not limited to heart, kidney, liver and lung. The success of solid organ transplantation has led several clinical teams to apply this technology to patients with non-reconstructable injuries such as severe burns or limb amputation. This therapy is now known as Vascularized Composite Allografts (VCA). VCA refers to the transplantation of multiple tissues such as muscle, bone, nerve and skin, as a functional unit (e.g. a hand, or face) from a donor to a patient in need of such therapy. These grafts serve as potential replacements for traumatic tissue losses such as those resulting in limb loss from explosive devices, accidents with farm machinery, burns or other major injuries. VCAs have limited ischemia time (cannot be processed or stored), require rapid re-establishment of blood flow, and donor-recipient matching, thus sharing identical issues with transplanted organs (governed by UNOS regulations) rather than tissue (for which none of these stipulations apply). These facts must be considered for regulatory purposes.

Currently, most reconstructive procedures for major tissue defects secondary to trauma, tumor removal, or congenital anomalies are performed with autologous (the patient’s own) tissue. However, there are severe defects that cannot be reconstructed this way. In complex injuries or defects not amenable to conventional reconstruction, VCA could potentially achieve near normal tissue restoration and improved functional and aesthetic outcomes. Early successes in this area of transplant have established the proof of concept that VCA can be successful and indicate areas most in need of further investigation.

General Considerations for Investment

The consensus view is that VCA has gained increasing importance in clinical practice and may evolve into an important component of multidisciplinary approaches to reconstruction after severe injuries. Given the risks, expense, and complexity involved, it is unlikely that VCA will be appropriate for solely cosmetic concerns, but rather as therapy for injuries associated with major functional or psychological deficits. Investment to mature VCA research is now becoming
essential, should be targeted to specific critical areas of need, and administered only after appropriate peer review. Studies should include applicable animal models, translational research, and clinical outcome studies. If this important field is to advance, it is critical to support early clinical successes with a solid clinical and basic research structure to better understand VCA and ultimately optimize outcomes.

VCA - The Challenges and Opportunities

1. Composite tissue grafts, like most transplanted organs, are subject to immune rejection by the recipient. However, unlike in other solid organ transplantation, VCAs are composed of multiple tissues with different immunogenic and functional properties, including skin, muscle, bone and nerve. Therefore, there is a need to elucidate the basic aspects of the unique immunological features, and mechanisms of VCA rejection.

2. To date, human VCA has proceeded successfully with drug regimens similar to those used for solid organ transplantation; recipients of VCA grafts appear to require life-long immunosuppressive medications to prevent rejection. Not unexpectedly, this therapy may result in complications known to be associated with immunosuppression in other settings. However, unlike most solid organ recipients, VCA grafts require potentially toxic medications in the treatment of non-life threatening conditions. Studies in relevant animal models indicate that less toxic approaches can be developed for clinical use. The development of strategies to diminish the requirement for immunosuppressive drugs is an important aspect of VCA implementation and requires investment in pre-clinical animal models to generate the supportive data necessary for rationally designed clinical regimens, and for clinical trials to validate these regimens.

3. As with all new fields, VCA has yet to fully define accepted standards to define success. This limits the ability to interpret and compare outcomes from disparate groups, particularly in light of the small number of patients being treated worldwide. Specifically, the criteria for assessing complications, diagnosing immune rejection, and comparing the results of VCA relative to other therapeutic options (e.g. prostheses, extensive reconstructive surgery) are not validated. Thus, investment is required to develop objective histopathological evaluation of VCA grafts, the coding of outcomes, and outcomes research to adequately assess improvement, or lack of same, over current standard of reconstruction. Importantly, surgical, medical and psychological strategies for coping with graft failure (e.g. suboptimal functional outcomes, unacceptable immune complications, requirement for graft excision) need to be developed and codified.

4. Similar to other solid organ transplants, VCA requires a multi-disciplinary team (including reconstructive and transplant surgeons, immunologists, pathologists, infectious disease specialists, psychiatrists, ethicists, therapists, and social workers) along with a comprehensive institutional infrastructure. Given the complexity of VCA requiring advanced surgical and medical sub-specialities, and a commitment to multidisciplinary therapeutic and rehabilitative teams, investments should be made in centers with clear institutional commitment to VCA specifically, as well as clinical transplantation, reconstructive surgery, and trauma rehabilitation in general.
5. Unlike organ transplants, functionality of VCAs is dependent on growth of recipient nerves into the grafted donor tissue. To date, nerve growth has been shown to occur, but the rate of growth is a limiting factor in return of graft function. In addition, the means by which the central nervous system accommodates to and organizes new nerve growth remains incompletely understood. As such, investment in nerve repair and growth is required for optimal use of VCA. These issues may be similar to those associated with traumatic nerve and brain injury and may be able to be merged with research portfolios in these areas.

In summary, the recommendations of the AST’s VCA Task Force for prioritized funding are as follows:

**Clinical Research:**
Multi-center clinical outcome studies based on registry data allowing institutional protocols with the goal to define:

1. Optimal immunosuppression in VCA
2. Diagnostic criteria to define both clinical and histopathological aspects of rejection
3. Standards for measuring functional outcomes including nerve regeneration and rehabilitation
4. Quality of life, social and economic outcomes including comparative effectiveness analysis studies to assess the degree of improvement of VCA over current standard of reconstructive surgery

**Basic Research:**

1. Develop animal models of VCA to study the unique immunological features and mechanisms of VCA rejection and graft acceptance in each of the component tissues
2. Explore VCA-specific aspects of Rejection and Treatment emphasizing immune activation and immunogenicity peculiar to VCA

*Approved by the AST Executive Committee on June 1, 2011*
*Revised by the AST Board of Directors on August 11, 2015*

**Contacts:**

Shandie Covington, Executive Director, scovington@myast.org; 856-316-0924
Bill Applegate, Director of Government Relations, bill.applegate@bryancave.com; 202-258-4989