

VASCULARIZED COMPOSITE ALLOTRANSPLANTATION (VCA) RESEARCH

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 transplantation to patients with non-reconstructible injuries such as severe burns or limb amputation. This type of transplant is now known as Vascularized Composite Allografts (VCA). VCA refers to the non-autologous transfer of peripheral tissue including skin, muscle, nerve, bone, as a functional unit (e.g. hand). Unlike other solid organ transplants, VCAs are primarily performed to improve quality of life rather than extend life. Currently, fewer than 100 patients have received limb transplantation worldwide.¹ In the U.S the Organ Procurement and Transplant Network/United Network of Organ Sharing (OPTN/UNOS) was charged with the oversight of VCA in July 3, 2014. Since the Final Rule, 61 VCA programs have been approved by the OPTN and 28 VCA transplants have been reported at 14 programs.² Of the VCA performed in the United States, the majority have been recipients of limb(s), face, or uterus. Early successes in this area of transplant have established the proof of concept that VCA can be a therapy for a selected group of patients. However, the early stages of the field also provide the opportunity and need of further investigation.

General Considerations for Investment

The consensus view is that VCA has moved from a theoretical to a practical therapy. Given the risks, the expense, the low numbers, the medical and surgical complexity, and the detailed membership requirements that are forthcoming, VCA may best be concentrated in specialized transplant centers. Investment to mature VCA research is now becoming essential, it 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 studies.

VCA: The Challenges and Opportunities

1. Vascularized composite allografts, 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. 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 require life-long immunosuppressive medications to prevent rejection. This therapy results in complications known to be associated with immunosuppression in other settings. Importantly and unlike most solid organ recipients, VCAs reconstruct 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 continue generating supportive data necessary for a rationally designed clinical regimens, and for clinical trials to validate these regimens.
3. 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. Investment is required to develop objective histopathological evaluation of VCA grafts, and outcomes definition(s) and research to adequately assess improvement, or lack of same, over current standard of reconstruction. Importantly, surgical, medical and psychological strategies for coping

¹ Shores JT, Brandacher G, Lee WP. Hand and upper extremity transplantation: an update of outcomes in the worldwide experience. *Plast Reconstr Surg.* 2015;135(2):351e-360e

² Cherikh WS, Cendales LC, Wholley CL, et al. Vascularized composite allotransplantation in the United States: A descriptive analysis of the Organ Procurement and Transplantation Network Data. *Am J Transplant.* 2019 Mar;19(3):865-875. doi: 10.1111/ajt.15062. Epub 2018 Sep 17.

with graft failure (e.g. suboptimal functional outcomes, requirement for graft excision) need to be developed.

4. VCA requires a multi-disciplinary team (e.g. reconstructive and transplant surgeons, immunologists, pathologists, infectious disease specialists, psychiatrists, ethicists, therapists, reproductive medicine specialists, gynecologists, social workers) along with a comprehensive institutional infrastructure. Given the complexity of VCA requiring advanced surgical and medical sub-specialties, and a commitment to multidisciplinary therapeutic, and rehabilitative teams, investments should be made in centers with clear institutional commitment to VCA.
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. The means by which the central nervous system accommodates to and organizes new nerve growth remains incompletely understood. 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:

1. Minimization of immunosuppression in VCA
2. Diagnostic criteria to define both clinical and histopathological aspects of rejection
3. Standards for measuring outcomes. These include but are not limited to nerve regeneration, rehabilitation, and children born of uterus transplants.
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 therapies.

Basic Research:

1. Application of animal models of VCA to study the unique immunological features and mechanisms of VCA rejection and graft acceptance
2. Explore VCA-specific aspects of rejection and treatment

Defining criteria for a vascularized composite allograft (VCA)

VCA means a body part:

1. That is vascularized and requires blood flow by surgical connection of blood vessels to function after transplantation
2. Containing multiple tissue types
3. Recovered from a human donor as an anatomical/structural unit
4. Transplanted into a human recipient as an anatomical/structural unit
5. Minimally manipulated (i.e., processing that does not alter the original relevant characteristics of the organ relating to the organ's utility for reconstruction, repair, or replacement)
6. For homologous use (the replacement or supplementation of a recipient's organ with an organ that performs the same basic function or functions in the recipient as in the donor)
7. Not combined with another article such as a device
8. Susceptible to ischemia and, therefore, only stored temporarily and not cryopreserved
9. Susceptible to allograft rejection, generally requiring immunosuppression that may increase infectious disease risk to the recipient³

Adapted from <http://federal.eregulations.us/fr/notice/7/3/2013/2013-15731> [13].

³ In exceptional cases (identical twins or sharing of highly concordant histocompatibility matching markers), the recipient might not require any immunosuppression.

*Approved by the AST Executive Committee on June 1, 2011
Revised by the AST Board of Directors on August 11, 2015
Revised by the AST Board of Directors on March 3, 2020*

American Society of Transplantation (AST)

1120 Route 73, Suite 200
Mount Laurel, NJ 08054
Phone: (856) 439-9986
Fax: (856) 439-9982
Email: info@myAST.org
Website: www.myAST.org

Contact:

Shandie Covington, Executive Director, scovington@myast.org; 856-316-0924

Bill Applegate, Director of Government Relations, bill.applegate@bclplaw.com; 202-258-4989