



US DEPARTMENT OF DEFENSE
BLAST INJURY RESEARCH PROGRAM
COORDINATING OFFICE

Extremity Injury

Tissue-engineered Vascular Grafts

It is estimated that 2,500 of the nearly 60,000 injured Service Members (roughly four percent) suffered a vascular injury amenable to repair during the period of the recent wars. The rate of traumatic vascular injury requiring surgical intervention has been higher in recent years due to the use of tourniquets and hemostatic agents compared to historical data (2005 versus 1965). Vascular injury as a proportion of overall trauma has increased from one to two percent in the American Civil War to about 12 percent during recent conflicts in Iraq and Afghanistan. In 2013, the Department of Defense (DoD) highlighted a critical need for “... managing disruption and hemorrhage from the junctional regions between the torso and the extremities” in injuries that impact the vasculature (USAMRMC Program Announcement for Forward Surgical and En Route Care, Funding Opportunity Number W81XWH-13-CCCJPC6-FSERC). Autologous vein grafts currently remain the standard of care, with the saphenous vein being the primary donor site, despite the difficulty, or impossibility in many instances. The saphenous vein is often too small for an adequate repair, or difficult for a less experienced surgeon to locate. Synthetic vascular reconstruction using synthetic vascular grafts made from Teflon polytetrafluoroethylene (PTFE)/Dacron is relatively contraindicated, since Improvised Explosive Device (IED) wounds are always “dirty”, and bacteria in the wound can colonize the synthetic graft, causing abscesses and sepsis, therefore there is a need for alternative conduit to PTFE. The effort to salvage limb tissue may be hampered by damage to the vasculature that prevents re-establishment of blood flow to preserve the limb, necessitating amputation. The Human Acellular Vessel (HAV; see Figure 1) from Humacyte®, Inc. is a decellularized, off-the-shelf vascular conduit capable of tolerating high pressure perfusion, and which is rapidly infiltrated by recipient cells.¹ Humacyte® has developed this important new technology by culturing banked human cells in bioreactors in the laboratory followed by decellularizing the construct to produce a mechanically strong, tissue-based graft that is non-immunogenic and can be implanted into any recipient. Humacyte® is attempting to obtain a primary indication in a relatively low risk application as a hemodialysis (HD) shunt.^{2,3} This effort will be followed by an indication for arterial reconstruction bypass. These HAVs can be shipped to hospitals and field locations, and can be stored until needed. Humacyte® began US Food and Drug Administration (FDA) regulated clinical trials for the HD indication in December 2012, and the shunt has been implanted in more than 100 patients with no immune reactions reported. The product is currently in a Phase 3 clinical trial for this indication with Biologic License Application filing with FDA projected for fiscal year 2018 (FY18). Further, there has been no structural degradation, and only one

- 1 Dahl, S. L. M., Kypson, A. P., Lawson, J. H., Blum, J. L., Strader, J. T., Li, Y., ... Niklason, L. E. (2011). Readily available tissue-engineered vascular grafts. *Science Translational Medicine*, 3(68), 68ra9. <https://doi.org/10.1126/scitranslmed.3001426>
- 2 Benrashid, E., McCoy, C. C., Youngwirth, L. M., Kim, J., Manson, R. J., Otto, J. C., & Lawson, J. H. (2016). Tissue engineered vascular grafts: Origins, development, and current strategies for clinical application. *Regenerative Medicine*, 99, 13–19. <https://doi.org/10.1016/j.ymeth.2015.07.014>
- 3 Lawson, J. H., Glickman, M. H., Ilzecki, M., Jakimowicz, T., Jaroszynski, A., Peden, E. K., ... Niklason, L. E. (2016). Bioengineered human acellular vessels for dialysis access in patients with end-stage renal disease: two phase 2 single-arm trials. *Lancet (London, England)*, 387(10032), 2026–2034. [https://doi.org/10.1016/S0140-6736\(16\)00557-2](https://doi.org/10.1016/S0140-6736(16)00557-2)





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graft infection reported to date from the clinical development program. A reduction in infection rates has also been demonstrated in a murine model of bacterial graft contamination with lower infection rates observed compared to synthetic graft material. The grafts are also self-healing making them amenable to the frequent re-cannulation required for HD. The product is a first-in-man regenerative medicine product, and the HD indication was attempted first in a lower risk patient population with less urgent need for intervention. However, the supporting systems and processes developed (quality, manufacturing, shipping) will support all indications. The effort to extend application to arterial reconstruction was initiated in October 2013 with a study of above-knee femoral-popliteal bypass grafts in Poland. A 20-subject study has been successfully completed. Army funded efforts to gain FDA approval for the arterial graft in the US have been ongoing through the AFIRM II consortium, and an Investigational New Drug (IND) “safe to proceed” letter was received from the FDA in July 2016.

FIGURE 1: Humacyte’s HAV

