



US DEPARTMENT OF DEFENSE

BLAST INJURY RESEARCH PROGRAM COORDINATING OFFICE

Extremity Trauma Rehabilitation and Treatment

A Graft-embedded Loco-regional Immunosuppressive Therapy Platform for Vascularized Composite Allotransplantation (VCA)

Surgical reconstruction by VCA offers life-enhancing benefits for Service Members who have sustained devastating injuries, such as loss of the hands. Wider clinical acceptance of VCA has been hampered by the requirement for lifelong and systemic immunosuppression, which has significant drawbacks including organ toxicity and risk of graft attrition upon medication non-compliance. Unlike the transplantation of solid organs, VCA offers a unique opportunity for graft access wherein immunosuppression can be administered directly to VCA tissues through targeted therapeutic technologies. Supported by the Clinical and Rehabilitative Medicine Research Program (CRM RP) and Reconstructive Transplant Research Programs, researchers from the US Army Institute of Surgical Research (USAISR), Brigham and Women's Hospital, University of Pittsburgh, and the Institute for Stem Cell Biology and Regenerative Medicine have collaborated to develop a graft embedded, loco-regional immunosuppressive therapy (GEL-IT®) platform (Figure 1). In initial studies, an approach was established wherein the immunosuppressive drugs tacrolimus and rapamycin were encapsulated within amphiphilic triglycerol monostearate gels through self-assembly. A key feature of the hydrogel design is a nanofibrous matrix which degrades when proteolytic enzyme mediators of inflammation and allograft rejection are present in the biological milieu, thereby increasing the bioavailability of immunosuppressive drugs in relevant tissues. In vitro studies implementing an inflammatory-like state confirmed that the release of the encapsulated immunosuppressive drugs occurs primarily in the presence of a proteolytic enzyme. An injectable formulation of the GEL-IT® hydrogels was then tested in small animal models of syngeneic and allogeneic hind limb transplantation. Results of the study showed that a single administration of GEL-IT® hydrogels laden with tacrolimus alone or in combination with rapamycin prolonged graft survival for more than 60 days post-transplant, whereas Grade 3 rejection was detected approximately 21 days post-transplant in animals treated with rapamycin-containing hydrogels alone. Analysis of blood and tissue samples demonstrated that the level of drug released in vivo was proportional to the degree of inflammation, with initial burst release followed by drug concentrations maintained in a therapeutic range with minimal systemic exposure. The GEL-IT® platform is a novel approach to reducing the overall dosing, frequency, and duration of systemic immunosuppression required for allograft survival following VCA. This localized and self-titrating immunomodulation system will also obviate the risk of medication non-adherence and graft attrition resulting from uncontrolled rejection. Overall, the GEL-IT® platform is expected to benefit wounded Service Members by offering an optimized immunomodulation approach with lower risk of morbidity to enhance quality of life (QOL) and facilitate rehabilitation outcomes following VCA.





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FIGURE 1: Encapsulation of tacrolimus in smart hydrogels and enzyme-triggered, on-cue drug release. Illustration courtesy of University of Pittsburgh, Brigham and Women's Hospital and Institute for Stem Cell Biology and Regenerative Medicine collaborators: VS Gorantla, J Karp, N Joshi, P Vemula, AA Dhayani, A Fries, S Lawson, and MR Davis.

