Transplants and Grafts

Biomimetic Microparticles Promote Survival of Vascularized Composite Allografts

Surgical reconstruction by Vascularized Composite Allotransplantation (VCA) offers life-enhancing benefits for Service members who have sustained devastating injuries, such as loss of the hands, limbs, or face. Lifelong systemic exposure to the potent immunosuppression medications used to prevent rejection can produce deleterious side effects which have hampered wider clinical acceptance of VCA as a treatment option. Immunomodulation strategies which target the allograft directly would enable VCA survival while reducing the need for systemic anti-rejection medication. Regulatory T cells (Treg) support the homeostasis of the immune system and their presence within transplanted tissues can prevent the process of rejection. Differentiation of naïve T cells to Treg is facilitated by dendritic cells and cytokine signals including interleukin 2 (IL-2) and transforming growth factor beta (TGF-β). Immunosuppression medications such as rapamycin expand the population of Treg by similar mechanisms. Additionally, the secretion of chemokines such as C-C Motif Chemokine Ligand 22 (CCL22) can locally attract endogenous Treg.

Researchers from the University of Pittsburgh (Pittsburgh, Pennsylvania) and Wake Forest Institute for Regenerative Medicine (Winston-Salem, North Carolina) have developed a biomimetic microparticle system capable of delivering key cytokines and immunosuppressive agents (Expansion-MP) or chemokines (Recruitment-MP) directly to the allograft (Figure 1). This study will optimize the microsphere formulations and examine whether Expansion-MP or Recruitment-MP can prolong allograft survival in a preclinical study of VCA. The efficacy of Expansion-MP on allograft survival was assessed in vivo using a rodent model of hind limb transplantation. Expansion-MP containing various combinations of IL-2, TGF-β, and rapamycin were administered subcutaneously to the transplanted limb peri- and post-operatively. In a parallel study, rodents were administered Recruitment-MP containing CCL22 with the same approach. Animals were monitored daily by physical exam until the emergence of Grade III rejection or allograft survival beyond 150 days. Preliminary results demonstrated that Expansion-MP containing a triple cocktail of IL-2, TGF-β, and rapamycin, but not any other iteration of these factors, effectively prolonged the onset of rejection beyond 150 days in nearly all transplant recipients. Similar results were obtained using Recruitment-MP containing the chemokine, CCL22. Expansion-MP and Recruitment-MP did not prolong allograft survival when injected into the limb contralateral, thereby confirming the local effects of these interventions.

The bioinspired microsphere technology is expected to benefit wounded Service members by offering an optimized immunomodulation approach with lower risk of toxicity to enhance quality of life and facilitate positive outcomes of VCA.

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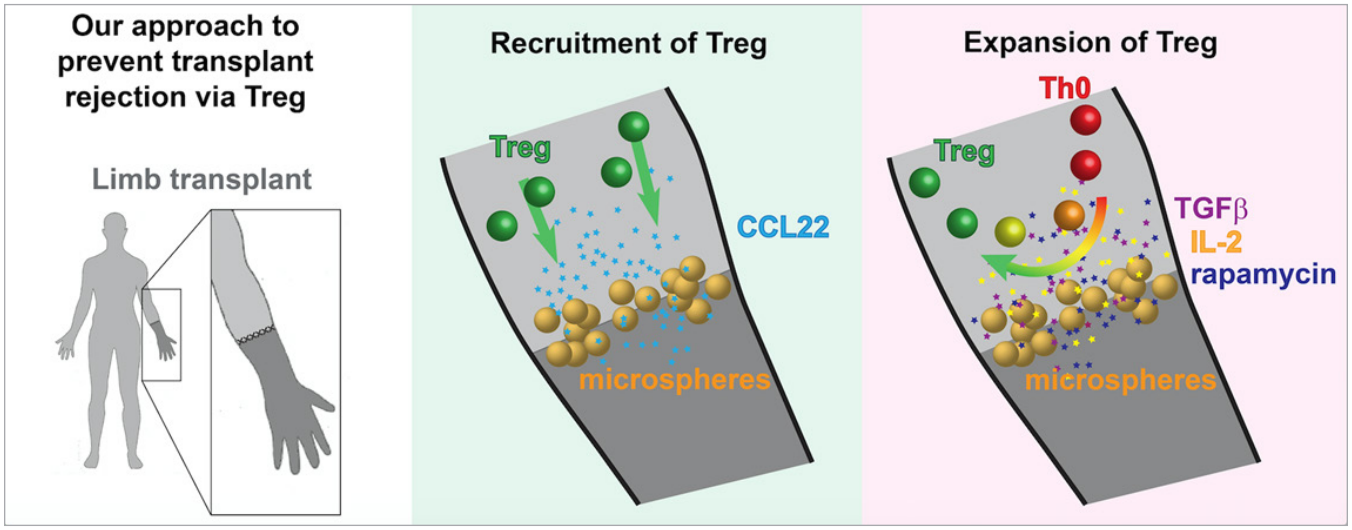

FIGURE 1: Bioinspired Microspheres for Preventing Rejection in Vascularized Composite Allografts: Microsphere-based technologies consist of cell-sized, safe, degradable constructs that possess the ability to locally enrich suppressor lymphocytes know as regulatory T cells (Treg). (Figure used with permission from the authors)