2018 ACS-IRG Pilot Grant

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Project Title: Enhanced T-cell regeneration using cell instructive scaffolds

Abstract:

Deficiency of T-cell number and disorder of function are the basis for a range of diseases ranging from congenital immunodeficiency to the autoimmune and impaired immune surveillance disorders that accumulate with age. In allogeneic hematopoietic stem cell transplantation (HSCT), there is a marked deficiency in post-transplant donor T-cell generation, which renders patients susceptible to infectious agents such as cytomegalovirus, and may contribute to graft-versus-host disease (GVHD) (>80% of recipients). These complications may be fatal and limit the use of HSCT in settings where it can be curative for multiple types of cancers. The timely regeneration of T-cells post-HSCT, along with the restoration of the T-cell repertoire remains a significant unmet clinical need.

The applicant has previously developed a synthetic cell-free scaffold for promoting T-cell neogenesis. The scaffold is referred to as a bone marrow cryogel (BMC), and facilitates T-cell lineage specification of hematopoietic progenitor cells. BMCs subcutaneously injected at the time of HSCT rapidly interfaced with the host vasculature. BMCs presented lineage-instructive cues to donor recruited progenitor cells in vivo, with the effect of enhanced T-cell progenitor seeding of the thymus, T-cell neogenesis, expanded the T-cell receptor repertoire and enhanced peripheral T-cell reconstitution ~sixfold in mice. In post-HSCT mice, BMC treatment increased donor chimerism, induced a robust antigen specific generation of $CD8^+$ T-cells after vaccination and enhanced T-cell activation after stimulation.

The regeneration of functional T-cells mediated by the BMC suggested that there is likely immunologic benefit beyond that of replenishing cell numbers. It is hypothesized that *enhanced in vivo donor T-cell neogenesis can promote adaptive immunity and facilitate the alleviation of post-HSCT immunological complications*.