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MOBILIZING T-CELLS WITH EXERCISE FOR ADOPTIVE TRANSFER IMMUNOTHERAPY

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KEY WORDS: Hematopoietic stem cell transplantation, Viral infections, beta-2 adrenergic receptor, Virus-specific T-cells, T-cell mobilization

Hematopoietic stem cell transplantation (HSCT) is the preferred treatment for a wide range of hematological cancers and genetic disorders. While HSCT is a potentially curative treatment, viral infections and disease relapse are still common, accounting for ~78% of all deaths in the post transplant period. The conditioning regimen that is required to remove the underlying malignancy also eradicates the patient's immune system. As such, widespread latent herpesviruses including cytomegalovirus (CMV) and Epstein-Barr virus, as well as non-latent community viruses such as adenovirus (AdV), influenza and respiratory syncytial virus, can result in significant levels of morbidity and mortality in both adult and pediatric patients in the post transplant phase. The 21st century has seen adoptive T-cell transfer immunotherapy come of age, and many HSCT patients are now receiving donor-derived T-cell products to help prevent and control viral infections and disease relapse. Allogeneic (donor to patient) adoptive T-cell immunotherapy involves the extraction of antigen-specific T-cells from the peripheral blood of a healthy donor for subsequent transfer to the HSCT patient. The T-cells are transferred either immediately or after a period of *ex vivo* expansion that is designed to increase the number and purity of antigen-specific T-cells prior to transfer. The transferred T-cells are then able to proliferate and persist in the new host (sometimes for more than a decade after transplant) and have been shown through many clinical trials to effectively and safely prevent and treat post-transplant viral infections and virus-associated malignancies in a large number of patients.

Unfortunately, the logistical constraints associated with using donor-derived T-cells for transplant eliminates adoptive T-cell therapy as a treatment option for a large portion

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of HSCT patients. The 'direct isolation' method used to extract virus reactive T-cells from donor blood for immediate adoptive transfer is swift (1-2 days processing) but limited by the very low numbers of virus-reactive T-cells in the peripheral circulation (<1% of all lymphocytes). As such, very large and impractical volumes of blood are required to isolate enough virus reactive T-cells and, even then, the extracted cells still have to undergo a period of 'ex vivo expansion' using cell culture techniques to generate sufficient numbers of antigen-specific T-cells for the transfer to be clinically effective. This expansion process can sometimes take several weeks depending on the antigen-specificity requirements of the T-cell therapeutic, causing critical delays in the delivery of the T-cell product. Some of these methods are also complex (i.e. involving gene transfer, clinical grade vectors or live virus) and costly. Although new 'rapid manufacturing protocols' can help increase the numbers of donor-derived viral-specific T-cells through *ex vivo* expansion in just 10-14 days, this is still too long for some patients and the numbers generated are not consistently large enough to be clinically effective after transfer. Moreover, the adoptive transfer of T-cells recognizing cancer antigens is considered a highly promising method for the prevention and treatment of disease relapse after HSCT, but translating this work into effective, clinically applicable treatments has been challenging, largely due to the difficulties in manufacturing enough tumor reactive T-cells from healthy donors. Thus, identifying new methods to increase the yield of virus and tumor-reactive reactive T-cells from donor blood using both 'direct isolation' (1-2 days processing) and 'rapid manufacturing' (10-14 days processing) techniques is critical to increase the availability of adoptive T-cell therapy to a larger proportion of HSCT patients.

We have purported that the leukocytosis evoked by a single bout of dynamic exercise might augment our access to highly specialized and functional cell types from the peripheral blood compartment of healthy donors that would otherwise not be readily available under resting conditions. Our laboratory has focused on the potential adjuvant effects of exercise for mobilizing and expanding antigen-specific T-cells for adoptive transfer immunotherapy. We have shown that a single exercise bout mobilizes CD4+ and CD8+ T-cells specific to a wide range of latent herpesvirus antigens (including those derived from CMV, EBV and AdV) to the bloodstream of healthy donors. Although this mobilization is transient, it has allowed us to detect and isolate up to 5-times more virus-specific T-cells from a fixed volume of donor blood after exercise. We have also found that when T-cells are extracted from blood after exercise, they respond more readily to peptide stimulation and this has allowed us to manufacture many more virus and tumor-antigen specific T-cells from donor blood after exercise. Importantly, the T-cell products isolated and manufactured after exercise retain their ability to kill autologous target cells *in vitro* in both an antigen and MHC-restricted manner, indicating that they are likely to be effective *in vivo* following adoptive transfer. These findings indicate that exercise may serve as a simple and economical adjuvant to overcome some of the limitations associated with isolating and expanding sufficient numbers of antigen-specific T-cells from healthy donors for adoptive transfer.

Our more recent work has shown that exercise augments the mobilization and ‘priming’ of antigen-specific T-cells by signaling through the β_2 adrenergic receptor, thus providing a potential target to augment the mobilization and *ex vivo* expansion of therapeutic T-cell products. Translating these findings to a clinical trial will ultimately determine if exercising healthy donors prior to/during blood collection will result in ⁽ⁱ⁾ a greater proportion of HSCT patients receiving allogeneic adoptive T-cell transfers to prevent/treat post transplant viral infections and disease relapse; (ii) larger T-cell numbers being transferred to the patient; (iii) shorter wait times for the patient to receive the T-cell product; and (iv) improvements in clinical outcomes such as lower relapse rates and reduced incidence and severity of post-transplant viral infections. It is our hope that the successful ‘bench to bedside’ translation of these findings will result in single exercise bouts being used routinely in the clinic to augment the recovery and manufacture of donor-derived T-cell therapeutics.