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Augmenting anti-tumor efficacy of adoptive immunotherapy with marrow infiltrating lymphocytes

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Despite the ability to generate tumor-specific immunity in both murine and human models, the efficacy of immune-based therapeutic interventions has met with limited success. Effective immunotherapy requires: the precursor frequency of antigen specific T cells be present in sufficient numbers; T cell trafficking to the tumor site; and recognition and killing of their target upon antigen encounter. We have taken a step-wise approach in an effort to address these issues. We utilized a whole tumor cell approach in conjunction with a GM-CSF – producing bystander cell in an effort to prime an immune response towards a broad range of tumor antigens and simplify vaccine production. Furthermore, by administering these vaccines within the context of an autologous stem cell transplant, we hoped to augment the anti-tumor response in a setting of minimal residual disease, lymphopenia, and a condition in which the host tolerogenic mechanisms had been disrupted. These studies demonstrated the ability to prime measurable tumor-specific responses. Interestingly, lymphoid reconstitution was significantly delayed and T cell responsiveness blunted. To improve T cell reconstitution, we activated and expanded peripheral T cells with anti-CD3/CD28

beads. This procedure resulted in a 250-fold *in vitro* expansion of T cells that enabled us to infuse approximately 2.5×10^9 CD3/kg. Interestingly, in addition to the significant *in vitro* expansion, we observed additional *in vivo* expansion. Baseline CD3 numbers of 500 μ L increased to 3900 μ L by day 21 post-autologous transplant and persisted at levels above historical controls for greater than 6 months. However, rapid lymphoid reconstitution was not associated with a significant increase in clinical benefit. We then asked whether lymphocytes obtained from the tumor microenvironment may possess greater tumor specificity upon activation. Marrow infiltrating lymphocytes (MILs) from myeloma patients demonstrate enhanced anti-tumor activity over peripheral blood lymphocytes (PBLs). Furthermore, MILs expand more rapidly upon activation, possess greater expression of activation markers. Importantly, they demonstrate markedly greater tumor specificity than PBLs upon activation and express greater levels of surface receptors that increase their likelihood of trafficking to the marrow upon reinfusion. Taken together, MILs possess many features that make them attractive candidates to utilize with or without vaccination in an effort to improve anti-tumor immunotherapy.