



Hyundai Hope on Wheels Hyundai Scholar Research

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Allogeneic stem cell transplantation (alloSCT) is a well-established therapy for hematologic malignancies. Despite its curative potential, alloSCT is a procedure severely hampered by three factors: (1) morbidity and mortality from the conditioning regimen, graft versus host disease (GVHD), and infections (2) lack of efficacy, especially in relapsed or refractory solid tumors and hematologic malignancies, and (3) limited availability of human leukocyte antigen (HLA)-identical donors. Innovative strategies to address these factors are urgently needed. Dr. Symons' ongoing research projects address these issues and bring novel immunotherapies to patients with high risk hematologic and solid tumor malignancies.

In the laboratory, Dr. Symons is working to make allogeneic lymphocyte infusion a feasible and effective treatment option for both solid tumor and hematologic malignancies patients for whom standard or even reduced intensity alloSCT is not an option or is deemed unlikely to be effective. The basis for this project is that an individual's immune system should be capable of recognizing growing tumor cells as foreign and destroy them, as is done with viral and bacterial infections. One possible explanation for why this does not happen with cancer cells is that growing tumors do not provide a danger signal and thus, do not activate the immune system. This model of immunity is based on the idea that the immune system is more concerned with things that do damage than with those that are foreign. Dr. Symons has been investigating ways to awaken a cancer-bearing individual's immune system with help from donor immune cells in order to force cancerous cells to appear dangerous. The basic strategy we are developing is the infusion of transiently engrafting lymphocytes, not so much to induce a direct anti-tumor effect, but rather to awaken an endogenous anti-tumor immune response by providing an exogenous source of CD4⁺ T cell help for endogenous, tumor-specific CD8⁺ T cells.

The underlying hypothesis of this strategy is that cancer-bearing individuals contain CD8⁺ T cells that can destroy malignant cells, but these T cells do not respond because of insufficient help from CD4⁺ T cells, which have been turned into anti-tumor "suppressor", or "regulatory" T cells (Figure 1). By the time the cancer is diagnosed clinically, these immunological events pose two problems for the treating physician. First, the regulatory CD4⁺ T cells, or T_{regs}, inhibit a destructive anti-tumor response by CD8⁺ T cells, even in

the presence of danger signals. Second, the diversion of CD4⁺ T cells to the regulatory phenotype effectively depletes the immune system of CD4⁺ T cell help, which is required for the maintenance of an anti-tumor CD8⁺ T cell response. This hypothesis generates a two-step strategy for the induction of effective anti-tumor immunity that we have established in the laboratory. In the first step, nonmyeloablative conditioning with cyclophosphamide (Cy) selectively eliminates CD4⁺ T_{regs}. In the second step, tumor-specific CD8⁺ T cells of the host are effectively awakened by an infusion of allogeneic (haploidentical) lymphocytes, which provide an exogenous source of CD4⁺ T cell help. Our preliminary in a mouse model demonstrate that the combination of Cy followed by CD8⁺ T cell-depleted allogeneic donor lymphocyte infusion (CD8⁻ DLI) prolongs survival from disseminated malignancies, in part by rekindling an anti-tumor immune response from host CD8⁺ T cells. Two attractive features of this therapy for clinical translation are that the infused lymphocytes engraft only transiently, thereby posing no risk of graft-versus-host disease (GVHD), and that there is no requirement for close histocompatibility matching between donor and host. Ultimately, we hope to provide an effective but relatively non-toxic form of adoptive immunotherapy for patients with hematologic and solid tumor malignancies.

In a second project, Dr. Symons is running an alloSCT clinical trial utilizing myeloablative chemotherapy, haploidentical donors, and T cell replete grafts. This trial is currently enrolling patients. Historically, alloSCT using haploidentical donors has been associated with significant risks of graft rejection and severe GVHD. The purpose of this trial is to (1) allow more patients to undergo alloSCT as only 1/3 of patients in need of alloSCT have HLA-identical donors, while the majority of patients in need of alloSCT have haploidentical (half-matched) donors; (2) minimize graft-versus host-disease, engraftment failure, and transplant related mortality with a novel alloSCT regimen including post-transplant cyclophosphamide. The primary objective of this trial is to estimate the incidence of full donor chimerism by day 60. Secondary objectives include estimating the incidence of graft rejection at day 60 and severe graft versus-host disease (GVHD) in patients receiving myeloablative conditioning and transplantation of haploidentical bone marrow from first-degree relatives. Additional secondary objectives will be to estimate the incidence of the overall survival (OS), relapse, non-relapse mortality (NRM), and event-free survival (EFS). In addition, we will retrospectively examine the relationship between killer immunoglobulin mismatch (KIR) mismatch and relapse, OS, PFS, engraftment and GVHD as we have previously shown that KIR mismatches improve outcome in a nonmyeloablative alloSCT setting. We are also performing correlative laboratory studies to look at the reconstitution of T cells, B cells, and NK cells after myeloablative haploidentical BMT with post-transplantation Cy. Patients will also have blood drawn to determine the incidence of de novo or recurring HLA specific antibodies following mismatched BMT, which has been correlated with engraftment failure.

The Hyundai Hope on Wheels Scholarship will allow Dr. Symons to have protected time to continue her research as well as provide support for laboratory supplies for both her bench and bedside research. This

Scholarship will be instrumental in providing Dr. Symons with the necessary funds to continue her novel cancer immunotherapeutic projects.