CELLULAR THERAPY AND HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR CANCER

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Abstract

The Center for Cellular Therapy and Hematopoietic Stem Cell Transplantation for Cancer was established in July 2007 to promote translational and clinical research in cellular therapy for cancer. The primary goal of the Center is translate discoveries from bench-to-clinic through phase I and early phase II cellular therapy clinical trials. To achieve this objective, the Center has brought together the unique expertise in hematopoiesis, immunology, gene therapy, graft engineering, and clinical hematopoietic stem cell transplantation (HCT) available at IUPUI. Since its establishment, we have completed two phase I clinical trials developing novel preparative regimens for allogeneic and autologous stem cell transplantation for patients with refractory leukemia and lymphoma, respectively. In addition, we have also initiated 5 additional early phase clinical trials that directly translate IUPUI laboratory discoveries to patients with hematological cancers. The Center has successfully competed for external funding through peer-reviewed grants and pharmaceutical contracts.

In this presentation, we highlight some important examples of the Center's ongoing and completed research. An important clinical research focus of our Center is the ability to extend the curative potential of allogeneic HCT to patients without suitably HLA-matched donors. We are currently exploring ways to improve the outcomes of umbilical cord blood (UCB) and haplotype-mismatched stem cell transplantation for patients with hematological cancers. The discovery in Dr. Broxmeyer's Laboratory, Indiana University, Indianapolis, that inhibition of the enzyme CD26 promotes homing and engraftment of limiting numbers of UCB stem cells has been translated to the first clinical trial *in vivo* CD26 inhibition using sitagliptin in adult leukemia patients undergoing UCB transplantation. Our preliminary data indicates that high-dose sitagliptin is well tolerated and appears to shorten the time of engraftment. As our data is further confirmed in this pilot study, we plan to investigate this potentially paradigm changing approach in a larger national study. As an extension of this research, Dr. Pelus' Laboratory, Indiana University, Indianapolis, has shown that short-term *ex vivo* treatment of hematopoietic progenitors using PGE2 will also promote engraftment. We are currently investigating the potential synergy of PGE2 treatment with CD26 inhibition to further enhance engraftment, which if results appear promising will also be translated to a phase I clinical trial. In haplotype-mismatched allogeneic HCT, mismatching of donor KIR receptors on natural killer (NK) cells

with recipient KIR ligands expressed on the patient's tumor cells exerts a NK cell-mediated anti-leukemia effect that contributes to reduced relapse after transplantation. We (Dr. Farag's Laboratory, Indiana University, Indianapolis) have shown that *in vivo* donor derived NK cells developing from donor stem cells have an "inhibitory" receptor phenotype that may sub-optimally function against leukemia. This has resulted in a phase I trial of purified NK cell infusion following mismatched HCT to investigate the feasibility and safety of this approach, as a prelude to a larger study to investigate its efficacy. Although the highest dose level of NK cells has not yet been investigated, the preliminary data indicates that such a novel approach is feasible. In additional studies based on our laboratory findings, we are exploring the harnessing of NK cells in the therapy of cancer through the monoclonal antibodies that block KIR receptors in combination with immuno-modulatory agents (e.g., lenalidomide) and antibodies that promote antibody-dependent cellular cytotoxicity (e.g., rituximab, anti-CS1). We have initiated patents for these discoveries, and are currently planning to transplant these into phase I clinical trials. Other ongoing research includes enhancing immune function against cancer through STAT3 inhibition to overcome tumor-mediated impairment of dendritic cell maturation, *ex vivo* specific expansion of cytotoxic of NK cell subsets for clinical use, and enhancing immune cell function following transplantation.

The continued success of our Center will depend on a continuing pipeline of novel laboratory discoveries and their translation to early phase clinical trials to assess feasibility and safety as a prelude to larger trials assessing efficacy. Initial funding of the Center by IUPUI has allowed the Center's conception, and the bringing together of basic and clinical researchers to the "research table" to make this translational/clinical research endeavor a reality, and has allowed us to be competitive for external funding. An important developing outcome of this initiative is the preparation for a Program Project grant in Mobilization and Engraftment of Stem Cells.