

# Hematologists Recruit Licensed Natural-Born Killers for Stem Cell Transplants

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Allogeneic hematopoietic stem cell transplantation (HSCT) is used in the management of high-risk hematologic malignancies in first remission as well as for relapsed and chemotherapy-resistant disease. Despite their formidable toxicity, allogeneic approaches typically result in lower relapse rates than autologous regimens because of the donor immune response against recipient alloantigens, the so-called graft-versus-leukemia (GVL) effect. Traditional allogeneic transplant strategies employ major histocompatibility complex (MHC) matched sibling or unrelated grafts, with GVL resulting from donor T-cell recognition of minor MHC disparities on recipient antigen-presenting cells. When major MHC mismatches exist between donor and recipient, the GVL effect is increased, but at the expense of increasingly severe graft-versus-host disease (GVHD). Consequently, haplotype-mismatched donor sources require T-cell depletion prior to transplant to avoid uncontrollable, lethal GVHD. In such situations, an immune effect is still achieved but is mediated by an alternative population of donor leukocytes, natural killer (NK) cells. This year's Scientific Committee session on Transplantation Biology was devoted to the biology and therapeutic potential of this unique population of innate immune cells, with several interesting presentations by experts in the field.

Dr. Wayne Yokoyama began the program with a review of NK-cell self-tolerance. Previous work had suggested that NK cells, unlike traditional T cells, are induced to kill upon encountering targets that lack self-MHC molecules (the missing-self hypothesis). MHC knockout mice, however, do not possess autoreactive NK-cell populations, suggesting additional requirements for NK-cell activation. Dr. Yokoyama reviewed some of his own laboratory studies showing that NK cells are initially "licensed to kill," by engaging self-MHC, and that this priming is required for their subsequent activation by additional receptor-ligand interactions. Interestingly, NK cells primed in such a manner are in turn inhibited by the same MHC interactions driving their licensing. As a result, two populations of self-tolerant NK cells are hypothesized to exist: those primed and subsequently deactivated by self-MHC, and "unlicensed" cells not previously exposed to the requisite self-antigen.

Dr. Michael Caligiuri continued the presentation by reviewing several other aspects of human NK-cell biology. He discussed the roles of IL-15, c-kit ligand, and Flt3 ligand in NK-cell differentiation and expansion, and presented data from his own lab showing that NK-cell development from bone-marrow-derived precursors appears to occur within secondary lymphoid tissue. He went on to describe the *in-vivo* functions of different NK-cell subsets as defined by their surface levels of CD56.

Dr. Jeffrey S. Miller concluded the program by reviewing novel NK-cell-based treatment strategies for the management of human hematologic malignancies. Dr. Miller's group has focused on the use of haplotype-matched T-cell-depleted allogeneic NK-cell infusions for refractory cases of acute myeloid leukemia (AML). Such approaches have resulted in complete remissions for some patients, but have not generally produced long-term cures. Dr. Miller discussed strategies for improving the efficacy of NK-cell-based immunotherapy, including combining NK-cell adoptive transfer approaches with traditional myeloablative umbilical cord blood HSCT, enhancing NK-cell cytolytic activity by KIR receptor blockade, and sensitizing target cells using the proteasome inhibitor bortezomib.

For those wishing to learn more about NK-cell biology, several studies presented at the meeting may be of interest. Check out abstracts by Cooley, et al. (abstract #43), Vago, et al. (abstract #3274), Hurton, et al. (abstract #3271), Xing, et al. (abstract #3272), and Olson, et al. (abstract #2162).