Improved engraftment with minimal graft-versus-host disease after major histocompatibility complex-mismatched cord blood transplantation with photochemically treated donor lymphocytes.

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**Authors:** Bindu Kanathezhath, Myra Mizokami, Sharteny Stanislaus, Catherine Hounshell, Lynne Neumayr, Hua Guo, John E Hearst, Mark C Walters, Frans A Kuypers

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**Public Summary:**
There is a significant risk of severe graft-versus-host disease (GVHD) and graft failure after unrelated umbilical cord blood transplantation (CBT) if donor-recipient pairs are mismatched at major histocompatibility complex (MHC) loci. To mitigate these risks after mismatched CBT, we infused psoralen-treated, photochemically inactivated, mature donor T-lymphocytes with MHC mismatched murine donor fetal near-term peripheral blood (FNPB) cells after sublethal irradiation. We analyzed the rates of donor engraftment, GVHD and long-term survival in mismatched recipient mice. We observed superior engraftment and long-term survival with minimal GVHD after transplantation supplemented with psoralen-treated donor T-lymphocytes. This treatment facilitated durable engraftment of donor hematopoietic stem cells in the bone marrow and spleen, with complete but delayed recovery of all hematopoietic lineages. This CBT model establishes the possibility of ensuring donor engraftment across a MHC barrier without severe GVHD.

**Scientific Abstract:**
There is a significant risk of severe graft-versus-host disease (GVHD) and graft failure after unrelated umbilical cord blood transplantation (CBT) if donor-recipient pairs are mismatched at major histocompatibility complex (MHC) loci. To mitigate these risks after MHC-mismatched CBT, we infused psoralen-treated, photochemically inactivated, mature donor T-lymphocytes with MHC H2-haplotype mismatched murine donor fetal near-term peripheral blood (FNPB) cells after sublethal irradiation. We analyzed the rates of donor engraftment, GVHD and long-term survival in H2 haplotype disparate (C57BL/6 [H-2b]/Thy1.1 --> AKR [H-2k]/Thy1.2) recipient mice. We observed inconsistent donor engraftment after transplantation with cord blood alone, but superior engraftment and long-term survival after FNPB transplantation supplemented with psoralen-treated donor T-lymphocytes. Additionally, there was fatal GVHD after FNPB co-infusion with untreated donor T-lymphocytes, but minimal GVHD after FNPB supplemented with psoralen-treated donor T-lymphocytes transplantation. Donor MHC(high)/c-Kit(+) /lineage(-)/CD34(-) stem cells were noted in the recipient bone marrow compartment following co-infusion of photochemically inactivated T-cells with FNPB. Despite the non-myeloablative preparation before FNPB infusion, complete hematological recovery was delayed until 50-60 d after transplantation. We observed that co-transplantation of psoralen-treated donor T-lymphocytes with FNPB facilitated durable engraftment of donor hematopoietic stem cells in the marrow and splenic compartments with complete but delayed recovery of all hematopoietic lineages. This CBT model establishes the possibility of ensuring donor engraftment across a MHC barrier without severe GVHD.