HCT improved - less naïve, more useful

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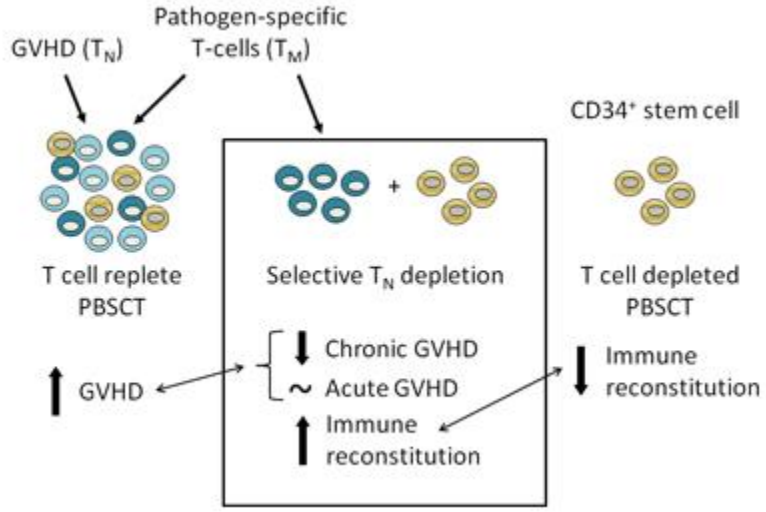

Selective naïve T cell depletion of allogeneic peripheral blood stem cells (PBSC). The results of the first clinical trial of naïve T cell depletion in HLA-matched HCT showed: a) a lower rate of chronic GVHD compared to T cell replete HCT; b) the same frequency of acute GVHD as from standard treatment, although universally corticosteroid-sensitive; and c) improved immune reconstitution compared with complete T cell depletion.

Image provided by Dr. Marie Bleakley

Leukemia and other hematologic malignancies may be cured through allogeneic hematopoietic stem cell transplantation (HCT), in which donor cells not only support the patients' healthy blood cell production, but also aid their immune defense in specifically recognizing and attacking malignant cells, the "graft-versus-leukemia effect." However, there is a fly in the ointment in the form of graft-versus-host disease (GVHD), signified by donor cells attacking also the recipients' healthy cells - a major cause of illness, disability, and even death after transplantation. Despite preventive medication, 30 to 70% of HLA-matched recipients develop acute GVHD, and 40 to 63% develop chronic GVHD.

Strategies to overcome GVHD without compromising the graft-versus-leukemia effect have been pursued by researchers for many years, but advances were reported by a Fred Hutch team in the July issue of *The Journal of Clinical Investigation*. Drs. Marie Bleakley, Shelly Heimfeld, and Stanley Riddell from the Clinical Research Division developed a first-in-human trial of naïve T cell (T_N)-depleted stem cell grafts, in collaboration with Dr. Warren Shlomchik at the University of Pittsburgh. Following standard conditioning with external total body irradiation and chemotherapy, 35 high-risk leukemia patients were transplanted with allogeneic peripheral blood stem cell grafts that lacked T_N.

The issue with naïve T cells in the context of transplantation is that subsets of T cells are specialized for different tasks, depending on their activation. T_N can respond to pathogens that the immune system has not been exposed to previously, with the purpose of initiating an immune response. Some then transform into long-lived memory T cells (T_M) ensuring that the body remembers how to deal with the foreign invaders, should they reappear. The challenge for the researchers was to find a strategy for separating the beneficial tumor-attacking functions of transplanted T cells from the adverse self-attacking properties that result from release into a new environment. Mouse studies had shown that T_N were associated with severe GVHD, and that the effect was much less likely caused by T_M. In addition, T_M evidently transferred the valuable graft-versus-leukemia effect and acquired "antigen experience" to the new host. In a set of in vitro experiments, Dr. Bleakley found analogous results in the human setting; the human T_N population comprised significantly more GVHD-triggering T cells than the T_M population, supporting the hypothesis. A new graft-engineering strategy was subsequently developed using immunomagnetic beads that selectively bound CD45RA, an antigen that is expressed by all T_N but absent in most T_M (Bleakley et al. 2014). In 2009, they were ready to start the first clinical trial.

The T_N-depleted transplants engrafted in all 35 patients, and the overall two-year survival was 78%. Chronic GVHD occurred in only 9% (median follow-up 932 days) - an extraordinarily small fraction. Although the rate of acute GVHD was unchanged, those who developed the condition responded much better to anti-GVHD corticosteroid treatment compared with T cell replete recipients. Graft T_M initiated quick recovery of T cells and transferred protective immunity, as anticipated.

The study demonstrated that T_N are key players in GVHD pathogenesis. "If you take the naïve T cells out of a stem cell graft you alter the natural history of GVHD essentially leading to a milder, consistently treatment-responsive form of acute GVHD that rarely progresses to classic chronic GVHD," Dr. Bleakley explained. The data also provide compelling proof-of-concept of the novel graft-engineering technique. "It is possible to engineer allogeneic hematopoietic stem cell grafts and achieve a reduction of GVHD without compromising immune reconstitution and increasing the rate of opportunistic infections," said Dr. Bleakley, who is currently enrolling patients for two clinical trials with T_N-depleted HCT at Fred Hutch. In the first of the two, eight children with acute leukemia have been treated so far and are doing well; twelve remain until completion of the study. In the second trial 80 adult patients with immunologically compatible ("HLA-matched") unrelated donors will be treated, including a lower-intensity conditioning arm enabling enrollment also of older patients and patients who are less fit for transplantation due to other medical conditions.

There is still plenty to learn, however, both regarding optimization of T_N-depleted transplantation and regarding the biology of the observed (mild) acute GVHD. Furthermore, little is known about any potential long-term effects on the immune system from this technique. Dr. Bleakley concluded, "if we continue to observe positive outcomes with a very low rate of chronic GVHD and good immune reconstitution we will plan larger trials with other centers in addition to the hutch and University of Pittsburgh, and possibly randomized controlled trials."

Bleakley M, Heimfeld S, Loeb KR, Jones LA, Chaney C, Seropian S, Gooley TA, Sommermeyer F, Riddell SR, Shlomchik WD. 2015. Outcomes of acute leukemia patients transplanted with naive T cell-depleted stem cell grafts. *J Clin Invest*. 125(7):2677-89.

See also: Bleakley M, Heimfeld S, Jones LA, Turtle C, Krause D, Riddell SR, Shlomchik W. 2014. Engineering human peripheral blood stem cell grafts that are depleted of naïve T cells and retain functional pathogen-specific memory T cells. *Biol Blood Marrow Transplant*. 20(5):705-16.

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