Semin Immunopathol (2008) 30:425–437
DOI 10.1007/s00281-008-0132-5

REVIEW

Reconstitution of the immune system after hematopoietic stem cell transplantation in humans

Jan Storek · Michelle Geddes · Faisal Khan · Bertrand Huard · Claudine Helg · Yves Chalandon · Jakob Passweg · Eddy Roosnek

Received: 5 August 2008 / Accepted: 30 September 2008 / Published online: 24 October 2008

Abstract Hematopoietic stem cell transplantation is associated with a severe immune deficiency. As a result, the patient is at high risk of infections. Innate immunity, including epithelial barriers, monocytes, granulocytes, and NK cells recovers within weeks after transplantation. By contrast, adaptive immunity recovers much slower. B- and T-cell counts normalize during the first months after transplantation, but in particular, T-cell immunity may remain impaired for years. During the last decade, much of the underlying mechanisms have been identified. These insights may provide new therapies to accelerate recovery.

Keywords Hematopoietic stem cell transplantation · Immunity · Immune deficiency · Thymus · Homeostasis

Introduction

Hematopoietic stem cell transplantation (HSCT) is an effective treatment for various hematological disorders. Conditioning of the patient should ablate, or at least strongly constrain host hematopoiesis to provide space for engraftment and suppress the patient's immune system to prevent graft rejection. Although their intensity may vary with the type of disease and the clinical condition of the patients, most protocols destroy the patient's immune system almost completely. In addition, alloreactive donor T cells cotransfused with the graft will eradicate the remaining patient cells of hematopoietic origin so that the patient's immunity after transplant will have to come from the transplanted donor cells.

After transplantation, monocytes are the first cells to engraft, rapidly followed by granulocytes, platelets, and natural killer (NK) cells. Clinical engraftment, the first day that the number of granulocytes is >0.5 G/L (and remains so for at least three consecutive days) usually occurs between day 10 and 25 after transplantation. Thereafter, the number of most leukocyte subsets normalizes rapidly (Fig. 1). This repopulation of cells in the host restores much of the innate immunity; antibacterial prophylaxis can be lowered, and infection surveillance decreased when the number of granulocytes has reached a critical threshold.

Judging the competence of the adaptive immune system by the number of regenerated T- and B-cells would however be a huge mistake. Although the number of lymphocytes increases rapidly during the first months after transplant, and the counts of most lymphocyte subsets (except for CD4 T cells) reach normal values in a considerable number of patients, the frequency of infections remains extremely high (1–9). The reasons for this are manifold. Most T cells present during the first year after transplantation are progeny of the donor T cells co-transfused with the graft that have expanded after entering the patient's "empty" T-cell compartment. Despite the fact that the number of mature lymphocytes in the graft could be theoretically sufficient to contain all the necessary antigen

J. Storek · M. Geddes · F. Khan
Division of Hematology and Hematologic Malignancies, Department of Medicine, University of Calgary, Calgary, AB, Canada

B. Huard · C. Helg · Y. Chalandon · J. Passweg · E. Roosnek
Division of Hematology, Department of Internal Medicine, Geneva University Hospitals and University of Geneva, Geneva, Switzerland

E. Roosnek (✉)
Division of Hematology, HUG, 24 rue Micheli-du-Crest, CH-1211 Geneva 14, Switzerland
e-mail: eddy.roosnek@unige.ch

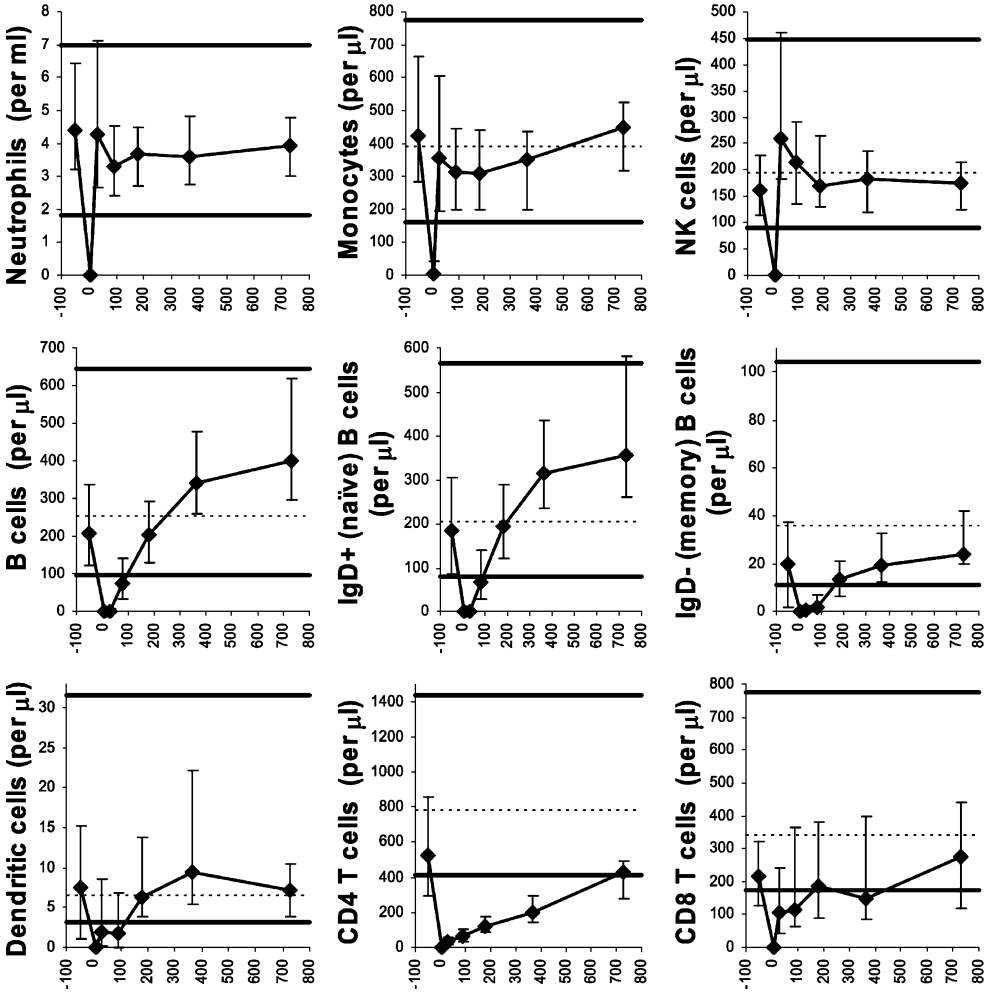

Fig. 1 Recovery of leukocyte subsets. All *horizontal axes* display days posttransplant. Patient medians (*diamonds*) and 25th–75th percentiles (*error bars*) are shown. Normal medians are indicated by the *dashed horizontal lines* (neutrophils not available). The *thick horizontal lines* denote the normal fifth and 95th percentiles (neutrophils 2.5th and 97.5th percentiles). Pretransplant studies are arbitrarily shown as day −100. Reproduced from [92] with permission

specificities, transfer of the donor's immunity is poor. Posttransplant, the conditions for lymphocyte activation in the patient are very different compared to normal conditions in which antigen, antigen-induced cytokines in secondary lymphoid organs, interaction between lymphocytes with the same antigen-specificity and available space are the key parameters that determine the size of clones with a particular specificity. During the first weeks, the high level of inflammatory cytokines induced by the conditioning (10–12) in combination with the available space that favors homeostatic expansion of T cells changes the composition of the transferred lymphocyte pool dramatically. The clonal size of a limited number of T cells may grow extensively so that the majority of the T cell pool contains only a few antigen specificities (13–15). Most of the cells will have lost the necessary homing receptors to enter secondary lymphoid organs to interact with antigen-presenting cells and stimulate B cells. The latter disappear almost completely from the circulation and are replenished after 2–3 months (Fig. 1; 8, 16–18). However, even if the B-cell repertoire is restored relatively fast, antibody responses will be hampered by the lack of T-cell help and will either be absent or, at best, resemble primary B cell responses (16, 19–23).

T- and B-cell responses will be incomplete for a long period after transplantation. Restoration of the T-cell compartment is prerequisite for functional immune recovery and at the same time is most cumbersome, in particular, in the elderly patient (24–26). Here, we will discuss the reconstitution of the patient's immunity for each part of the immune system separately. Early after transplant denotes in the first 3 months while late after transplant denotes after 6 months.

Nonhematological cells of the immune system

The first defense against infections consists of physical barriers such as the skin. Radiation, chemotherapy, or acute graft-versus-host disease (GVHD)-induced damage to the skin, the respiratory and digestive mucosa increases the chance of pathogen penetration into the patient early posttransplant. Late posttransplant, the epithelium is healed; the volume of protective secretions (e.g., tears or saliva)

become gradually normal in patients without chronic GVHD but often continues to be subnormal in those with chronic GVHD (27). There is typically no deficiency of serum complement, which is mainly produced by hepatocytes (28). Hence, physical barriers such as skin and serum proteins that play a role in the defense against pathogens usually recover rapidly in patients without severe GVHD. However, serum protein deficiencies that were asymptomatic before transplantation may become clinically manifest after transplant and be at the origin of severe infections (29).

Phagocytes and antigen-presenting cells

Neutrophil counts usually become normal by approximately 2 weeks after G-CSF mobilized blood stem cell grafting, 3 weeks after bone marrow grafting and 4 weeks after cord blood grafting (30). Neutrophil function (e.g., chemotaxis, phagocytosis, superoxide production, and killing of bacteria) early posttransplant may be subnormal, particularly in patients with acute GVHD. Neutrophil function may remain subnormal in patients with chronic GVHD (31). This could reflect the negative effect of corticosteroids (used for GVHD treatment) on neutrophil function.

Monocyte counts normalize by 1 month posttransplant (30). Macrophages are relatively chemo/radioresistant, so their numbers do not drop substantially; recipient macrophages are gradually replaced with donor macrophages over several months posttransplant (32). The first monocytes in the circulation are produced by the transplanted HSC (33). G-CSF mobilized PBSC grafts contain a large number of monocytes [approximately two logs more than marrow grafts (8)] but most of the monocytes infused with PBSCs probably either die or become tissue macrophages within days because monocytes in the blood of PBSC recipients become virtually undetectable by day 7 (Storek, unpublished). The function (e.g., IL-1 production or antigen presentation) of the recovering monocytes may be subnormal for approximately a year (34, 35), though several studies suggest normal function already early posttransplant (36–38).

Dendritic cells can be subdivided into at least five categories according to their location: (1) epithelial dendritic cells that migrate to the extrafollicular areas of lymph nodes upon encounter of antigen, (2) dendritic cells in the extrafollicular areas of lymph nodes and spleen, whose main function is to present antigen to T cells and provide costimulatory signals, (3) blood dendritic cells, which may represent the precursors of dendritic cells in the epithelium and the extrafollicular areas of spleen/lymph nodes, (4) thymic dendritic cells that play a role in deletion of autoreactive T cells, and (5) follicular dendritic cells in the germinal centers of lymph nodes and spleen that play a role in the maturation of the B cell (generation of somatically mutated and IgD/IgM→IgG/IgA/IgE-switched B cells).

Langerhans cells (epithelial dendritic cells in the skin) are low in number early posttransplant and near-normal by 6 months posttransplant (39). Dendritic cells in the extrafollicular areas of lymph nodes are present in about one third of transplant recipients, but a well-organized structure of follicles and germinal centers in lymph nodes and spleen is seldom observed during the first 6 months after transplantation (40–42). The grafted HSC produce blood dendritic cells detectable at 2–3 weeks (33) that remain low in quantity in the first 3 months posttransplant (Fig. 1); subsequently, counts of DC1 (conventional or myeloid dendritic cells, CD11c+) tend to normalize whereas counts of DC2 (plasmacytoid dendritic cells, CD123+) are low even at 1 year posttransplant (12, 43, 44). Thymic dendritic cells appear in the thymus within weeks posttransplant in mice (45); the recovery of these cells in humans has not been studied. Follicular dendritic cells appear to recover extremely slowly—even at 1 year after grafting, these cells appear sparse (40, 46). This could explain why germinal centers appear only late posttransplant (40–42, 46) and the reconstitution of memory B cells is slow (47).

Recipient epithelial dendritic cells may be important for the pathogenesis of GVHD because they will efficiently prime the alloreactive T cells in the graft. In mice, skin GVHD occurred in the presence but not in the absence of recipient Langerhans cells (48). In man, recipient Langerhans cells are present early after transplant (39), but it is not formally proven that these cells initiate GVHD of the skin.

NK cells

NK-cells counts as well as NK cell in vitro cytotoxicity recover during the first weeks after transplantation (8, 12, 17, 49–52). The number of NK cells is supranormal during 1–3 months posttransplant (Fig. 1) and, consistent with their role in defense against herpes viruses (53, 54), this phenomenon is more pronounced in cytomegalovirus-positive recipients (49, 55). The phenotype of the NK cells repopulating the patient is different from that in normal individuals (12, 50, 52, 56–59). The hallmark is the overrepresentation of $CD56^{high}CD16^{-}$ cells that produce more IFN-γ and are less cytotoxic than NK cells in normal individuals (12, 50, 52, 56). The classical view has been that these cells are immature precursors of $CD56^{dim}CD16^{+}$ cytotoxic NK-cells representing the major population in the peripheral blood of normal individuals. However, phenotypes of NK cells change rapidly when stimulated by

cytokines such as IL-2, IL-12, and IL-15 (60, 61), and it cannot be excluded that the IL-15 rich cytokine milieu posttransplant (12, 58, 59) is the major cause of the unusual phenotypes observed.

Recently, the characteristics of NK cells that repopulate the patients have received much interest. During the first months after transplantation, NK cells kill target cells without ligands for their killer cell immunoglobulin receptors inhibitory (KIR) more efficiently (62). As a result, NK cells may have a significant antileukemic effect, in particular, against AML (63–65). This effect is clinically most relevant in patients lacking KIR ligands present in the (haploidentical) HSC donor but may be present more generally (reviewed in (66)). Such alloreactive NK cells may also have a beneficial effect because they eliminate host APC that prime alloreactive T cells causing GVHD (63). This topic will be reviewed in more detail in the contribution of A. Velardi and colleagues in this issue of Springer seminars in Immunopathology.

T cells

A blood count is generally the first test performed when a patient shows signs of an immune deficiency. This test is often informative because many clinical symptoms can simply be attributed to a low number of a particular leukocyte subset. During the first years of clinical transplantation, it was not well understood why after HSCT the number of T cells does not correlate well with infections. Only after the advent of lymphocyte-subset specific monoclonal antibodies, it became clear that during the first year after transplantation, the T-cell compartment was abnormal and contained many activated (HLA-DR$^+$) cells and considerably more CD8$^+$ and much less naïve T cells than in normal individuals (17, 67–69). Furthermore, responses to mitogenic stimuli in vitro were decreased (69–71) and in vitro responses to recall antigens were virtually absent (70, 72).

Although these long-lasting alterations may explain why the patient's T-cell immunity remained deficient for a prolonged period and vaccinations were ineffective during the first year, the underlying mechanism remained unclear. Mackall and Gress demonstrated that the human T cell compartment is repopulated after intensive chemotherapy by two different pathways (24, 73). One is similar to ontogeny when thymic emigrants replenish the T-cell compartment and depends therefore on a functioning thymus. In addition, the T-cell compartment can be repopulated through peripheral expansion of mature T cells. The latter pathway is predominant when the thymic activity is low (74), which is likely to be the case in adult patients. Several publications (72, 75–78) followed showing that, not unexpectedly, the situation was even more radical after HSCT. This has been demonstrated most intelligibly in patients conditioned with total body irradiation and cyclophosphamide and transplanted with an in vitro T-cell depleted allogeneic HSC graft. The infusion of very low numbers of donor cells into these patients had two consequences. First, the lack of alloreactivity allowed the few recipient T cells not eliminated by the conditioning to survive. Because the conditioning destroys the patient's HSC (79), every T cell of patient origin after transplantation must be the progeny of the few T cells present at transplant, and the increase of T cells must therefore be the result of expansion. Second, the number of donor T cells co-infused with the graft is so low that, during the first 2 weeks, the T-cell compartment is virtually empty. This induces a rapid parallel expansion of donor and recipient T cells that reconstitute the T cell compartment before the appearance of the first donor-derived naive T cells produced by the thymus (78). The latter can be easily monitored because, under these conditions, the T-cell compartment that has been reconstituted by expansion uniquely, comprises only T cells that express memory markers. Rufer has described a patient transplanted with a T-cell depleted bone marrow from a donor with CD4$^+$ memory T cells expressing high amounts of CD45RA, the isoform of CD45 expressed by naïve cells that is downregulated upon activation. This phenotype without apparent functional consequences is present in ~1% of the population and is caused by a point mutation in the exon A of CD45 that leads to an abnormal splicing pattern (80). This allowed direct visualization of the entire process (81) because patient (CD45RA$^-$RO$^+$) and donor (CD45RA^{bright}RO$^+$) memory/effector CD4$^+$ T cells could be discriminated by flow cytometry. Naïve (CD45RA$^+$RO$^-$) T cells appeared after approximately 6 months and were entirely of donor origin. The thymus independent pool of patient T cells predominated during the first years and persisted for more than 7 years. The size of the pool of donor memory/effector increased, most likely because ongoing immune responses recruited cells from the naïve T-cell pool produced by the thymus (81). This pattern of reconstitution is representative for patients after depletion of the mature T cell pool. In adults, naïve T cells do not emerge during the first 4 months, and partial restoration of the naïve T cell pool may require 1 to 2 years and may only occur in individuals younger than 45–50 years (24, 72, 78, 82).

Repopulation of the posttransplant T-cell compartment by expansion is the consequence of natural homeostatic mechanisms that control the size of the T-cell pool. In normal individuals, T cells compete for available space through competition for homeostatic cytokines such as IL-7 and IL-15 that are produced by cells of nonhematological origin. Triggering of the T-cell receptor by antigen

increases the T cell's "competitiveness" so that new memory cells can enter the memory pool without increasing its size because they replace less competitive cells (83). After transplantation, IL-7 and IL-15 are produced but not instantly consumed, which results in supranormal serum levels of these homeostatic cytokines (11, 12). The amounts of IL-7 and IL-15 produced to maintain a complete naïve and memory T-cell compartment are available to the few T cells present after transplantation; these will expand until they reach a number that is in the range of that of the memory pool in normal individuals. Although homeostatic expansion also occurs when T cells are triggered by self-peptides (83, 84), and therefore is not strictly antigen-dependent, the presence of antigen favors proliferation to such an extent that initially, the T-cell compartment is filled up mainly by cells that recognize the antigens present in the host at the moment of transplant (85). As a result, large parts of the T-cell repertoire after transplantation may be directed against mismatched histocompatibility antigens (14, 86, 87) or against herpes viruses (88–91) that are present in the majority of patients at the moment of transplant while other specificities may be lost completely (85).

The fact that after transplantation the T-cell compartment is reconstituted through homeostasis based on the rules described above is able to explain many of the phenomena that have been reported since the start of clinical transplantation. The abundance of cells with activated phenotypes (17, 67–69), the high percentage of cells in cell cycle (92), and the rapid shortening of telomeres in T cells (93, 94) during the first months reflect the initial repopulation by expansion. The lack of correlation between the number of $CD8^+$ T cells after transplantation and the wide (2–3 log) range of $CD8^+$ T cells infused (8, 51, 95) illustrates the remarkable potential of mature T cells to repopulate the periphery until a particular number is reached. The inversed CD4/CD8 ratio (Fig. 1), much more prominent in cytomegalovirus-positive patients (96, 97) and in patients suffering from GvHD (67) shows that repopulation by expansion is driven by antigen. Furthermore, because these cells can only be recruited from the few T cells present at transplant, their T-cell receptors may dominate the entire repertoire (13–15, 98). The paucity of naïve T cells early after transplant emphasizes the initial insignificance of the thymic pathway while the kinetics of their recovery, much slower in adults than in children (25, 75, 78, 99) reflects the inefficiency of the posttransplant thymic rebound.

Repopulation of the T-cell compartment by homeostatic expansion does not restore T-cell immunity. Although the frequency of infections decreases considerably after the innate immune system has recovered, patients remain at high risk during the first 2 years posttransplant and suffer considerably more from infectious morbidity than their age-matched controls. Late posttransplant and in the absence of GVHD, infections are less frequent (though still more frequent than in healthy individuals), and the predominant pathogens are viruses (1, 3, 4, 6, 7, 9). Furthermore, responses to vaccinations during the first year are low or completely absent (9, 100–102).

Posttransplant T-cell immune deficiency is caused by the destruction of the patient's T cells, by the lack of efficient transfer of donor immunity and by the incapacity of the thymus to produce sufficient numbers of naïve T cells. The latter is not only owed to the decreased thymic function in adults but also to the damage inflicted by the conditioning and by donor alloreactive donor T cells transferred with the graft. As a consequence, variables such as the treatment of the graft, the intensity of the conditioning, the occurrence of GVHD and the age of the recipient are significantly correlated with the recovery of the patient's immunity. The posttransplant immunity is entirely of donor origin unless the conditioning and/or the manipulation of the graft strongly favor the survival of recipient T cells (91, 103). The extent of transferred immunity and the significance thereof is controversial. There are many studies describing the transfer of T- or B-cell immunity (4, 91, 104–108). After boosting the donor in the weeks before transplantation with tetanus toxoid or with *Haemophilus influenzae* polysaccharide–protein conjugate, specific antibody is found in the patient (104, 105, 108, 109). However, it is not clear to what extent the antigen-specific antibody production may be attributed to aspecific triggering of the transferred B cells, a phenomenon frequently observed after transplantation (110). Sustained antibody production does require encounter with antigen (100, 111) and, for most antigens, T-cell help.

T-cell immunity against poliovirus, tetanus, diphtheria, and measles is lost after transplantation (2, 104, 112). Interestingly, CMV- or EBV-specific T-cells are readily detected early after transplant (3, 4, 88, 89, 91, 113), usually at much higher frequencies (up to 25% of the $CD8^+$ T cells) than in normal individuals (91, 113). The key difference is the presence of antigen that triggers a supranormal expansion of T cells encountering antigen under lymphopenic conditions (85). As a result, transferred immunity against the antigens present at the moment of transplant persists, while other specificities are lost. The latter may simply be the result of the homeostatic competition of T cells triggered by antigen. Another explanation could be that after transplantation, transferred T cells lose the homing receptors requisite to circulate through lymph nodes so that they cannot be primed by antigen presented by DC.

If donor immunity is preserved more efficiently in the presence of antigen at the onset of homeostatic expansion, very early immunizations might be effective. Two studies

reported that vaccination with *H. influenzae* polysaccharide–protein conjugate or tetanus toxoid of the patient shortly before transplantation enhanced responses to vaccinations with the same antigen at 2–3 months posttransplant (108, 114), a time point at which patients usually do not respond at all (100, 101, 108). Although the rise in antibody titers obtained were modest, these encouraging data may warrant further study.

It is notable that T-cell depletion of the graft interferes less with the transfer of immunity than would have been expected on the basis of the number of T cells transferred (4, 91, 106, 107, 115). Although after T-cell depletion, the T-cell receptor repertoire is more limited (15, 76), several studies show that the number of T cells specific for CMV, EBV, Candida (i.e. the antigens commonly present) are comparable in recipients of unmanipulated or T-cell-depleted grafts (4, 91, 106, 107). Functional immunity early posttransplant may not be significantly lower in recipients of T-cell depleted grafts (104, 116–120). Potential explanations for this include the possibility that the number of antigen-specific T cells transferred is not of great importance since the expansion potential of T cells in the presence of antigen is sufficient, or perhaps more importantly, that after T-cell depletion, immunological reconstitution is less often impaired by GVHD or its prophylaxis/treatment than in recipients of unmanipulated grafts.

Once the T-cell compartment has been reconstituted by expansion and many antigen-specificities have been lost, a complete T-cell repertoire can only come from naïve T cells produced by the thymus (72, 75, 121). Reconstitution does not occur in thymectomized patients (122) and is less efficient in elderly patients or in patients who have suffered from GVHD (24–26, 75, 78, 123, 124). This clearly illustrates the diminishing capacity of the adult thymus to produce T cells and the thymic damage inflicted by GVHD (see also the contribution by W. Krenger in this issue of Springer Seminars in Immunopathology). Measuring the thymic rebound may thus be helpful to determine the optimal time to start the revaccination (72).

B cells

B cells are low in number or undetectable during the first 2 months after marrow grafting (reviewed in (18)). They subsequently increase, and blood B cell counts often become supranormal by 1–2 years after grafting. The rise is faster in autologous than allogeneic marrow recipients. It is faster in patients without GVHD than in those with GVHD (16, 55), probably because GVHD and/or its treatment hamper B-lymphopoiesis (125, 126).

During the first 1–2 years posttransplant, memory B cells are scarce (Fig. 1). Most B cells are naïve (membrane IgD^{high}, membrane IgM^{high}) (18), lack somatically mutated VDJ genes (19–21), and produce IgM rather than IgG or IgA (16, 22, 23). After an initial fall early posttransplant, serum isotype levels recover in the same sequence as in young children: IgM → IgG1/IgG3 → IgG2/IgG4/IgA (127). Hence, B cell reconstitution after HSCT resembles a recapitulation of ontogeny that is likely to occur more slowly than in young children because follicular dendritic cells and CD4 T cells in germinal centers needed for isotype switching are scarce. It is noticeable that total (isotype) immunoglobulin levels are imperfect markers of posttransplant humoral immunity since many of the antibodies produced may be autoantibodies or mono/oligoclonal antibodies of irrelevant specificity rather than specific for infectious agents (110). Antibodies with a relevant specificity usually fall early posttransplant. The magnitude of the decrease is substantial after allogeneic HSCT; however, it is only minor (or undetectable) after autologous HSCT. Subsequent to that, the levels of antibodies with relevant specificities depend on the posttransplant encounter of the antigen. Without encounter of the antigen, the levels of pathogen-specific antibodies become gradually undetectable, often over a course of years (128). If the encounter of the antigen occurs (e.g., CMV in patients that were CMV-seropositive pretransplant) the levels of CMV-specific antibodies normalize within about 1 year—earlier in patients with and later in patients without immune donors (129, 130). This is only true for protein antigens. In the case of polysaccharide antigens (e.g., pneumococcal capsular polysaccharides), the levels of specific antibodies may normalize only very late (2–20 years after transplant) even if the encounter of the antigen is likely (131, 132).

Antibody response to vaccination is another measure of B cell immunity. Early posttransplant, responses to any antigen are subnormal. Responses to protein antigens recover faster (usually within 1–2 years) than responses to polysaccharide antigens (usually at ≥2 years posttransplant). Responses to protein recall antigens (e.g., poliovirus or tetanus toxoid) tend to recover faster than responses to protein neo-antigens. The recovery of antibody responses to any antigen is delayed in patients with chronic GVHD (reviewed in (133)). T-cell depletion of the graft or posttransplant treatment with anti-T-cell antibodies may delay the recovery of antibody responses (134). Also, the responses may recover faster in young versus old individuals (134), which could be related to the faster recovery of CD4 T cells in younger patients.

Are post-allotransplant B cells and plasma cells of donor or recipient origin? Virtually all circulating B cells are of donor origin after T cell replete grafting with high intensity conditioning; after T-cell-depleted transplantation and after transplantation with low intensity or no conditioning, a variable degree of incomplete chimerism of B cells is

frequently established (reviewed in (133)). Antibodies are primarily of recipient origin early posttransplant; even in patients with complete chimerism of lymphocytes, the conversion to only donor-type antibodies takes months or years (reviewed in (133)). This is likely due to the relative radioresistance and longevity of recipient plasma cells (135, 136) and the lack of B cells early posttransplant.

Do posttransplant B cells originate from the B cells infused with the graft or from the infused stem cells? This has not been determined conclusively. Antigen-specific antibody production can be adoptively transferred from immune donors with T-cell-depleted grafts (107). Recipients of blood stem cell grafts that contain 18 times more B cells than marrow grafts have higher B cell counts in the first 3 months posttransplant compared to marrow graft recipients (8). This suggests that early posttransplant, the infused B cells contribute to the recipient B cell pool. However, there is also indirect evidence for the origin of B cells from stem cells, as supranormal amounts of B-cell precursors are frequently found in the marrow at 2–12 months after transplant, i.e., prior to the overshoot of circulating B cell counts above the normal adult range (125, 137–139), and in recipients of B cell-purged autologous marrow, the tempo of B-cell reconstitution is not slower than in the recipients of unmanipulated marrow (140–142). Thus, both B-cell-derived and stem-cell-derived B cells may coexist after grafting. The B cells derived from infused B cells may predominate early, whereas the stem cell-derived B cells probably predominate late posttransplant.

What could be done to increase posttransplant immunity?

As T-lymphocytopenia appears to be an important cause of posttransplant infectious diseases, especially due to herpesviruses, research to improve T-cell restoration after grafting is ongoing. This can be achieved by (1) infusing mature T cells from the donor to the recipient or (2) stimulating recipient de novo T-cell production (thymopoiesis)—(1) Infusion of a high number of T cells from the donor may reduce the frequency of infections (8) but is associated with an unacceptably high risk of GVHD (143). Infusion of virus-specific T cells decreases the incidence of viral infections without increasing the incidence of GVHD (144–151). It is likely that this will enter clinical practice when manufacturing of virus-specific T cells has been simplified. An alternative approach under investigation is the infusion of T cells depleted of T cells reactive to host alloantigens (152–154). (2) Stimulation of thymopoiesis is attractive, as it should theoretically restore a broad T-cell repertoire, including against pathogens present in the recipient (155, 156). In mice, the following strategies have yielded improved thymopoiesis: (1) interleukin-7 (IL-7) administration (157–160), (2) growth hormone administration (161), and (3) protection of thymic epithelium from conditioning- or GVHD-induced damage by keratinocyte growth factor (KGF) administration (162, 163). Whether these approaches can enhance thymopoiesis in primates is controversial. IL-7 administration to monkeys resulted in increased T cell counts in four studies (164–167); however, in three of these studies, this was purely due to increased T-cell proliferation and not increased thymopoiesis (164–166). In the only study of IL-7 in human reported so far, IL-7 administration increased T-cell counts primarily or entirely due to increased T-cell proliferation; potential contribution of increased thymopoiesis was unlikely as the increase of T-cell receptor excision circle-containing T-cell counts was insignificant and unrelated to patient age, and by computer tomography, there was no thymic enlargement (156). Growth hormone effect on thymopoiesis in primates has not been studied. KGF given to macaques to protect the thymus from radiation damage resulted in only mild and inconsistent improvement of thymopoiesis (168).

HSCT is often the best chance of curing several forms of hematological malignancies and of congenital immune deficiencies. An at least transient immune deficiency is one of the side effects that seems unavoidable given the fact that an intense immunosuppressive conditioning must be given to allow engraftment. More research is needed but in the next future, a combination of the strategies mentioned above may improve posttransplant immunity considerably.

Acknowledgment Eddy Roosnek's group is supported by a grant from the Swiss National Science Foundation and by the 'Dr Henri Dubois-Ferrière-Dinu Lipatti' Foundation.

References

1. Witherspoon RP, Lum LG, Storb R (1984) Immunologic reconstitution after human marrow grafting. Semin Hematol 21:2–10
2. Lum LG, Munn NA, Schanfield MS, Storb R (1986) The detection of specific antibody formation to recall antigens after human bone marrow transplantation. Blood 67:582–587
3. Reusser P, Riddell SR, Meyers JD, Greenberg PD (1991) Cytotoxic T-lymphocyte response to cytomegalovirus after human allogeneic bone marrow transplantation: pattern of recovery and correlation with cytomegalovirus infection and disease. Blood 78:1373–1380
4. Lucas KG, Small TN, Heller G, Dupont B, O'Reilly RJ (1996) The development of cellular immunity to Epstein-Barr virus after allogeneic bone marrow transplantation. Blood 87:2594–2603
5. Morrison VA, Haake RJ, Weisdorf DJ (1994) Non-Candida fungal infections after bone marrow transplantation: risk factors and outcome. Am J Med 96:497–503 doi:10.1016/0002-9343(94)90088-4

6. Ochs L, Shu XO, Miller J, Enright H, Wagner J, Filipovich A, Miller W, Weisdorf D (1995) Late infections after allogeneic bone marrow transplantation: comparison of incidence in related and unrelated donor transplant recipients. Blood 86:3979–3986
7. Storek J, Gooley T, Witherspoon RP, Sullivan KM, Storb R (1997) Infectious morbidity in long-term survivors of allogeneic marrow transplantation is associated with low CD4 T cell counts. Am J Hematol 54:131–138 doi:10.1002/(SICI)1096-8652(199702)54:2<131::AID-AJH6>3.0.CO;2-Y
8. Storek J, Dawson MA, Storer B, Stevens-Ayers T, Maloney DG, Marr KA, Witherspoon RP, Bensinger W, Flowers ME, Martin P, Storb R, Appelbaum FR, Boeckh M (2001) Immune reconstitution after allogeneic marrow transplantation compared with blood stem cell transplantation. Blood 97:3380–3389 doi:10.1182/blood.V97.11.3380
9. Antin JH (2002) Clinical practice. Long-term care after hematopoietic-cell transplantation in adults. N Engl J Med 347:36–42 doi:10.1056/NEJMcp010518
10. Antin JH, Ferrara JL (1992) Cytokine dysregulation and acute graft-versus-host disease. Blood 80:2964–2968
11. Bolotin E, Annett G, Parkman R, Weinberg K (1999) Serum levels of IL-7 in bone marrow transplant recipients: relationship to clinical characteristics and lymphocyte count. Bone Marrow Transplant 23:783–788 doi:10.1038/sj.bmt.1701655
12. Chklovskaia E, Nowbakht P, Nissen C, Gratwohl A, Bargetzi M, Wodnar-Filipowicz A (2004) Reconstitution of dendritic and natural killer cell subsets after allogeneic stem cell transplantation: effects of endogenous flt3 ligand. Blood 103:3860 doi:10.1182/blood-2003–04–1200
13. Gorochov G, Debré P, Leblond V, Sadat-Sowti B, Sigaux F, Autran B (1994) Oligoclonal expansion of CD8 + CD57 + T cells with restricted T-cell receptor b chain variability after bone marrow transplantation. Blood 83:587–595
14. Gaschet J, Denis C, Milpied M, Hallet M-M, Romagné F, Necker A, Vivien R, David-Ameline J, Davodeau F, Bonneville M, Vié H (1995) Alterations of T cell repertoire after bone marrow transplantation: characterization of over-represented subsets. Bone Marrow Transplant 16:427–435
15. Roux E, Helg C, Chapuis B, Jeannet M, Roosnek E (1996) T-cell repertoire complexity after allogeneic bone marrow transplantation. Hum Immunol 48:135–138 doi:10.1016/0198-8859(96)00085-7
16. Small TN, Keever CA, Weiner-Fedus S, Heller G, O'Reilly RJ, Flomenberg N (1990) B-cell differentiation following autologous, conventional, or T-cell depleted bone marrow transplantation: a recapitulation of normal B-cell ontogeny. Blood 76:1647–1656
17. Leino L, Lilius EM, Nikoskelainen J, Pelliniemi TT, Rajamaki A (1991) The reappearance of 10 differentiation antigens on peripheral blood lymphocytes after allogeneic bone marrow transplantation. Bone Marrow Transplant 8:339–344
18. Storek J, Ferrara S, Ku N, Giorgi JV, Champlin RE, Saxon A (1993) B cell reconstitution after human bone marrow transplantation: recapitulation of ontogeny? Bone Marrow Transplant 12:387–398
19. Storek J, King L, Ferrara S, Marcelo D, Saxon A, Braun J (1994) Abundance of a restricted fetal B cell repertoire in marrow transplant recipients. Bone Marrow Transplant 14:783–790
20. Suzuki I, Milner ECB, Glas AM, Hufnagle WO, Rao SP, Pfister L, Nottenburg C (1996) Immunoglobulin heavy chain variable region gene usage in bone marrow transplant recipients: lack of somatic mutation indicates a maturational arrest. Blood 87:1873–1880
21. Glas AM, van Montfort EH, Storek J, Green EG, Drissen RP, Bechtold VJ, Reilly JZ, Dawson MA, Milner EC (2000) B-cell-autonomous somatic mutation deficit following bone marrow transplant. Blood 96:1064–1069
22. Gerritsen EJA, Van Tol MJD, Van't Veer MB, Wels JMA, Khouw IMSL, Touw CR, Jol-van der Zijde CM, Hermans J, Rümke HC, Radl J, Vossen JM (1994) Clonal dysregulation of the antibody response to tetanus-toxoid after bone marrow transplantation. Blood 84:4374–4382
23. Storek J, Witherspoon RP, Luthy D, Storb R (1995) Low IgG production by mononuclear cells from marrow transplant survivors and from normal neonates is due to a defect of B cells. Bone Marrow Transplant 15:679–684
24. Mackall CL, Fleisher TA, Brown MR, Andrich MP, Chen CC, Feuerstein IM, Horowitz ME, Magrath IT, Shad AT, Steinberg SM, Wexler LH, Gress RE (1995) Age, thymopoiesis, and CD4 + T-lymphocyte regeneration after intensive chemotherapy. N Engl J Med 332:143–149 doi:10.1056/NEJM199501193320303
25. Small TN, Papadopoulos EB, Boulad F, Black P, Castro-Malaspina H, Childs BH, Collins N, Gillio A, George D, Jakubowski A, Heller G, Fazzari M, Kernan N, MacKinnon S, Szabolcs P, Young JW, O'Reilly RJ (1999) Comparison of immune reconstitution after unrelated and related T-cell- depleted bone marrow transplantation: effect of patient age and donor leukocyte infusions. Blood 93:467–480
26. Hakim FT, Gress RE (2002) Reconstitution of thymic function after stem cell transplantation in humans. Curr Opin Hematol 9:490–496 doi:10.1097/00062752-200211000-00004
27. Chaushu G, Itzkovitz-Chaushu S, Yefenof E, Slavin S, Or R, Garfunkel AA (1995) A longitudinal follow-up of salivary secretion in bone marrow transplant patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 79:164–169 doi:10.1016/S1079-2104(05)80276-8
28. Noel DR, Witherspoon RP, Storb R, Atkinson K, Doney K, Mickelson EM, Ochs HD, Warren RP, Weiden PL, Thomas ED (1978) Does graft-versus-host disease influence the tempo of immunologic recovery after allogeneic human marrow transplantation? An observation on 56 long-term survivors. Blood 51:1087–1105
29. Mullighan CG, Heatley S, Doherty K, Szabo F, Grigg A, Hughes TP, Schwarer AP, Szer J, Tait BD, Bik To L, Bardy PG (2002) Mannose-binding lectin gene polymorphisms are associated with major infection following allogeneic hemopoietic stem cell transplantation. Blood 99:3524–3529 doi:10.1182/blood.V99.10.3524
30. Cornelissen J (2004) Hematopoietic reconstitution after hematopoietic stem cell transplantation. In: Atkinson KA, Champlin R, Ritz J, Fibbe WE, Ljungman P, Brenner MK (eds) Clinical bone marrow and blood stem cell transplantation. Cambridge University Press, Cambridge, pp 160–19
31. Zimmerli W, Zarth A, Gratwohl A, Speck B (1991) Neutrophil function and pyogenic infections in BMT recipients. Blood 77:393–399
32. Nakata K, Gotoh H, Watanabe J, Uetake T, Komuro I, Yuasa K, Watanabe S, Ieki R, Sakamaki H, Akiyama H, Kudoh S, Naitoh M, Satoh H, Shimada K (1999) Augmented proliferation of human alveolar macrophages after allogeneic bone marrow transplantation. Blood 93:667–673
33. Auffermann-Gretzinger S, Lossos IS, Vayntrub TA, Leong W, Grumet FC, Blume KG, Stockerl-Goldstein KE, Levy R, Shizuru JA (2002) Rapid establishment of dendritic cell chimerism in allogeneic hematopoietic cell transplant recipients. Blood 99:1442–1448 doi:10.1182/blood.V99.4.1442
34. Cayeux S, Meuer S, Pezzutto A, Korbling M, Haas R, Schulz R, Dorken B (1989) Allogeneic mixed lymphocyte reactions during a second round of ontogeny: normal accessory cells did not restore defective IL-2 synthesis in T cells but induced responsiveness to exogeneous IL-2. Blood 74:2278–2284

35. Sahdev I, O'Reilly R, Black P, Heller G, Hoffmann M (1996) Interleukin-1 production following T cell depleted and unmodified marrow grafts. Pediatr Hematol Oncol 13:55–67 doi:10.3109/08880019609033372
36. Tsoi MS, Storb R, Brkic S, Ramberg E, Thomas ED, Storb R (1984) Cellular interactions in marrow-grafted patients, II, Normal monocyte antigen-presenting and defective T cell proliferative function early after grafting and during chronic graft-versus-host disease. Transplantation 37:556–561 doi:10.1097/00007890-198406000-00006
37. Shiobara S, Witherspoon RP, Lum LG, Storb R (1984) Immunoglobulin synthesis after HLA-identical marrow grafting. V. The role of peripheral blood monocytes in the regulation of in vitro immunoglobulin secretion stimulated by pokeweed mitogen. J Immunol 132:2850–2856
38. Brkic S, Tsoi MS, Mori T, Lachman L, Gillis S, Thomas ED, Storb R (1985) Cellular interactions in marrow-grafted patients. III. Normal interleukin-1 and defective interleukin-2 production in short-term patients and in those with chronic GVHD. Transplantation 39:30–35 doi:10.1097/00007890-198501000-00001
39. Collin MP, Hart DN, Jackson GH, Cook G, Cavet J, Mackinnon S, Middleton PG, Dickinson AM (2006) The fate of human Langerhans cells in hematopoietic stem cell transplantation. J Exp Med 203:27–33 doi:10.1084/jem.20051787
40. Dilly SA, Sloane JP (1988) Cellular composition of the spleen after human allogeneic bone marrow transplantation. J Pathol 155:151–160 doi:10.1002/path.1711550212
41. Dilly SA, Sloane JP, Psalti IS (1986) The cellular composition of human lymph nodes after allogenic bone marrow transplantation: an immunohistological study. J Pathol 150:213–221 doi:10.1002/path.1711500310
42. Horny HP, Ruck M, Kaiserling E, Ehninger G (1990) Immunohistology of the human spleen after bone marrow transplantation for leukemia with special reference to the early post-transplantation period. Pathol Res Pract 186:775–783
43. Fearnley DB, Whyte LF, Carnoutsos SA, Cook AH, Hart DN (1999) Monitoring human blood dendritic cell numbers in normal individuals and in stem cell transplantation. Blood 93:728–736
44. Klangsinsirikul P, Carter GI, Byrne JL, Hale G, Russell NH (2002) Campath-1G causes rapid depletion of circulating host dendritic cells (DCs) before allogeneic transplantation but does not delay donor DC reconstitution. Blood 99:2586–2591 doi:10.1182/blood.V99.7.2586
45. Wu L, Li CL, Shortman K (1996) Thymic dendritic cell precursors: relationship to the T lymphocyte lineage and phenotype of the dendritic cell progeny. J Exp Med 184:903–911 doi:10.1084/jem.184.3.903
46. Sale GE, Alavaikko M, Schaefers KM, Mahan CT (1992) Abnormal CD4:CD8 rations and delayed germinal center reconstitution in lymph nodes of human graft recipients with graft-versus-host disease: an immunohistological study. Exp Hematol 20:1017–1021
47. Storek J, Witherspoon RP, Maloney DG, Chauncey TR, Storb R (1997) Improved reconstitution of CD4 T cells and B cells but worsened reconstitution of serum IgG levels after allogeneic transplantation of blood stem cells instead of marrow. Blood 89:3891–3893
48. Merad M, Hoffmann P, Ranheim E, Slaymaker S, Manz MG, Lira SA, Charo I, Cook DN, Weissman IL, Strober S, Engleman EG (2004) Depletion of host Langerhans cells before transplantation of donor alloreactive T cells prevents skin graft-versus-host disease. Nat Med 10:510–517 doi:10.1038/nm1038
49. Hokland M, Jacobsen N, Ellegaard J, Hokland P (1988) Natural killer function following allogeneic bone marrow transplantation. Very early reemergence but strong dependence of cytomegalovirus infection. Transplantation 45:1080–1084 doi:10.1097/00007890-198806000-00016
50. Jacobs R, Stoll M, Stratmann G, Leo R, Link H, Schmidt RE (1992) CD16− CD56+ natural killer cells after bone marrow transplantation. Blood 79:3239–3244
51. Ottinger HD, Beelen DW, Scheulen B, Schaefer UW, Grosse-Wilde H (1996) Improved immune reconstitution after allotransplantation of peripheral blood stem cells instead of bone marrow. Blood 88:2775–2779
52. Vitale C, Pitto A, Benvenuto F, Ponte M, Bellomo R, Frassoni F, Mingari MC, Bacigalupo A, Moretta L (2000) Phenotypic and functional analysis of the HLA-class I-specific inhibitory receptors of natural killer cells isolated from peripheral blood of patients undergoing bone marrow transplantation from matched unrelated donors. Hematol J 1:136–144 doi:10.1038/sj.thj.6200018
53. Biron CA, Byron KS, Sullivan JL (1989) Severe herpesvirus infections in an adolescent without natural killer cells. N Engl J Med 320:1731–1735
54. Kuijpers TW, Baars PA, Dantin C, van den Burg M, van Lier RA, Roosnek E (2008) Human NK cells can control CMV infection in the absence of T cells. Blood 112:914–915 doi:10.1182/blood-2008-05-157354
55. Kook H, Goldman F, Padley D, Giller R, Rumelhart S, Holida M, Lee N, Peters C, Comito M, Huling D, Trigg M (1996) Reconstruction of the immune system after unrelated or partially matched T-cell-depleted bone marrow transplantation in children: immunophenotypic analysis and factors affecting the speed of recovery. Blood 88:1089–1097
56. Shilling HG, McQueen KL, Cheng NW, Shizuru JA, Negrin RS, Parham P (2003) Reconstitution of NK cell receptor repertoire following HLA-matched hematopoietic cell transplantation. Blood 101:3730–3740 doi:10.1182/blood-2002-08-2568
57. Vitale C, Chiossone L, Morreale G, Lanino E, Cottalasso F, Moretti S, Dini G, Moretta L, Mingari MC (2004) Analysis of the activating receptors and cytolytic function of human natural killer cells undergoing in vivo differentiation after allogeneic bone marrow transplantation. Eur J Immunol 34:455–460 doi:10.1002/eji.200324668
58. Boyiadzis M, Memon S, Carson J, Allen K, Szczepanski MJ, Vance BA, Dean R, Bishop MR, Gress RE, Hakim FT (2008) Up-regulation of NK cell activating receptors following allogeneic hematopoietic stem cell transplantation under a lymphodepleting reduced intensity regimen is associated with elevated IL-15 levels. Biol Blood Marrow Transplant 14:290–300 doi:10.1016/j.bbmt.2007.12.490
59. Dulphy N, Haas P, Busson M, Belhadj S, Peffault de Latour R, Robin M, Carmagnat M, Loiseau P, Tamouza R, Scieux C, Rabian C, Di Santo JP, Charron D, Janin A, Socie G, Toubert A (2008) An unusual CD56(bright) CD16(low) NK cell subset dominates the early posttransplant period following HLA-matched hematopoietic stem cell transplantation. J Immunol 181:2227–2237
60. Loza MJ, Perussia B (2004) The IL-12 signature: NK cell terminal CD56 + high stage and effector functions. J Immunol 172:88–96
61. Ferlazzo G, Thomas D, Lin SL, Goodman K, Morandi B, Muller WA, Moretta A, Munz C (2004) The abundant NK cells in human secondary lymphoid tissues require activation to express killer cell Ig-like receptors and become cytolytic. J Immunol 172:1455–1462
62. Ruggeri L, Capanni M, Casucci M, Volpi I, Tosti A, Perruccio K, Urbani E, Negrin RS, Martelli MF, Velardi A (1999) Role of natural killer cell alloreactivity in HLA-mismatched hematopoietic stem cell transplantation. Blood 94:333–339

63. Ruggeri L, Capanni M, Urbani E, Perruccio K, Shlomchik WD, Tosti A, Posati S, Rogaia D, Frassoni F, Aversa F, Martelli MF, Velardi A (2002) Effectiveness of donor natural killer cell alloreactivity in mismatched hematopoietic transplants. Science 295:2097–2100 doi:10.1126/science.1068440
64. Leung W, Iyengar R, Turner V, Lang P, Bader P, Conn P, Niethammer D, Handgretinger R (2004) Determinants of anti-leukemia effects of allogeneic NK cells. J Immunol 172:644–650
65. Ruggeri L, Mancusi A, Capanni M, Urbani E, Carotti A, Aloisi T, Stern M, Pende D, Perruccio K, Burchielli E, Topini F, Bianchi E, Aversa F, Martelli MF, Velardi A (2007) Donor natural killer cell allorecognition of missing self in haploidentical hematopoietic transplantation for acute myeloid leukemia: challenging its predictive value. Blood 110:433–440 doi:10.1182/blood-2006-07-038687
66. Passweg JR, Huard B, Tiercy JM, Roosnek E (2007) HLA and KIR polymorphisms affect NK-cell anti-tumor activity. Trends Immunol 28:437–441 doi:10.1016/j.it.2007.07.008
67. Gratama JW, Naipal A, Oljans P, Zwaan FE, Verdonck LF, De Witte T, Vossen JM, Bolhuis RL, de Gast GC, Jansen J (1984) T lymphocyte repopulation and differentiation after bone marrow transplantation. Early shifts in the ratio between T4+ and T8+ T lymphocytes correlate with the occurrence of acute graft-versus-host disease. Blood 63:1416–1423
68. Ault KA, Antin JH, Ginsburg D, Orkin SH, Rappeport JM, Keohan ML, Martin P, Smith BR (1985) Phenotype of recovering lymphoid cell populations after marrow transplantation. J Exp Med 161:1483–1502 doi:10.1084/jem.161.6.1483
69. Soiffer RJ, Bosserman L, Murray C, Cochran K, Daley J, Ritz J (1990) Reconstitution of T-cell function after CD6-depleted allogeneic bone marrow transplantation. Blood 75:2076–2084
70. Holl RA, Dooren LJ, Vossen JM, Roos MT, Schellekens PT (1981) Bone marrow transplantation in children with severe aplastic anemia: reconstitution of cellular immunity. Transplantation 32:418–423 doi:10.1097/00007890-198111000-00016
71. Roosnek E, Brouwer MC, Vossen JM, Roos MT, Schellekens PT, Zeijlemaker WP, Aarden LA (1987) The role of interleukin-2 in proliferative responses in vitro of T cells from patients after bone marrow transplantation. Evidence that minor defects can lead to in vitro unresponsiveness. Transplantation 43:855–860
72. Roux E, Dumont-Girard F, Starobinski M, Siegrist C-A, Helg C, Chapuis B, Roosnek E (2000) Recovery of immune reactivity after T cell depleted bone marrow transplantation depends on thymic activity. Blood 96:2299–2303
73. Mackall CL, Fleisher TA, Brown MR, Magrath IT, Shad AT, Horowitz ME, Wexler LH, Adde MA, McClure LL, Gress RE (1994) Lymphocyte depletion during treatment with intensive chemotherapy for cancer. Blood 84:2221–2228
74. Mackall CL, Granger L, Sheard MA, Cepeda R, Gress RE (1993) T-cell regeneration after bone marrow transplantation: Differential CD45 isoform expression on thymic-derived versus thymic-independent progeny. Blood 82:2585–2594
75. Weinberg K, Annett G, Kashyap A, Lenarsky C, Forman SJ, Parkman R (1995) The effect on thymic function on immunocompetence following bone marrow transplantation. Biol Blood Marrow Transplant 1:18–23
76. Roux E, Helg C, Dumont-Girard F, Chapuis B, Jeannet M, Roosnek E (1996) Analysis of T cell repopulation after allogeneic bone marrow transplantation: significant differences between recipients of T cell depleted and unmanipulated grafts. Blood 87:3984–3992
77. Mackall CL, Hakim FT, Gress RE (1997) Restoration of T-cell homeostasis after T-cell depletion. Semin Immunol 9:339–346 doi:10.1006/smim.1997.0091
78. Dumont-Girard F, Roux E, Van Lier RA, Hale G, Helg C, Chapuis B, Starobinski M, Roosnek E (1998) Reconstitution of the T cell compartment after bone marrow transplantation: restoration of the repertoire by thymic emigrants. Blood 92:4464–4471
79. Roux E, Abdi K, Speiser D, Helg C, Chapuis B, Jeannet M, Roosnek E (1993) Characterization of mixed chimerism in patients with chronic myeloid leukemia transplanted with T-cell-depleted bone marrow: involvement of different hematologic lineages before and after relapse. Blood 81:243–248
80. Thude H, Hundrieser J, Wonigeit K, Schwinzer R (1995) A point mutation in the human CD45 gene associated with defective splicing of exon A. Eur J Immunol 25:2101–2106 doi:10.1002/eji.1830250745
81. Rufer N, Helg C, Chapuis B, Roosnek E (2001) Human memory T cells: lessons from stem cell transplantation. Trends Immunol 22:136–141 doi:10.1016/S1471-4906(00)01849-4
82. Hakim FT, Memon SA, Cepeda R, Jones EC, Chow CK, Kasten-Sportes C, Odom J, Vance BA, Christensen BL, Mackall CL, Gress RE (2005) Age-dependent incidence, time course, and consequences of thymic renewal in adults. J Clin Invest 115:930–939
83. Jameson SC (2002) Maintaining the norm: T-Cell homeostasis. Nat Rev Immunol 2:547–556
84. Goldrath AW, Bevan MJ (1999) Low-affinity ligands for the TCR drive proliferation of mature CD8+ T cells in lymphopenic hosts. Immunity 11:183–190 doi:10.1016/S1074-7613(00)80093-X
85. Mackall CL, Bare CV, Granger LA, Sharrow SO, Titus JA, Gress RE (1996) Thymic-independent T cell regeneration occurs via antigen-driven expansion of peripheral T cells resulting in a repertoire that is limited in diversity and prone to skewing. J Immunol 156:4609–4616
86. Soiffer RJ, Gonin R, Murray C, Robertson MJ, Cochran K, Chartier S, Cameron C, Daley J, Levine H, Nadler LM, Ritz J (1993) Prediction of graft-versus-host disease by phenotypic analysis of early immune reconstitution after CD6-depleted allogeneic bone marrow transplantation. Blood 82:2216–2223
87. Mutis T, Gillespie G, Schrama E, Falkenburg JH, Moss P, Goulmy E (1999) Tetrameric HLA class I-minor histocompatibility antigen peptide complexes demonstrate minor histocompatibility antigen-specific cytotoxic T lymphocytes in patients with graft-versus-host disease. Nat Med 5:839–842 doi:10.1038/10563
88. Gratama JW, van Esser JW, Lamers CH, Tournay C, Lowenberg B, Bolhuis RL, Cornelissen JJ (2001) Tetramer-based quantification of cytomegalovirus (CMV)-specific CD8(+) T lymphocytes in T-cell-depleted stem cell grafts and after transplantation may identify patients at risk for progressive CMV infection. Blood 98:1358–1364 doi:10.1182/blood.V98.5.1358
89. Cwynarski K, Ainsworth J, Cobbold M, Wagner S, Mahendra P, Apperley J, Goldman J, Craddock C, Moss PA (2001) Direct visualization of cytomegalovirus-specific T-cell reconstitution after allogeneic stem cell transplantation. Blood 97:1232–1240 doi:10.1182/blood.V97.5.1232
90. Falco DA, Nepomuceno RR, Krams SM, Lee PP, Davis MM, Salvatierra O, Alexander SR, Esquivel CO, Cox KL, Frankel LR, Martinez OM (2002) Identification of Epstein–Barr virus-specific CD8+ T lymphocytes in the circulation of pediatric transplant recipients. Transplantation 74:501–510 doi:10.1097/00007890–200208270–00012
91. Chalandon Y, Degermann S, Villard J, Arlettaz L, Kaiser L, Vischer S, Walter S, Heemskerk MH, van Lier RA, Helg C, Chapuis B, Roosnek E (2006) The pre-transplant CMV-specific T-cells protect recipients of T-cell depleted grafts against cytomegalovirus related complications. Blood 187:389–396 doi:10.1182/blood-2005-07-2746
92. Storek J, Zhao Z, Lin E, Berger T, McSweeney PA, Nash RA, Akatsuka Y, Metcalf MD, Lu H, Kalina T, Reindl M, Storb R,

Hansen JA, Sullivan KM, Kraft GH, Furst DE, Maloney DG (2004) Recovery from and consequences of severe iatrogenic lymphopenia (induced to treat autoimmune diseases). Clin Immunol 113:285–298 doi:10.1016/j.clim.2004.07.006
93. Rufer N, Brümmendorf TH, Chapuis B, Helg C, Lansdorp PM, Roosnek E (2001) Accelerated telomere shortening is limited to the first year following stem cell transplantation. Blood 97:575–577 doi:10.1182/blood.V97.2.575
94. Roelofs H, De Pauw ES, Zwinderman AH, Opdam SM, Willemze R, Tanke HJ, Fibbe WE (2002) Homeostasis of telomere length rather than telomere shortening after allogeneic peripheral blood stem cell transplantation. Blood 101:358–362 doi:10.1182/blood-2002-06-1832
95. Thomson BG, Robertson KA, Gowan D, Heilman D, Broxmeyer HE, Emanuel D, Kotylo P, Brahmi Z, Smith FO (2000) Analysis of engraftment, graft-versus-host disease, and immune recovery following unrelated donor cord blood transplantation. Blood 96:2703–2711
96. Verdonck LF, de Gast GC (1984) Is cytomegalovirus infection a major cause of T cell alterations after (autologous) bone-marrow transplantation? Lancet 1:932–935 doi:10.1016/S0140-6736(84)92391-2
97. Janossy G, Prentice HG, Grob JP, Ivory K, Tidman N, Grundy J, Favrot M, Brenner MK, Campana D, Blacklock HA et al (1986) T lymphocyte regeneration after transplantation of T cell depleted allogeneic bone marrow. Clin Exp Immunol 63:577–586
98. Eyrich M, Croner T, Leiler C, Lang P, Bader P, Klingebiel T, Niethammer D, Schlegel PG (2002) Distinct contributions of CD4(+) and CD8(+) naive and memory T-cell subsets to overall T-cell-receptor repertoire complexity following transplantation of T-cell-depleted CD34-selected hematopoietic progenitor cells from unrelated donors. Blood 100:1915–1918 doi:10.1182/blood-2001-11-0005
99. Weinberg K, Blazar BR, Wagner JE, Agura E, Hill BJ, Smogorzewska M, Koup RA, Betts MR, Collins RH, Douek DC (2001) Factors affecting thymic function after allogeneic hematopoietic stem cell transplantation. Blood 97:1458–1466 doi:10.1182/blood.V97.5.1458
100. Singhal S, Mehta J (1999) Reimmunization after blood or marrow stem cell transplantation. Bone Marrow Transplant 23:637–646 doi:10.1038/sj.bmt.1701640
101. Avigan D, Pirofski LA, Lazarus HM (2001) Vaccination against infectious disease following hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 7:171–183 doi:10.1053/bbmt.2001.v7.pm11302551
102. Ljungman P, Engelhard D, de la Camara R, Einsele H, Locasciulli A, Martino R, Ribaud P, Ward K, Cordonnier C (2005) Vaccination of stem cell transplant recipients: recommendations of the infectious diseases working party of the EBMT. Bone Marrow Transplant 35:737–746 doi:10.1038/sj.bmt.1704870
103. Montagna D, Locatelli F, Moretta A, Lisini D, Previdere C, Grignani P, DeStefano P, Giorgiani G, Montini E, Pagani S, Comoli P, Maccario R (2004) T lymphocytes of recipient origin may contribute to the recovery of specific immune response towards viruses and fungi in children given cord blood transplantation. Blood 103:4322–4329 doi:10.1182/blood-2003-11-4041
104. Wimperis JZ, Brenner MK, Prentice HG, Reittie JE, Karayiannis P, Griffiths PD, Hoffbrand AV (1986) Transfer of a functioning humoral immune system in transplantation of T-lymphocyte-depleted bone marrow. Lancet 1:339–343 doi:10.1016/S0140-6736(86)92315-9
105. Saxon A, Mitsuyasu R, Stevens R, Champlin RE, Kimata H, Gale RP (1986) Designed transfer of specific immune responses with bone marrow transplantation. J Clin Invest 78:959–967 doi:10.1172/JCI112686
106. de Gast GC, Gratama JW, Verdonck LF, van Heugten JG, Zwaan FE, Phillips DI, Mudde GC (1989) The influence of T cell depletion on recovery of T cell proliferation to herpesviruses and Candida after allogeneic bone marrow transplantation. Transplantation 48:111–115 doi:10.1097/00007890-198907000-00026
107. Wimperis JZ, Gottlieb D, Duncombe AS, Heslop HE, Prentice HG, Brenner MK (1990) Requirements for the adoptive transfer of antibody responses to a priming antigen in man. J Immunol 144:541–547
108. Labadie J, van Tol MJ, Dijkstra NH, Zwaan FE, Vossen JM (1992) Transfer of specific immunity from donor to recipient of an allogeneic bone marrow graft: effect of conditioning on the specific immune response of the graft recipient. Br J Haematol 80:381–390 doi:10.1111/j.1365-2141.1992.tb08149.x
109. Molrine DC, Guinan EC, Antin JH, Parsons SK, Weinstein HJ, Wheeler C, McGarigle C, Blanding P, Phillips NR, Kinsella K, Deans K, Ciamarra A, Goorin A, George S, Ambrosino DM (1996) Donor immunization with Haemophilus influenzae type b (HIB)-conjugate vaccine in allogeneic bone marrow transplantation. Blood 87:3012–3018
110. Gerritsen EJA, Van Tol MJD, Lankester AC, Van der Weijden-Ragas CPM, Jol-van der Zijde CM, Oudeman-Gruber NJ, Radl J, Vossen JM (1993) Immunoglobulin levels and monoclonal gammopathies in children after bone marrow transplantation. Blood 82:3493–3502
111. Parkman R, Weinberg KI (1997) Immunological reconstitution following bone marrow transplantation. Immunol Rev 157:73–78 doi:10.1111/j.1600-065X.1997.tb00975.x
112. Ljungman P, Wiklund-Hammarsten M, Duraj V, Hammarstrom L, Lonnqvist B, Paulin T, Ringden O, Pepe MS, Gahrton G (1990) Response to tetanus toxoid immunization after allogeneic bone marrow transplantation. J Infect Dis 162:496–500
113. Chakrabarti S, Milligan DW, Pillay D, Mackinnon S, Holder K, Kaur N, McDonald D, Fegan CD, Waldmann H, Hale G, Rickinson A, Steven N (2003) Reconstitution of the Epstein–Barr virus-specific cytotoxic T-lymphocyte response following T-cell-depleted myeloablative and nonmyeloablative allogeneic stem cell transplantation. Blood 102:839–842 doi:10.1182/blood.V102.3.839
114. Storek J, Dawson MA, Lim LC, Burman BE, Stevens-Ayers T, Viganego F, Herremans MM, Flowers ME, Witherspoon RP, Maloney DG, Boeckh M (2004) Efficacy of donor vaccination before hematopoietic cell transplantation and recipient vaccination both before and early after transplantation. Bone Marrow Transplant 33:337–346 doi:10.1038/sj.bmt.1704336
115. Chen CS, Boeckh M, Seidel K, Clark JG, Kansu E, Madtes DK, Wagner JL, Witherspoon RP, Anasetti C, Appelbaum FR, Bensinger WI, Deeg HJ, Martin PJ, Sanders JE, Storb R, Storek J, Wade J, Siadak M, Flowers ME, Sullivan KM (2003) Incidence, risk factors, and mortality from pneumonia developing late after hematopoietic stem cell transplantation. Bone Marrow Transplant 32:515–522 doi:10.1038/sj.bmt.1704162
116. Grob JP, Grundy JE, Prentice HG, Griffiths PD, Hoffbrand AV, Hughes MD, Tate T, Wimperis JZ, Brenner MK (1987) Immune donors can protect marrow-transplant recipients from severe cytomegalovirus infections. Lancet 1:774–776 doi:10.1016/S0140-6736(87)92800-5
117. Wimperis JZ, Berry NJ, Prentice HG, Lever A, Griffiths PD, Brenner MK (1987) Regeneration of humoral immunity to herpes simplex virus following T-cell-depleted allogeneic bone marrow transplantation. J Med Virol 23:93–99 doi:10.1002/jmv.1890230111
118. Wimperis JZ, Brenner MK, Prentice HG, Thompson EJ, Hoffbrand AV (1987) B cell development and regulation after

T cell-depleted marrow transplantation. J Immunol 138:2445–2450
119. Schmeiser T, Wiesneth M, Bunjes D, Arnold R, Hertenstein B, Heit W, Kurrle E (1989) Infectious complications after allogeneic bone marrow transplantation with and without T-cell depletion of donor marrow. Infection 17:124–130 doi:10.1007/BF01644010
120. Anderson KC, Soiffer R, DeLage R, Takvorian T, Freedman AS, Rabinowe SL, Nadler LM, Dear K, Heflin L, Mauch P et al (1990) T-cell-depleted autologous bone marrow transplantation therapy: analysis of immune deficiency and late complications. Blood 76:235–244
121. Gandhi MK, Wills MR, Okecha G, Day EK, Hicks R, Marcus RE, Sissons JG, Carmichael AJ (2003) Late diversification in the clonal composition of Human Cytomegalovirus-specific CD8+ T-cells following allogeneic haemopoietic stem cell transplantation. Blood 102:3427–3438 doi:10.1182/blood-2002-12-3689
122. Heitger A, Neu N, Kern H, Panzer-Grumayer ER, Greinix H, Nachbaur D, Niederwieser D, Fink FM (1997) Essential role of the thymus to reconstitute naive (CD45RA+) T-helper cells after human allogeneic bone marrow transplantation. Blood 90:850–857
123. Storek J, Joseph A, Dawson MA, Douek DC, Storer B, Maloney DG (2002) Factors influencing T-lymphopoiesis after allogeneic hematopoietic cell transplantation. Transplantation 73:1154–1158 doi:10.1097/00007890-200204150-00026
124. Haynes BF, Markert ML, Sempowski GD, Patel DD, Hale LP (2000) The role of the thymus in immune reconstitution in aging, bone marrow transplantation, and HIV-1 infection. Annu Rev Immunol 18:529–560
125. Storek J, Witherspoon RP, Webb D, Storb R (1996) Lack of B cell precursors in marrow transplant recipients with chronic GVHD. Am J Hematol 52:82–89 doi:10.1002/(SICI)1096-8652(199606)52:2<82::AID-AJH3>3.0.CO;2-1
126. Storek J, Wells D, Dawson MA, Storer B, Maloney DG (2001) Factors influencing B lymphopoiesis after allogeneic hematopoietic cell transplantation. Blood 98:489–491 doi:10.1182/blood.V98.2.489
127. Sullivan KM, Storek J, Kopecky KJ, Jocom JJ, Longton G, Flowers M, Siadak M, Nims J, Witherspoon RP, Anasetti C, Bowden R, Applebaum FR, Buckner CD, Deeg HJ, Hansen JA, McDonald GB, Sanders JE, Storb R (1996) A controlled trial of long-term administration of intravenous immunoglobulin to prevent late infection and chronic GVHD following marrow transplantation: clinical outcome and effect on subsequent immune recovery. Biol Blood Marrow Transplant 2:44–53
128. Ljungman P, Lewensohn-Fuchs I, Hammarström V, Aschan J, Brandt L, Bolme P, Lonnqvist B, Johansson N, Ringden O, Gahrton G (1994) Long-term immunity to measles, mumps, and rubella after allogeneic bone marrow transplantation. Blood 84:657–663
129. Engelhard D, Weinberg M, Or R, Shaked O, Naparstek E, Haikin H, Slavin S, Sarov I (1991) Immunoglobulins A, G, and M to cytomegalovirus during recurrent infection in recipients of allogeneic bone marrow transplantation. J Infect Dis 163:628–630
130. Lutz E, Ward KN, Szydlo R, Goldman JM (1996) Cytomegalovirus antibody avidity in allogeneic bone marrow recipients: evidence for primary or secondary humoral responses depending on donor immune status. J Med Virol 49:61–65 doi:10.1002/(SICI)1096-9071(199605)49:1<61::AID-JMV10>3.0.CO;2-5
131. Lortan JE, Vellodi A, Jurges ES, Hugh-Jones K (1992) Class- and subclass-specific pneumococcal antibody levels and response to immunization after bone marrow transplantation. Clin Exp Immunol 88:512–519
132. Storek J, Joseph A, Espino G, Dawson MA, Douek DC, Sullivan KM, Flowers ME, Martin P, Mathioudakis G, Nash RA, Storb R, Appelbaum FR, Maloney DG (2001) Immunity of patients surviving 20 to 30 years after allogeneic or syngeneic bone marrow transplantation. Blood 98:3505–3512 doi:10.1182/blood.V98.13.3505
133. Storek J, Witherspoon RP (2004) Immunological reconstitution after hemopoietic stem cell transplantation. In: Atkinson K, Champlin R, Ritz J, Fibbe WE, Ljungman P, Brenner MK (eds) Clinical bone marrow and blood stem cell transplantation. Cambridge University Press, Cambridge, pp 194–226
134. Guinan EC, Molrine DC, Antin JH, Lee MC, Weinstein HJ, Sallan SE, Parsons SK, Wheeler C, Gross W, McGarigle C, Blanding P, Schiffman G, Finberg RW, Siber GR, Bolon D, Wang M, Cariati S, Ambrosino DM (1994) Polysaccharide conjugate vaccine responses in bone marrow transplant patients. Transplantation 57:677–684 doi:10.1097/00007890-199403150-00009
135. Miller JJ, Cole LJ (1967) The radiation resistance of long-lived lymphocytes and plasma cells in mouse and rat lymph nodes. J Immunol 98:982–990
136. Slifka MK, Antia R, Whitmire JK, Ahmed R (1998) Humoral immunity due to long-lived plasma cells. Immunity 8:363–372 doi:10.1016/S1074-7613(00)80541-5
137. Asma GEM, Langois R, VanDenBergh RL, Vossen JM (1987) Regeneration of TdT+, pre-B and B cells in bone marrow after allogeneic bone marrow transplantation. Transplantation 43:865–870
138. Uckun FM, Haissig S, Ledbetter JA, Fidler P, Myers DE, Kuebelbeck V, Weisdorf D, Gajl-Peczalska K, Kersey JH, Ramsay KC (1992) Developmental hierarchy during early human B cell ontogeny after autologous bone marrow transplantation using autografts depleted of CD19 + B cell precursors by an anti-CD19 pan-B-cell immunotoxin containing pokeweed antiviral protein. Blood 79:3369–3379
139. Leitenberg D, Rappeport JM, Smith BR (1994) B cell precursor bone marrow reconstitution after bone marrow transplantation. Am J Clin Pathol 102:231–236
140. Baumgartner C, Morell A, Hirt A, Bucher U, Forster HK, Doran JE, Matter L, DelRe GB, Wagner HP (1988) Humoral immune function in pediatric patients treated with autologous bone marrow transplantation for B cell non-Hodgkin's lymphoma: The influence of ex vivo marrow decontamination with anti-Y29/55 monoclonal antibody and complement. Blood 71:1211–1217
141. Bengtsson M, Smedmyr B, Festin R, Oberg G, Simonsson B, Totterman TH (1989) B lymphocyte regeneration in marrow and blood after autologous bone marrow transplantation: increased numbers of B cells carrying activation and progression markers. Leuk Res 13:791–797 doi:10.1016/0145-2126(89)90092-1
142. Pedrazzini A, Freedman AS, Andersen J, Heflin L, Anderson K, Takvorian T, Canellos GP, Whitman J, Coral F, Ritz J, Nadler LM (1989) Anti-B cell monoclonal antibody-purged autologous BMT for B cell non-Hodgkin's lymphoma: Phenotypic reconstitution and B cell function. Blood 74:2203–2211
143. Cutler C, Giri S, Jeyapalan S, Paniagua D, Viswanathan A, Antin JH (2001) Acute and chronic graft-versus-host disease after allogeneic peripheral-blood stem-cell and bone marrow transplantation: a meta-analysis. J Clin Oncol 19:3685–3691
144. Walter EA, Greenberg PD, Gilbert MJ, Finch RJ, Watanabe KS, Thomas ED, Riddell SR (1995) Reconstitution of cellular immunity against cytomegalovirus in recipients of allogeneic bone marrow by transfer of T-cell clones from the donor. N Engl J Med 333:1038–1044 doi:10.1056/NEJM199510193331603
145. O'Reilly RJ, Lacerda JF, Lucas KG, Rosenfield NS, Small TN, Papadopoulos EB (1996) Adoptive cell therapy with donor lymphocytes for EBV-associated lymphomas developing after allogeneic marrow transplants. Important Adv Oncol 149–166
146. Rooney CM, Smith CA, Ng CY, Loftin SK, Sixbey JW, Gan Y, Srivastava DK, Bowman LC, Krance RA, Brenner MK, Heslop HE (1998) Infusion of cytotoxic T cells for the prevention and

treatment of Epstein–Barr virus-induced lymphoma in allogeneic transplant recipients. Blood 92:1549–1555
147. Einsele H, Roosnek E, Rufer N, Sinzger C, Riegler S, Loffler J, Grigoleit U, Moris A, Rammensee HG, Kanz L, Kleihauer A, Frank F, Jahn G, Hebart H (2002) Infusion of cytomegalovirus (CMV)-specific T cells for the treatment of CMV infection not responding to antiviral chemotherapy. Blood 99:3916–3922 doi:10.1182/blood.V99.11.3916
148. Peggs KS, Verfuerth S, Pizzey A, Khan N, Guiver M, Moss PA, Mackinnon S (2003) Adoptive cellular therapy for early cytomegalovirus infection after allogeneic stem-cell transplantation with virus-specific T-cell lines. Lancet 362:1375–1377 doi:10.1016/S0140-6736(03)14634-X
149. Cobbold M, Khan N, Pourgheysari B, Tauro S, McDonald D, Osman H, Assenmacher M, Billingham L, Steward C, Crawley C, Olavarria E, Goldman J, Chakraverty R, Mahendra P, Craddock C, Moss PA (2005) Adoptive transfer of cytomegalovirus-specific CTL to stem cell transplant patients after selection by HLA-peptide tetramers. J Exp Med 202:379–386 doi:10.1084/jem.20040613
150. Feuchtinger T, Matthes-Martin S, Richard C, Lion T, Fuhrer M, Hamprecht K, Handgretinger R, Peters C, Schuster FR, Beck R, Schumm M, Lotfi R, Jahn G, Lang P (2006) Safe adoptive transfer of virus-specific T-cell immunity for the treatment of systemic adenovirus infection after allogeneic stem cell transplantation. Br J Haematol 134:64–76 doi:10.1111/j.1365-2141.2006.06108.x
151. Leen AM, Myers GD, Sili U, Huls MH, Weiss H, Leung KS, Carrum G, Krance RA, Chang CC, Molldrem JJ, Gee AP, Brenner MK, Heslop HE, Rooney CM, Bollard CM (2006) Monoculture-derived T lymphocytes specific for multiple viruses expand and produce clinically relevant effects in immunocompromised individuals. Nat Med 12:1160–1166 doi:10.1038/nm1475
152. Andre-Schmutz I, Le Deist F, Hacein-Bey-Abina S, Vitetta E, Schindler J, Chedeville G, Vilmer E, Fischer A, Cavazzana-Calvo M (2002) Immune reconstitution without graft-versus-host disease after haemopoietic stem-cell transplantation: a phase 1/2 study. Lancet 360:130–137 doi:10.1016/S0140-6736(02)09413-8
153. Mielke S, Solomon SR, Barrett AJ (2005) Selective depletion strategies in allogeneic stem cell transplantation. Cytotherapy 7:109–115 doi:10.1080/14653240510018172
154. Amrolia PJ, Muccioli-Casadei G, Huls H, Adams S, Durett A, Gee A, Yvon E, Weiss H, Cobbold M, Gaspar HB, Rooney C, Kuehnle I, Ghetie V, Schindler J, Krance R, Heslop HE, Veys P, Vitetta E, Brenner MK (2006) Adoptive immunotherapy with allodepleted donor T-cells improves immune reconstitution after haploidentical stem cell transplant. Blood 108:1797–1808 doi:10.1182/blood-2006-02-001909
155. Kalina T, Lu H, Zhao Z, Blewett E, Dittmer DP, Randolph-Habecker J, Maloney DG, Andrews RG, Kiem HP, Storek J (2005) De novo generation of CD4 T cells against viruses present in the host during immune reconstitution. Blood 105:2410–2414 doi:10.1182/blood-2004-01-0348
156. Sportes C, Hakim FT, Memon SA, Zhang H, Chua KS, Brown MR, Fleisher TA, Krumlauf MC, Babb RR, Chow CK, Fry TJ, Engels J, Buffet R, Morre M, Amato RJ, Venzon DJ, Korngold R, Pecora A, Gress RE, Mackall CL (2008) Administration of rhIL-7 in humans increases in vivo TCR repertoire diversity by preferential expansion of naive T cell subsets. J Exp Med 205:1701–1714 doi:10.1084/jem.20071681
157. Bolotin E, Smogorzewska M, Smith S, Widmer M, Weinberg K (1996) Enhancement of thymopoiesis after bone marrow transplant by in vivo interleukin-7. Blood 88:1887–1894
158. Alpdogan O, Schmaltz C, Muriglan SJ, Kappel BJ, Perales MA, Rotolo JA, Halm JA, Rich BE, van Den Brink MR (2001) Administration of interleukin-7 after allogeneic bone marrow transplantation improves immune reconstitution without aggravating graft-versus-host disease. Blood 98:2256–2265 doi:10.1182/blood.V98.7.2256
159. Mackall CL, Fry TJ, Bare C, Morgan P, Galbraith A, Gress RE (2001) IL-7 increases both thymic-dependent and thymic-independent T-cell regeneration after bone marrow transplantation. Blood 97:1491–1497 doi:10.1182/blood.V97.5.1491
160. Okamoto Y, Douek DC, McFarland RD, Koup RA (2002) Effects of exogenous interleukin-7 on human thymus function. Blood 99:2851–2858 doi:10.1182/blood.V99.8.2851
161. Chen BJ, Cui X, Sempowski GD, Chao NJ (2003) Growth hormone accelerates immune recovery following allogeneic T-cell-depleted bone marrow transplantation in mice. Exp Hematol 31:953–958 doi:10.1016/S0301-472X(03)00196-6
162. Min D, Taylor PA, Panoskaltsis-Mortari A, Chung B, Danilenko DM, Farrell C, Lacey DL, Blazar BR, Weinberg KI (2002) Protection from thymic epithelial cell injury by keratinocyte growth factor: a new approach to improve thymic and peripheral T-cell reconstitution after bone marrow transplantation. Blood 99:4592–4600 doi:10.1182/blood.V99.12.4592
163. Rossi S, Blazar BR, Farrell CL, Danilenko DM, Lacey DL, Weinberg KI, Krenger W, Hollander GA (2002) Keratinocyte growth factor preserves normal thymopoiesis and thymic microenvironment during experimental graft-versus-host disease. Blood 100:682–691 doi:10.1182/blood.V100.2.682
164. Fry TJ, Moniuszko M, Creekmore S, Donohue SJ, Douek DC, Giardina S, Hecht TT, Hill BJ, Komschlies K, Tomaszewski J, Franchini G, Mackall CL (2003) IL-7 therapy dramatically alters peripheral T-cell homeostasis in normal and SIV-infected nonhuman primates. Blood 101:2294–2299 doi:10.1182/blood-2002-07-2297
165. Storek J, Gillespy T, Lu H, Joseph A, Dawson MA, Gough M, Morris JC, Hackman RC, Horn PA, Sale GE, Andrews RG, Maloney DG, Kiem H-P (2003) Interleukin-7 improves CD4 T cell reconstitution after autologous CD34 cell transplantation in monkeys. Blood 101:4209–4218 doi:10.1182/blood-2002-08-2671
166. Lu H, Zhao Z, Kalina T, Gillespy T 3rd, Liggitt D, Andrews RG, Maloney DG, Kiem HP, Storek J (2005) Interleukin-7 improves reconstitution of antiviral CD4 T cells. Clin Immunol 114:30–41 doi:10.1016/j.clim.2004.08.008
167. Beq S, Nugeyre MT, Ho Tsong Fang R, Gautier D, Legrand R, Schmitt N, Estaquier J, Barre-Sinoussi F, Hurtrel B, Cheynier R, Israel N (2006) IL-7 induces immunological improvement in SIV-infected rhesus macaques under antiviral therapy. J Immunol 176:914–922
168. Seggewiss R, Lore K, Guenaga FJ, Pittaluga S, Mattapallil J, Chow CK, Koup RA, Camphausen K, Nason MC, Meier-Schellersheim M, Donahue RE, Blazar BR, Dunbar CE, Douek DC (2007) Keratinocyte growth factor augments immune reconstitution after autologous hematopoietic progenitor cell transplantation in rhesus macaques. Blood 110:441–449 doi:10.1182/blood-2006-12-065623