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REVIEW ARTICLE

Prevention of relapse after allogeneic hematopoietic cell transplantation by donor and cell source selection

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Abstract

Allogeneic hematopoietic cell transplantation (HCT) is the most established form of cancer immunotherapy and has been successfully applied for the treatment and cure of otherwise lethal neoplastic blood disorders. Cancer immune surveillance is mediated to a large extent by alloreactive T and natural killer (NK) cells recognizing genetic differences between patient and donor. Profound insights into the biology of these effector cells has been obtained over recent years and used for the development of innovative strategies for intelligent donor selection, aiming for improved graft-versus-leukemia effect without unmanageable graft-versus-host disease. The cellular composition of the stem cell source plays a major role in modulating these effects. This review summarizes the current state-of the-art of donor selection according to HLA, NK alloreactivity and stem cell source.

Introduction

Donor selection is becoming an increasingly relevant issue in allogeneic hematopoietic cell transplantation (HCT), given the dramatic increase in donor options over the last years [1]. Whereas human leukocyte antigen (HLA)-identical siblings were the sole donor source in the very early days, now over 30 million volunteer unrelated donors (VUD) and over 600.000 cord blood units (CBUs) are registered worldwide, and a donor is available for most patients in need. Additionally, over recent years, HCT from HLA-haplotype (haplo) mismatched family donors has become a successful and widely used alternative [1]. Relapse is the principal cause of death after 100 days following allogeneic HCT from HLA-identical sibling, as well as unrelated donors [2, 3], making its reduction a paramount priority. The complex mechanisms underlying graft-versus-leukemia (GvL) for the control of post-transplant relapse may vary considerably according to donor type, as they are modulated by both clinical and genetic factors of donor and host, as well as by the cellular composition of the stem cell graft. This review will summarize selected approaches for donor selection according to HLA, natural killer (NK) cell alloreactivity and stem cell source. These concepts were presented at the 3rd International Workshop on Biology, Prevention, and Treatment of Relapse after Stem Cell Transplantation held in Hamburg/Germany in November 2016 under the auspices of European Society for Blood and Marrow Transplantation (EBMT) and American Society of Blood and Marrow Transplantation (ASBMT). Therefore, the presented approaches are not fully comprehensive, and we refer to further literature for the interested reader.

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Donor selection according to HLA

Principles of HLA matching in HCT

The major histocompatibility complex (MHC) human chromosome 6p is the most polymorphic gene complex in eukaryotes, with 18,181 HLA alleles reported to date to the IMGT/HLA database (Release 3.32.0, 2018-04-16) [4]. Ubiquitously and constitutively expressed HLA class I A, B, C antigens, and cell-type-specific and inducible HLA class II DR, DQ, DP antigens represent the major histocompatibility barrier to allogeneic tissue transplantation [5, 6]. HLA alleles are inherited as haplotypes according to Mendelian rules and co-dominantly expressed, with a maximum of 12 different HLA antigens encoded by the six HLA loci on each chromosome. Except for cases of crossing-over due to genetic recombination, genotypically HLA-matched siblings share 12/12 HLA alleles because they have inherited the same maternal and paternal copy of chromosome 6. On the other hand, siblings have a 50% likelihood of being HLA-haploidentical, that is, to have inherited the same copy of chromosome 6 from one parent but not from the other. Parents are by definition HLA haploidentical to their off-springs and vice versa, and a parental chromosome 6 can also be found in the extended family. This accounts for the availability of at least one HLA haploidentical donor for most patients, with rising numbers of haplo HCT performed worldwide [7, 8]. An HLA-matched donor can also be identified in the international VUD or umbilical cord blood (UCB) registries [9, 10]. Generally, these donors do not share the same ancestral haplotype but are matched by chance for at least the most relevant HLA alleles. The probability of finding a suitably HLA-matched VUD varies according to the ethnic group of the patient between 60 and 90% [11, 12].

Mismatched HLA class I and class II antigens expressed on patient antigen-presenting cells (APC) are recognized by alloreactive donor T cells after HCT. The precursor frequency of alloreactive T cells is generally higher compared with conventional self-HLA-restricted, peptide antigen-specific T cells, ranging from 1 to 10% [13]. This is probably due to the cross-reactive nature of T-cell alloreactivity, whereby recognition of the same allogeneic HLA molecule is mediated by conventional self-HLA-restricted T cells

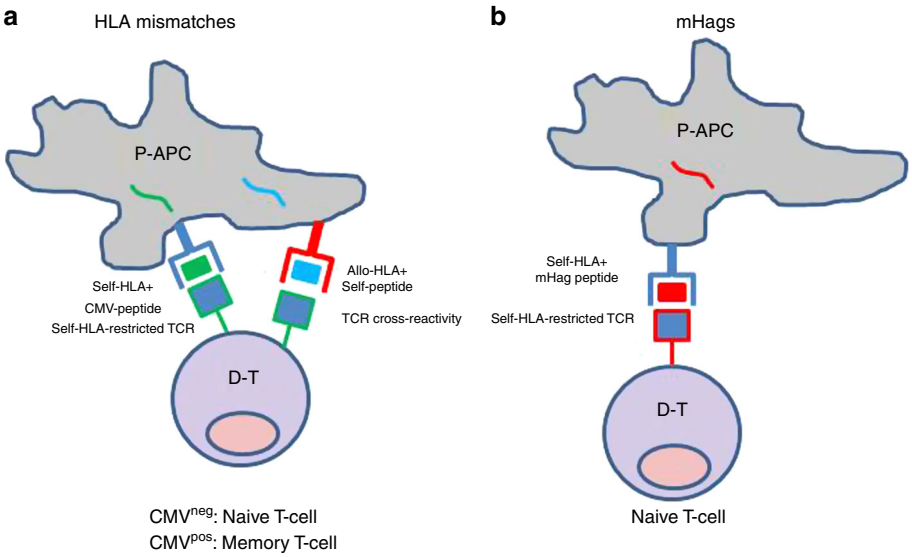

Fig. 1 T-cell alloreactivity to HLA antigens or mHAg-mediating GvL and GvHD after HCT. **a** Cross-reactive T-cell allorecognition of mismatched HLA antigens. Shown is an example in which patient and donor are matched for one HLA antigen of a given locus, and mismatched for the other, leading to the presence of both the self-HLA and the allo-HLA on the same patient antigen-presenting cell (P-APC). In this example, cytomegalovirus (CMV)-peptides (green) or self-peptides (blue) are presented in the peptide antigen-binding groove of the self-HLA (blue) or the allo-HLA molecules (red), respectively. Donor T cells (D-T) expressing a self-HLA-restricted T-cell receptor (TCR) specific for the CMV-peptide (green-lined blue square) recognize the CMV-self-HLA complex on the P-APC, thereby mediating protective anti-viral immunity. The same TCR can also be able to cross-recognize the allo-HLA-presenting self-peptide due to molecular mimicry, thereby mediating alloreactivity. According to the donor's CMV serostatus, the CMV-specific alloreactive T cells will be predominant in the naive or in the memory compartment. CMV is shown here as an example, self-HLA-restricted T cells specific for any foreign antigen can in principle display cross-reactive alloreactivity to mismatched HLA-presenting self-peptides. **b** Self-HLA-restricted T-cell allorecognition of mHag peptides. P-APC contain mHAg peptides (red), which are presented in the peptide antigen binding groove of self-HLA-molecules (blue). HLA-matched D-T expressing a self-HLA-restricted TCR specific for the mHag peptide (red-lined blue square) recognize the mHAg-self-HLA complex on P-APC and mediate alloreactivity. Unless primed by previous events such as pregnancies or blood transfusions, the donor T cells have not encountered the mHAg peptides before and are therefore in the naive repertoire

specific for different peptide antigens (Fig. 1a). These peptide antigens may or may not have been encountered previously, giving rise to alloreactive T cells against mismatched HLA antigens in the naive and memory repertoire, respectively [13–15]. This is in contrast to minor histocompatibility antigens (mHAgs), polymorphic peptides recognized in a conventional, self-HLA-restricted manner by alloreactive T cells, which generally have not previously encountered the same mHAg and are therefore confined to the naive repertoire [16–18] (Fig. 1b). These concepts need to be considered in the design of cellular immunotherapy protocols exploiting alloreactivity of specific T-cell subsets after HCT [19, 20]. Their differential pathophysiology also explains the weaker T-cell alloreactivity to mHAg compared with HLA mismatches [20–22]. Clinically, this translates into lower risks of clinically significant graft-versus-host disease (GvHD) but also to less efficient beneficial GvL effects mediated by donor T cells after gentoypically HLA-matched sibling HCT in which mHAgs are the sole targets of T-cell alloreactivity, compared with VUD, UCB or haploidentical HCT with varying degrees of additional HLA mismatches.

HLA mismatches and relapse according to different donor types

Based on the concepts outlined above, it is tempting to speculate that HLA mismatches might be exploitable to reduce relapse by fostering GvL after HCT. Probably due to the clinically counterbalancing toxic effect of GvHD associated with the same HLA mismatches, this concept is unfortunately not generally applicable (reviewed in Fleischhauer and Beelen [23]). It is well established that the probability of overall survival after VUD HCT decreases significantly with every antigen- or allele-mismatch at HLA-A, -B, -C, -DRB1 (8/8 alleles), although the impact of HLA disparity is lower in patients transplanted in advanced disease stage [24]. The relevance of 8/8 HLA matching has been confirmed in numerous independent studies and is valid also in modern times [25–28]. Nevertheless, a milestone study from the Japanese Registry showed that mismatches at HLA-C (but not at HLA-A, -B, -DRB1) are protective for relapse [29], an observation that might reflect the combined impact of T-cell and NK-cell alloreactivity, the latter being strongly influenced by missing HLA-C ligands as discussed in the following section. Importantly, VUD HCT is performed in over 80% of cases across mismatches at HLA-DPB1, which have been shown both experimentally and clinically to also be efficient GvL targets, with significantly lower relapse risks associated with HLA-DPB1 mismatches compared with matches [30]. It has been proposed that genetically governed differential expression levels of certain HLA-C and DPB1 alleles modulates the risk of GvHD after VUD HSCT, whereby mismatched low expression alleles in the patient confer a lower GvHD risk compared with high expression alleles [31, 32]. Interestingly, these "GvHD permissive" mismatches were not associated with increased relapse risk, in line with the notion that lower levels of T-cell alloreactivity are needed for disease control than for the immune attack of healthy tissues [33, 34]. Limited T-cell alloreactivity has also been proposed to be associated with matching for structural T-cell epitopes (TCE) at HLA-DPB1, which in turn reflect the combined impact of amino-acid polymorphism on T-cell alloreactivity, termed functional distance (FD) [26, 35–38]. Permissive HLA-DPB1 mismatches between alleles of the same TCE group or with similar FD scores were shown to provide a significant benefit for survival due to lower nonrelapse mortality and GvHD in the presence of a preserved GvL effect, compared with non-permissive HLA-DPB1 mismatches across different TCE groups or with distinct FD scores [39]. These proof-of-concept studies show that the identification of permissive mismatches in VUD HCT is feasible, and further insights into the role of presented peptides and/or the alloreactive T-cell repertoire might provide new avenues for their broader identification. This will be useful also in the context of UCB and haplo HCT where permissive mismatches are largely undefined to date [40, 41].

Overall, informed donor selection according to HLA represents a promising new strategy to harness T-cell alloreactivity after HCT, and is likely to become an instrumental tool complementary to cellular and pharmacological approaches that are being developed to this end.

Donor selection according to NK-cell alloreactivity

A GVL effect in HCT has long been observed [42], but harnessing its potential has been frustrated by gaps in knowledge about its exact mechanism. Recognition of the NK-cell as a major mediator of leukemic control has introduced a new optimism that donor selection based on NK biology can be an effective intervention in capturing GVL alloreactivity, minimizing relapse, and increasing survival in allogeneic HCT for the treatment of Acute Myeloid Leukemia (AML).

NK biology

First identified in 1975 [43], the NK-cell discriminates self from non-self, targeting cells that specifically lack self-MHC determinants ("missing self") [44]. The basis of such discrimination resides in the NK receptors that recognize MHC class I molecules, the Ly49 receptors in mice and the

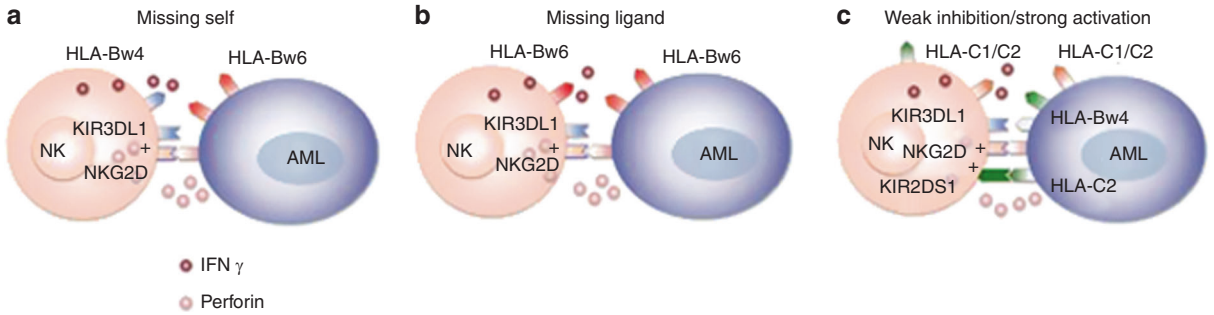

Fig. 2 NK-cell alloreactivity mediating GvL after HCT. **a** NK-cell alloreactivity based on missing self-HLA. In HLA-mismatched HCT, educated donor NK cells stimulated by activating ligands, such as NKG2D ligand, are not inhibited from killing the target leukemia cell due to the lack of self-HLA ligand on the target cell. **b** NK-cell alloreactivity based on missing ligand. In HLA-matched HCT, uneducated NK cells bearing KIR for which the patient lacks cognate HLA ligand can become activated under inflammatory conditions and can recognize and kill leukemic targets. **c** NK-cell alloreactivity due to minimized inhibition and maximized activation. In HLA-matched HCT, educated donor NK cells may experience less inhibition if the KIR-HLA interaction is characterized by low avidity. Heightened NK activity may occur if the donor NK-cell expresses activating KIR

killer Ig-like receptors (KIRs) in humans. The KIR genes demonstrate considerable inter-individual germline-encoded diversity, based on gene content [45, 46], copy number [47] and polymorphism [48]. Present in activating (KIR2DS1-4, KIR3DS1) and inhibitory (KIR2DL1-3, KIR3DL1-2) isoforms, KIR receptors interact with HLA class I ligands to "educate" the NK-cell and establish its degree of responsiveness. The inhibitory KIR2DL2/3, KIR2DL1 and KIR3DL1 interact with HLA-C1 (Ser77Asn80), HLA-C2 (Asn77Lys80) and HLA bearing the Bw4 epitope, respectively.

Although interaction between inhibitory KIR and its HLA class I ligand on the target cell leads to NK-cell inhibition, the same interaction in *cis* and *trans* titrates the response capacity of the NK-cell [49–52]. NK cells bearing an inhibitory KIR and cognate HLA ligand are "educated" for high response capacity. In contrast, NK cells bearing an inhibitory KIR for which the individual lacks the HLA class I ligand are "uneducated" and display lower effector capacity. This results in educated NK cells that are inhibited by self-HLA-bearing autologous cells but are highly effective at recognizing foreign or diseased cells that lack or have downregulated HLA. As a form of immune tolerance, uneducated NK cells are hyporesponsive to autologous cells lacking the cognate ligand. Under inflammatory conditions, however, uneducated cells can be activated for effector function [53, 54].

Activating KIR recognize HLA ligands as well. KIR3DS1 recognizes the open conformer of HLA-F [55], and HLA-C2 is the ligand for KIR2DS1, except in the setting of HLA-C2 homozygosity, where the NK response is suppressed [56, 57]. Activating KIR are predominantly found in KIR-B haplotypes, differing from the canonical KIR haplotype-A, which predominantly exhibits inhibitory KIR [46, 58].

Because expression of KIR receptors occurs largely stochastically, the behavior of the NK-cell at the single cell and population level is predictable based on genetics alone. This has facilitated several studies in allogeneic HCT to test how NK genetics impacts HCT outcomes, outlining interventions that may finally capture the elusive GVL effect.

Missing self in HLA-mismatched HCT

Examination of educated NK activation according to "missing self" in HCT requires HLA mismatching across KIR ligands (Fig. 2a). Initial studies in haploidentical HCT demonstrated that "missing self" in a graft-versus-host vector is associated with lower relapse in AML, but not in acute lymphatic leukemia (ALL) patients [59, 60]. This was followed by several studies in HLA-mismatched HCT [61–63], yielding inconsistent results. Nevertheless, the initial observation that "missing self" was associated with NK activation and decreased AML relapse was the first confirmation that educated NK cells play an important role in disease control in HCT.

NK-cell alloreactivity in HLA-matched HCT

Educated NK-cell activation by "missing self" requires HLA mismatching, typically avoided in HCT due to the risk of GvHD. However, the prospect of NK-mediated relapse protection in HLA-matched HCT emerged when several retrospective studies observed decreased relapse and higher survival among patients who simply lack HLA ligands for donor inhibitory KIR. Among patients "missing ligand" (Fig. 2b), the greatest protection was among Bw6/Bw6 individuals [64]. The highest relapse risk occurred for patients with all KIR ligands [64–66]. Mediating the missing ligand protection is the uneducated NK-cell, whose hyporesponsiveness can be augmented in the setting of post-HCT inflammation [67].

Activating KIR: an argument for KIR-based donor selection

Numerous activating KIR populate the centromeric and telomeric portions of the KIR haplotype, collectively producing a diverse collection of KIR-B haplotypes [45]. Telomeric KIR3DS1, the activating isoform to the inhibitory KIR3DL1, has been associated with lower transplant-related mortality (TRM) [68, 69]. Furthermore, donors with haplotypes rich in centromeric activating KIR have been associated with lower relapse and higher survival [70, 71]. Together, these early studies suggested that selecting donors with activating KIR can protect patients from relapse and TRM, increasing survival.

The HLA-C background of the individual shapes the activity of the KIR2DS1-bearing NK-cell, where homozygosity for the HLA-C2 ligand reduces NK function [56, 57]. Indeed, HLA-C2/C2 is a negative risk factor for AML relapse, neutralizing any KIR2DS1 benefit in HCT [72, 73]. Thus, when selecting donors based on activating KIR, one must also consider the HLA background of the donor.

Donor selection based on KIR alleles

KIR polymorphism provides yet another exploitable possibility for increasing NK alloreactivity. HCT patients lacking Bw4 experience low relapse, presumed due to lack of inhibition of KIR3DL1+ NK cells. Achieving a similar lack of inhibition in patients exhibiting the Bw4 epitope, may be possible as a result of KIR3DL1 polymorphism, encoding allotypes with a range of specificities for ligand [51, 74, 75]. Accordingly, NK cells expressing alleles with poor avidity for Bw4 ligand signal less inhibition, resulting in higher activity against leukemic targets (Fig. 2c). Clinically translated, HLA-matched donor–recipients with low inhibition KIR3DL1-Bw4 allele combinations experience lower relapse and higher survival following HCT [76].

KIR/HLA-based donor selection feasible and realistic

Together, these studies offer the possibility of capturing donor NK-cell alloreactivity and reducing AML relapse following HCT. From PCR-SSP and PCR-SSOP [77, 78] to high-throughput sequencing [79], KIR typing technology is increasingly accessible. At the least, donor KIR typing is prognostic for patients with only one donor option; however, its greatest utility is for patients for whom more than one HLA-equivalent donor is available. The most relevant inhibitory KIR alleles and activating KIR are commonly found, making donor selection to avoid NK inhibition and maximize NK activation a highly attainable goal.

Donor selection according to stem cell source

Cellular composition

The three commonly used cell sources for HCT are bone marrow (BM), Granulocyte-colony stimulating factors (G-CSF)-mobilized peripheral blood stem cells (PBSCs) and UCB. The overall cellularity, as well as the cellular composition of these products differs, particularly with regard to CD34+ cell counts and T cells [80–82], which may be expected to impact transplant outcomes, including relapse.

Relapse after HCT from BM vs PBSC

Holtick et al. [83] performed a meta-analysis, which included 1521 patients, transplanted between 1994 and 2009 in nine randomized control trials. In the cohort overall, there was no significant difference in the incidence of disease relapse, although a trend in favor of reduced relapse with PBSC was reported (hazards ratio [HR]1.3; 95% confidence interval [CI] 0.98–1.72, $P = 0.07$). There was significant heterogeneity between trials with regard to this outcome, where a clear reduction in relapse was found for patients transplanted from related donors (HR 2.73; 95% CI 1.47–5.08, $P = 0.001$), but not for those transplanted from VUD (HR 1.07; 95% CI 0.78–1.47, $P = 0.66$). Only one of these studies [84] included patients receiving reduced intensity conditioning (RIC). To address this, two large retrospective registry-based analyses in the RIC-VUD setting have recently been performed. The Center for International Blood and Marrow Transplant Research (CIBMTR) [85] studied patients transplanted between the years 2000–2008, and found that relapse risk was higher with BM (relative risk [RR] 1.55, 95% CI 1.13–2.12, $P = 0.006$) in the setting of calcineurin inhibitor (CNI) and mycophenolate as GvHD prophylaxis (but not different when a CNI and methotrexate were given). Similar findings were reported by the EBMT [86] in 602 patients with AML in complete remission transplanted between 2000 and 2007. On multivariate analysis, relapse incidence in the PBSC group was significantly reduced (HR 0.61; $P = 0.02$). This group also studied this outcome in a similar population of HLA-identical siblings, where no difference in relapse incidence was found [87].

There is currently little comparative data available to directly address this question in the haplo HCT setting, and none from prospective randomized studies. No difference in relapse was seen in several small retrospective studies [88, 89]. However, a retrospective analysis, which matched haplo-PBSC patients from several phase II studies on age and disease risk index [90] with haplo BM patients who had been transplanted on the Blood and Marrow Transplant

Clinical Trials Network (BMT CTN) 0603 [91] study, found a significantly lower relapse incidence at 1, 2 and 3 years post-transplant in the PBSC patients.

In summary, PBSC is associated with a reduced risk of relapse in related, but not in VUD transplantation using myeloablative conditioning. In contrast, in certain RIC settings, relapse risk is reduced with PBSC in VUD transplantation, but the studies in related donor transplants are conflicting.

Relapse after HCT from UCB vs BM/PBSC

Shi-Xia et al. [92] performed a meta-analysis to address the comparative outcomes for pediatric recipients of BM vs UCB. They identified 1453 patients treated in seven comparative studies (not prospective or randomized). The relapse rate was reported in five studies, which showed a significantly lower rate in UCB recipients compared with BM recipients (OR 0.66, 95% CI 0.51–0.86; $P < 0.001$). Fewer studies have reported this outcome in adult transplant recipients, where a difference in relapse risk does not seem to be found comparing UCB with BM [93, 94] or PBSC [93–96] grafts. A recent retrospective study [97] addressing this question only in adult recipients with myelodysplasia receiving RI regimens found a lower risk of relapse with PBSC grafts from a matched VUD (HR 0.57; 95% CI, 0.37–0.90; $P = 0.02$).

Recently it has been reported that there may be a relapse benefit when using UCB in the setting of minimal residual disease [98]. Milano et al. reported a retrospective analysis of 582 patients treated within a single institution with UCB or BM/PBSC from and VUD. They found an increased adjusted risk of relapse in the VUD (either stem cell source) compared to UCB (HR 1.95; 95% CI, 1.16–3.27; $P = 0.01$). Although relapse was significantly increased in recipients of BM/PBSC where Minimal residual disease (MRD) was present, this was not the case for recipients of UCB, where a nonsignificant increased HR of relapse was seen.

Single vs double UCB

Early retrospective studies suggested a reduced relapse risk in patients who received a double UCB graft compared with those receiving a single UCB unit [99, 100]. This has not, however, been confirmed in more recent retrospective studies [101, 102] or in a randomized study including 220 pediatric patients (BMT CTN 0501) [91]. No prospective study in adult patients has been performed.

In summary, in pediatric recipients UCB is associated with a lower risk of relapse than BM. In adults, relapse risk with UCB vs PBSC is generally found to be similar. Studies regarding the impact on relapse of a single vs a double UCB unit are conflicting.

Conclusions

Relapse remains a major impediment to the clinical success of allo-HCT for the treatment of malignant blood disorders, in particular leukemias [102]. In the era of rapidly emerging targeted therapies for these diseases, improving the safety and efficacy of allo-HCT is more important than ever. Deep insights into the biology of cellular subsets involved in GvL and GvHD, including alloreactive T and NK cells, and cellular components of the different stem cell graft sources, have refined the landscape of clinical donor selection. These include the use of TCE matching strategies for HLA-DPB1, available in the donor search tools of both the US and the German Stem Cell Donor Registries, the increasing application of KIR-based donor selection in both VUD and haploidentical HCT, and—in some cases—the preferential use of PBSC in HCT from related donors or from VUD in the RIC setting. Moreover, these insights have provided the basis for new approaches to cellular therapy for the prevention or treatment of relapse, including the use of allografts depleted from the naive T-cell compartment to dampen alloreactivity against mHags [16, 17] and the adoptive transfer of enriched NK-cell populations to prevent or treat relapse [103]. Both donor selection and cellular therapy approaches will have to be carefully adapted to individualized risk–benefit assessment, and importantly will have to be continuously re-challenged as clinical practice evolves. Although keeping in mind that there will be no "one-fits-all" solution to the prevention of relapse after HCT, continued efforts at increasing our knowledge on the immunogenetics, biology and function of the cellular players involved in this complex process are facilitated by the rapidly advancing technological possibilities and urgently warranted to reach this ambitious goal.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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