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A study of selected hematopoietic stem cell donors provided by an intermediate size registry

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Abstract

Objective: Planning new hematopoietic stem cell (HSC) donor recruitment strategies requires a sound understanding of the factors underlying donor selection, especially considering HLA-matching criteria.

Method: A total of 182 consecutive workups of Swiss donors performed from 2014 to 2017 were analyzed for HLA match level, locus disparities, number of potentially 10/10 matched donors in the international database, donor ranking on the lists, donor date of registration, age, ABO, CMV, gender matching, patient genotype frequency, and country performing the search.

Results: Matching status of the selected donors was 10/10 for 38.5%, 10-12/12 for 35.1%, and 8-9/10 for 26.4% donors, without differences in average donor age in the three categories. HLA-A and -C mismatches were most frequent and -DRB1 very rare. 8.2% patients were matched for HLA-DPB1 (12/12). ABO matching was 46.3%, and CMV matching was 59.1%. Based on "HaploStat"-derived genotype frequencies, 50.3% patients belonged to the "good," 38.5% to the "fair," and 11.2% to the "poor" search prognosis categories. 37.9% of transplants were gender-mismatched, and 42.3% of donors were female.

Conclusion: HLA typing quality (high resolution, all loci typed), great diversity of haplotypes and donor age are main factors impacting the selection of Swiss donors, while gender and ABO matching seem to be of secondary importance.

KEYWORDS
gender matching, HLA haplotype frequencies, HLA matching, national registry, recruitment strategy, stem cell donor

1 | INTRODUCTION

Assessment of the optimal number of donors of the national registry and HLA typing quality are important parameters that must be considered in planning new donor recruitment strategies. The probability to identify a highly compatible (ie a ≥10/10 match) HSC donor is defined by the frequency of the patient's HLA haplotypes. Because most registries include a large majority of donors of European descent, patients of other origins, for example, of African or East Indian descent, have much lower probabilities to find a compatible donor.[1] Even within European populations, HLA and haplotype frequencies vary greatly.[2-4]

Since a majority of donors of European origin are found in three national registries (Germany, UK, and USA), the question may arise about the utility of small or intermediate size European registries. Because low frequency HLA haplotypes often present a more restricted geographic distribution,[2,5] such registries may still provide highly matched donors to a substantial number of national patients

TABLE 1 Distribution of the selected 182 SBSC donors according HLA matching

Matching grade	Nb (ratio; %)
8/10	3 (1.7)
9/10[a]	45 (24.7)
10/10[b]	70 (38.5)
10/12[c]	17 (9.3)
11/12[d]	32 (17.6)
12/12	15 (8.2)

Note: Highly matched (11-12/12) as well as mismatched (8-9/10) donors represent each about 25% of the workups.
[a]Of the 45 mismatched patient/donor pairs, eight were also fully typed for HLA-DPB1.
[b]DPB1 typing of the patients not available.
[c]2 DPB1 mismatches.
[d]1 DPB1 mismatch.

as shown by four registries of small/intermediate size.[6-9] The Swiss registry SBSC (Swiss Blood Stem Cells), part of Swiss Transfusion SRC Ltd, has now more than 130 000 HLA-typed donors. It provides compatible HSC donors for <10% of national patients, essentially due to the high variability of HLA haplotypes in the Swiss population.[10] Despite its intermediate size, SBSC does however contribute internationally a high fraction of its registered donor pool.

In order to better understand the reasons for selecting SBSC donors and thereby establishing sound criteria for future donor recruitment, we reviewed all consecutive donations from Swiss donors (termed *work-ups*) from 2014 to 2017. We investigated the following donor and patient characteristics: patient HLA genotype frequencies, matching status, number of potential donors in Search & Match Service (formerly BMDW, Bone Marrow Donor Worldwide) of the WMDA (World Marrow Donor Association), donor age, ABO, CMV and gender matching.

2 | PATIENTS, DONORS, AND SEARCH REVIEWS

All consecutive workups performed from 2014 to 2017 were analyzed with the exception of three patient/donor combinations due to missing information. For 182 pairs, the following data were recorded: HLA match level, HLA locus disparities, number of potential 10/10 matched donors in the Search & Match Service of the WMDA, ranking of the SBSC donor on the list, date of registration of the selected donor, donor gender and age, ABO and CMV matching, and countries where the searches have been initiated. ABO typing and CMV testing for both patients and donors were available for 123 and 115 cases, respectively. Workup requests by the transplant centers were from the following countries (by decreasing order): Switzerland (27), USA (24), France (23), Germany (19), Italy (16), UK (14), Australia (10), Canada (8), Spain (7), Austria (5), Sweden (4), Turkey (4), Argentina (2), Belgium (2), Finland (2), Lithuania (2), Norway (2), Russian Federation (2), Netherlands (2), Czech Republic (1), Hungary (1), Ireland (1), Poland (1), Romania (1), Serbian Republic (1), and South Africa (1). In 96.7% of the workups, control typing of the donor was performed within 12 months before workup request (mean = 62 days).

Because the searches were performed retrospectively in 2018 (using the Search & Match Service at https://search.wmda.info), the number of potential donors can be slightly overestimated particularly for those patients with rare haplotypes. Searches for patients with rare alleles or very uncommon B-C or DRB1-DQB1 associations led to the identification of mismatched donors (8-9/10 match). However, due to ambiguities in registry typing data (HLA-A,B,DRB1 typing information available at 1st-field level only) or to lack of HLA-C and -DQB1 typing at the start of the search, the total number of potentially matched donors in the Search & Match database did not always reflect a successful search (10/10 match). HLA matching was evaluated on the basis of HLA-A,B,C,DRB1 and DQB1 loci (second-field level typing), without considering DRB3/B4/B5 loci. When DPB1 typing (second-field level) had been performed in 10/10 matched combinations for both patient and donor, such pairs were distributed in the 10-12/12 match category.

Search prognosis categories were obtained as described by Wadworth et al [11] Briefly most likely, genotype frequency (GF) information was derived from the publicly available *haplostats.org* application and the three search productivity categories defined as "good" (>2 10/10 matched donors), "fair" (1-2 10/10 or no 10/10 and >2 9/10 matched donors), and "poor" (no 10/10 and <3 9/10 matched donors). A "good" probability was assigned for GF > 2.2×10^{-7}, a "fair" probability for GF between 2.2×10^{-7} and 5.1×10^{-9}, and a "poor" probability for GF < 5.1×10^{-9}. Three patients were not included in the classification because of the presence of haplotypes that were characteristic of non-European populations.

Time lapse between registration date of each selected donor and transplantation date was recorded, and average time lapses were calculated for each of the three probability categories.

3 | RESULTS

3.1 | HLA match levels of selected donors

Of 182 SBSC donors that were selected for national and international patients over the 4 years under study, 70 (38.5%) had been selected on a 10/10, and 64 (35.2%) on a 10-12/12 match basis, whereas the last group comprised 48 (26.3%) 8-9/10 matched donors (Table 1). HLA-A (15 donors) and -C (13 donors) mismatches were the most frequently encountered disparities, accounting for 58.2% of the single locus mismatches (Table 2), followed by HLA-B and -DQB1 (seven donors each). HLA-DRB1 mismatches were the most rarely accepted disparities with only three patient/donor pairs in this category. Three donors had two incompatibilities (B + C, DRB1 + DQB1, B + DQB1). Among the 64 10-12/12 matched cases, 15 were also fully DPB1 compatible (12/12) and 32 had only one DPB1 mismatch (11/12). Thus, transplants with a 11-12/12 matched donor represented 25.8% of all HSCTs.

TABLE 2 Distribution of HLA mismatches among the 8-9/10 matched pairs (n = 48)

HLA mismatch	Match grade	Nb (ratio; %)
A[a]	9/10	15 (31.1)
B[a]	9/10	7 (14.6)
C[a]	9/10	13 (27.1)
DRB1[b]	9/10	3 (6.3)
DQB1[b]	9/10	7 (14.6)
B + C	8/10	1 (2.1)
B + DQB1	8/10	1 (2.1)
DRB1 + DQB1	8/10	1 (2.1)

Note: HLA-A and -C disparities occurred most frequently among the mismatched transplants.
[a]Single class I mismatches (HLA-A,B,C) represent 77.8% of the single disparities.
[b]Single class II mismatches (HLA-DRB1,DQB1) represent 22.2% of the single disparities.

3.2 | Workup requests by country and HLA-matching categories

Within the 2014-2017 period, 49.5% of the donors provided by the SBSC registry were selected by transplant centers from Switzerland and its four direct neighboring countries. The other European centers received stem cells from 22.5% and North American and Australian centers received stem cells from 23.1% of the 182 donors. The question arose whether search algorithms in different countries were based on different matching preferences (8/8, 10/10 or 12/12). Six countries with >10 workup requests were analyzed. As shown in Table S1, the ratio of transplants with SBSC donors in the 8-9/10 matched category was significantly lower in Switzerland (11.1%) and France (13%), compared with Germany (52.6%), UK (42.8%), and USA (41.7%; $P < .002$ for all comparisons). It is noteworthy that all three 8/10 matched transplants were done in USA, two of these exhibiting a DQB1 mismatch (see Table 2). On the other hand, in the 10-12/12 matched category the ratio of SBSC donors was higher in Switzerland (77.8%) and France (43.5%), compared with Germany (15.8%; $P < .005$ for all comparisons).

3.3 | Matching category, donor age, and recruitment period

Donor age at time of the workup was analyzed in each of the three main HLA-matching categories (Table 3). Average donor age was not different in the three categories: 32.2 years for the 10/10, 31.9 years for the 10-12/12, and 33.4 years for the 8-9/10 matched transplants. Similarly, the number of young donors (≤32 years) was comparable in all three HLA-matching categories ranging from 52.1% to 60.9%. Therefore, the overall rate of donors older than 32 years was 42.3%.

We retrieved donor recruitment times and only found a difference for the category of patient/donor pairs with HLA-DPB1 typing information: A higher ratio of donors recruited in the year preceding the workup was found in the 10-12/12 match category (57.8% vs 45.7% in the 10/10 match category and 41.7% in the 8-9/10 match category, P = ns, data not shown). Of the 182 selected donors, 20 (11%) had been registered for a period of 8-21 years preceding the workup.

TABLE 3 Age of donors at time of workup for the three HLA-matching categories

Matching grade	Nb	Mean donor age (range; y)	Nb donors ≤32 y (ratio; %)
8-9/10	48	33.4 (21-53)	25 (52.1)
10/10	70	32.2 (19-54)	41 (58.6)
10-12/12	64	31.9 (19-51)	39 (60.9)
All	182	32.4 (19-54)	105 (57.7)

3.4 | Estimation of the frequency of patients' haplotypes

In order to better understand the reasons for selecting SBSC donors, we investigated the frequency of patients' haplotypes by using two approaches. First, we retrospectively searched in the Search & Match Service of WMDA the number of potentially 10/10 matched donors for each of the 182 patients. As shown in Table S2, 18 patients (9.9%) had a unique or almost unique haplotype with 0 or only one potential donor in the international registry eventually resulting in the selection of a 8-9/10 mismatched SBSC donor for 15 of these 18 patients. For 29 patients (15.9%), there were 2-10 potentially matched donors in the WMDA list, while 36 patients (19.8%) had 11-30 donors, 33 patients (18.1%) had 31-100 donors and 66 patients (36.2%) a very high number of donors (101-10 000). Thus, for almost half of the patients SBSC donors were selected because they were among the few potentially matched donors (1-30; Table S2). On the other hand, 73.3% (11/15) of the 12/12 matched patient/donor pairs were selected among pools of >100 potentially HLA-A–, HLA-B–, HLA-C–, HLA-DRB1–, and HLA-DQB1–matched donors (range = 107-18 450; data not shown).

Because the ranking order of the donors on the WMDA list, as defined by the extent and quality of HLA typing information, is expected to impact the selection, we evaluated the position of the selected donors of the SBSC registry on the list for each of the 182 searches. Selected donors ranked among the first five donors in 85%, 71%, and 31% of the searches showing, respectively, 2-30, 31-100, and >100 potential donors (data not shown). Looking at the mismatched patient/donor pairs, we observed that in 76.2% of the cases (32 of 42 evaluable donors) the SBSC donor was listed among the first five donors with a mismatch at any of the HLA-A, -B, -C, or -DQB1 loci. Among the 10/10 matched HSCT pairs, 69.7% SBSC donors came out on the list among the first five donors (data not shown).

In a second approach, we determined for each of the 182 patients HLA haplotypes the genotype frequency as computed by the HaploStats web-based program provided by the National Marrow

TABLE 4 Average number of potentially 10/10 matched donors per patient in Search & Match Service (WMDA) and mean duration of registration in the three groups of matching probabilities that were defined on the basis of the *Haplostats*-derived most likely genotype frequencies [11]

Matching Probability	Nb	Mean nb donors/pat	Range	Mean duration registration (y)	Range (y)	Below 3 y (%)
Poor (GF ≤ 5.1×10^{-9})	20	25	0-336	4.66	0-19	10 (56)
Fair (GF < 2.2×10^{-7} and > 5.1×10^{-9})	69	59	0-1132	4.01	0-18	33 (50)
Good (GF ≥ 2.2×10^{-7})	90	1256	7-18 450	2.6	0- 21	55 (81)

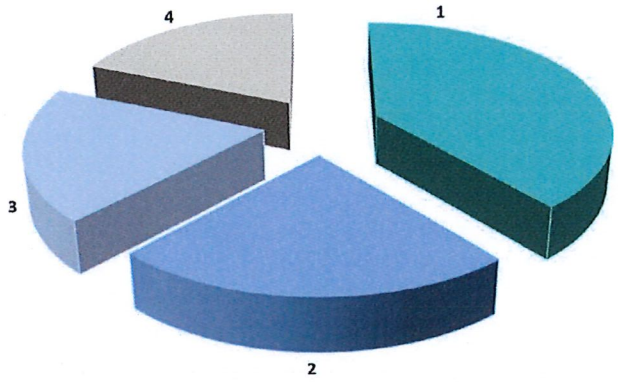

FIGURE 1 Gender-matching status of the 182 transplants performed with SBSC donors. 1: M→M (n = 71); 2: F→F (n = 42); 3: F→M (n = 35); 4: M→F (n = 34). For male patients (1 + 3), male donors were twice as more frequent than female donors. The overall gender mismatching rate is 37.9%

Donor Program (NMDP) Bioinformatics group (www.haplostats.org). As expected the lowest genotype frequencies could be observed in the category of 18 patients with 0-1 potential donor, 6 (33.3%) had a frequency <7×10^{-10} and none reached a frequency above 1.33×10^{-7}. Among the 65 patients with 2-30 donors in the WMDA list, the frequency of the genotypes was lower (7.7%), compared to the group of 99 patients with >30 donors in which only 2% had a GF < 7×10^{-10}.

We then classified the 182 patients who were transplanted with HSC from a SBSC donor using the recently proposed search prognostic scores[11] based on genotype frequencies (GF) as determined by the NMDP publicly available haplostats.org application. Briefly patients of European ancestry (described as "Whites" in the above-mentioned paper) with a GF ≥ 2.2×10^{-7} were classified in the "good" search prognosis category, that is, they had a >50% probability to have >2 10/10 matched donors. Patients with a GF between 2.2×10^{-7} and 5.1×10^{-9} were in the "fair" category and will likely have 1-2 10/10 matched donors. Patients with GF ≤ 5.1×10^{-9} were in the "poor" category and had no 10/10 and <3 potential 9/10 matched donors.

Of the 179 evaluable patients, 90 (50.3%) belonged to the "good" category (Table 4), with a mean number of potential donors in the WMDA list of 1256 (range = 7-18 450). With two exceptions, all patients were transplanted with a 10/10 matched or even a 11-12/12 matched donor. Sixty-nine patients (38.5%) were categorized in the "fair" probability with a mean number of donors of 59 (range = 1-1132). Of these 69 patients, 42 were transplanted with HSC from a 10/10 or a 11-12/12 matched donor. The "poor" category comprised 20 patients (11.2%) with a mean number of donors of 25 (range = 0-336). Patients in that category were transplanted with a 8/10 (n = 3), 9/10 (n = 13), 10/10 (n = 3), and 11/12 (n = 1) matched donor. Mean registration time was shortest in the "good" category, with a 81% rate of donors registered within the last 3 years.

3.5 | Blood group, CMV, and gender matching

For 123 workups with available blood groups for both patients and donors, ABO matching was 46.3% with a similar distribution in the three different HLA-matching categories (data not shown). As determined in 115 workups, the overall rate of CMV matching was higher (59.1%) compared with the ABO matching. There was a non-significant trend toward higher CMV matching in 10-12/12 matched transplants (61.2%), compared with 10/10 (55.6%) and 8-9/10 (59%) matched transplants (data not shown).

As shown in Figure 1, male donors accounted for 57.7% and female donors for 42.3% of the total number of selected donors. Overall gender matching was 62.1% (male: 39% and female: 23.1%). Among the 106 male patients, there were twice as many male donors (n = 71) compared with female donors (n = 35). Ratios of gender-mismatched transplants were comparable for female donors/male patients (F→M: 19.2%) and male donors/female patients (M→F: 18.7%) pairs (Figure 1).

Finally, gender matching was analyzed in the three HLA-matching categories. As shown in Table 5, gender matching was higher in the HLA 10-12/12 matching category compared with the 8-9/10 matching category (68.75% vs 56.25%, *P* = ns). However, F→M transplants accounted for 29.2% of the 8-9/10 matched transplants versus 12.5% of the 10-12/12 matched transplants (*P* = .01). When 12/12 matched transplants were analyzed separately, a high 46.7% rate of gender-mismatched transplants were computed (data not shown).

4 | DISCUSSION

Several studies have demonstrated the direct link between haplotype frequencies in different HSC registries and the probabilities of

TABLE 5 Distribution of gender mismatches in the three HLA-matching categories

Match grade	Nb	Gender match (%)	Gender mismatch (%)	
8-9/10	48	27 (56.25)	21 (43.75)	M→F: 7 (14.6) F→M: 14 (29.2)
10/10	70	42 (60)	28 (40)	M→F: 15 (21.4) F→M: 13 (18.5)
10-12/12	64	44 (68.75)	20 (31.25)	M→F: 12 (18.75) F→M: 8 (12.5)

identifying matched donors[1,7,12-16] which led to the development of various software programs computing the likelihoods to identify donors with suitable matching criteria.[17-20] With the increasing diversity of HLA haplotypes across Europe,[3,4,21] the need for continuing growth of small/intermediate size registries has become more obvious.[22] However, with few exceptions[9,23,24] no detailed analysis has been performed on the selected donors with respect to HLA and non-HLA characteristics.

The analysis of 182 consecutive workups performed by the SBSC registry (2014-2017) showed a wide range of patient/donor-matching status. Although three quarters of selected SBSC donors were 10/10 matched, we found a 26.4% rate of 8-9/10 matched donors, mostly with HLA class I mismatches (Table 1). HLA-DRB1 mismatches were scarce (Table 2), as noted previously.[24] The observation that 25.8% of selected donors were highly matched (11-12/12) strongly suggests that HLA-DPB1 typing information of SBSC donors has been crucial for donor selection, justifying our strategy of DPB1 typing for all newly recruited donors since 2012.

The number of potentially matched donors indicated in the international database may be overestimated particularly when the search is based on HLA-A, -B, and -DRB1 phenotypes only. The 38.5% rate of mismatched transplants observed among the 65 patients with 2-30 potentially matched donors can be explained by the absence of HLA-C/DQB1 typing data in 65% of these searches. When looking at WMDA search lists for patients with <100 potentially 10/10 matched donors or with mismatched donors only, the selected SBSC donor ranked among the first five donors in >70% of the cases. Although this observation should be interpreted cautiously because the analysis was retrospective and WMDA lists at the start of the search are not available, we believe that this could positively impact on the final selection of the donor. However, without access to search algorithms used by individual transplant centers, it is not possible to identify factors explaining why donors who were higher on the lists were not selected.

Overall, a high diversity of HLA phenotypes is observed in patients undergoing an unrelated HSC donor search in Switzerland,[25] linked to the large variability of haplotypes in the Swiss population[10] and also to the diverse origin (mainly European) of the patients. It is therefore expected that a substantial increase in the number of newly recruited donors should only modestly increase the number of SBSC donors for national patients. When using the HaploStats-based algorithm to classify patients in the three categories with "good," "fair," and "poor" probabilities to find a suitable donor,[11,18] we observed that 50.3% of the patients who received HSC from a SBSC donor belonged to the "good" probability group. Selection of Swiss donors mostly for international patients in face of many alternative donor options probably reflects the availability of the full HLA profile (including DPB1) of SBSC donors, combined with non-HLA criteria (age, sex, blood group, and CMV status). Indeed the average mean, registration time was only 2.6 years (Table 4) for these donors. The remaining half of selected SBSC donors belonged to categories with less frequent HLA haplotypes, that is, for searches expected to lead to the identification of 0-2 10/10 matched donors. This accounts for a 26.4% rate of 8-9/10 matched donors (Table 1) in the whole study group.

Almost half of SBSC donors were selected by transplant centers from Switzerland and its four bordering countries, although the distribution of mismatched and highly matched donors differed significantly between the countries. The rate of workups with 8-9/10 mismatched donors was lower in centers from Switzerland and France compared with those of Germany, UK, and USA, whereas the opposite was found for 10-12/12 (ie including DPB1) matched workups. These observations may result from different preferences in applying stringent HLA-matching criteria but should be interpreted cautiously due to low numbers.

This study reveals that young donors are preferentially selected with an average donor age of 32.4 years. Interestingly, the ratios of donors of ≤32 years were similar in all HLA-matching categories ranging from 52% to 61%, which is significantly higher than the 36% rate of young donors reported by the recent CIBMTR study.[26]

The overall rates of blood group and CMV matching were, respectively, 46.3% and 59.1%, but these figures cannot be compared in the absence of published data by individual registries. Although male-focused donor recruitment strategies are generally recommended, the present study shows that female donors still were selected for 42.3% of HSCTs. This ratio is significantly higher than the 18% (in 10/10 matched transplants) and 27% ratios (in 9/10 matched transplants) reported by the Canadian registry.[24] Almost one third of the HSCTs were mismatched for gender, and among those mismatched transplants, the ratios of female to male and male to female were almost identical. The high rate of gender-mismatched transplants in the 12/12 matched group, as well as the higher rate of female donors for male patients in the 8-9/10 matched group (29.2% compared to 12.5% in the 10-12/12 matched group), outlines the crucial importance of HLA-matching criteria for donor selection and the secondary role of gender matching.

Since it is a retrospective analysis from the perspective of the registry, its limitations lie in the lack of information on search algorithms that are expected to differ between countries and even between transplant centers, not to mention preferences of transplant physicians to work with certain registries.

Altogether, these results support an ongoing donor recruitment strategy with high-level HLA typing, focusing on young male donors, but certainly not excluding female donors since 42.3% of selected donors in the past 4 years were female. An increase in the number of SBSC donors should benefit local patients[22] although perhaps not as much as in other small/intermediate size registries (Croatia, Finland, Italy) due to the high haplotypic diversity of the Swiss population. Furthermore, such an increase will undoubtedly continue to be of significant help to international patients, particularly in those cases where a DPB1 match is requested or in cases of very rare HLA haplotypes where a full match cannot be achieved.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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