

# Current Status of Japan Marrow Donor Program (JMDP) and Its Roles in International Cooperation

Shinichiro Okamoto

*Keio University School of Medicine, International Committee, Japan Marrow Donor Program, Tokyo, Japan*

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## **Abstract**

Transplants for patients lacking an HLA identical sibling donor have become possible, and thank to the establishment of large registries of HLA typed volunteers. Japan Marrow Donor Program (JMDP) now stands at about 152,339 volunteer donors, and have provided 4,013 marrows nationally and internationally. Advancements in HLA typing technology and greater precision in donor recipient matching have greatly increased the safety of unrelated donor transplants. In the JMDP retrospective study the strongest risk factor for acute GVHD and mortality was found to be mismatching for the HLA-A locus. Better matching criteria using molecular typing, however, will reduce the likelihood of identification of donors, especially in minorities. The chance of finding a matched unrelated donor is likely to be higher in the registries which share the same ethnic background of a recipient. There are five marrow donor registries have been established in Asia and are actively functioning. The expansion of volunteer donor pool of those registries and their efficient collaboration is very important to increase the probability of finding a match. The identification of permissive antigens may increase flexibility in donor-recipient pair matching may also be achieved through integration of international efforts and the creation of larger HLA data base.

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Allogeneic hematopoietic stem cell transplantation (SCT) from a normal donor is an established life saving therapy for a range of malignant and non-malignant diseases. Improved clinical results have led to the use of SCT at earlier stages of several diseases and the number of patients in need of SCT will likely increase in the near future. A HLA-matched sibling is available to fewer than 30% of patients in Japan as well as Western Countries, and an extended family search usually identifies a one HLA locus-mismatched relative in less than 5% of patients. The decline in the fertility rate seen in most developed countries will most certainly aggravate the problem in the future. As a result, most transplantation requires an unrelated donor or other stem cell sources.

One of the vital components contributing to the success of unrelated SCT is an establishment of donor registry. The mission of marrow donor registry is to provide donor's gift of life to the patients who is in need of transplant in timely and efficiently fashion while ensuring donor's safety and confidentiality. Global efforts have led to the development of registries enlisting HLA-typed volunteer marrow donors all over the

world. Although development of online global network remains a goal to be achieved in the future, large donor networks have been established, and there are now more than 7 million potential volunteer donors typed for HLA-A and B, and half of those are also typed for HLA-DR throughout the world.

Japan Marrow Donor Program (JMDP) was formally established in 1992, and now stands at about 152,339 volunteer donors. The probability of finding at least one HLA-A-B and -DR serologically matched donor on the initial search has reached to 82%. By the end of March 2002, 4,013 marrow have been provided nationally and internationally through the JMDP

Unrelated donor SCT is generally associated with an increased incidence of acute and chronic GVHD, graft rejection, and lower overall survival when compared with HLA-matched sibling donor SCT. Many factors may affect an outcome of unrelated SCT, the age of recipient and the level of histocompatibility between the donor and the recipient have been identified as the most significant factors influencing the results of unrelated donor SCT.

Allelic disparities frequently occur among serologically matched donor-recipient pairs, and their impact on unrelated SCT is now actively evaluated with the increasing use of Class I and II allele level typing. The JMDP retrospectively examined allele DNA typing of HLA genes in 440 Japanese patients who received serologically matched HLA-A, -B, and -DR unrelated marrow transplants, and found that an incompatibility for HLA-A allele was an independent risk factor for severe acute GVHD and overall survival by multivariate analysis. Our recent analysis with more donor-recipient pairs and a longer follow-up period confirmed this observation, and also showed that the mismatching for Class II alleles has also an impact on the incidence of severe acute GVHD and survival after transplant. But the effect of Class II allele mismatches was not stronger than that of Class I allele mismatches. These results are not in line with the Seattle study that showed the probability of developing severe acute GVHD was mostly affected by Class II allele mismatches.

It is not clear why acute GVHD was more strongly associated with mismatching for HLA-A in the JMDP study whereas mismatching for DRB1 or DQB1 was more strongly associated with GVHD in the Seattle study. It is conceivable that genetic differences in these two distinct populations could account for the difference in clinical outcome. Notably the A-locus alleles found to be mismatched among Japanese patients and the A-locus alleles mismatched in Caucasian patients may not be the same. This finding suggests that different pairs of mismatched alleles may not cause the same kind of alloimmune response and it supports the hypothesis that certain allelic differences may be permissive mismatches.

HLA alleles are not randomly distributed because of linkage disequilibrium, and the frequency of HLA alleles

and linked haplotypes varies among racial groups. Thus the chance of finding a matched unrelated donor is likely to be higher in the registries which share the same ethnic background of a recipient. There are five marrow donor registries have been established in Asia and are actively functioning. The efficient collaboration among those registries is very important for patients with Asian-Pacific racial background. The expansion of the pool of volunteer donors in each registry is also important to increase the probability of finding a match.

Better matching criteria using molecular typing will decrease the incidence of acute and chronic GVHD, but it will also reduce the likelihood of identification of donors, especially in minorities. New methods of GVHD prevention and treatment are urgently needed; if their efficacy improves, it may be possible to employ mismatched donors, increasing the possibilities of performing transplants for subjects with rare HLA types. The identification of permissive antigens may increase flexibility in donor-recipient pair matching. This may also be achieved through integration of international efforts and the creation of larger HLA data base.

Because donor registries serve patients while attempting to minimize donor risk, they must confront ethical questions. As increased requests are made of donors, it can be anticipated that the principles of justice, autonomy, paternalism, and medical futility will increasingly be the subject of registry deliberations. Global consensus on these issues, which are vital to efficient international exchange of marrow or other stem cell products, must be established. This is probably best accomplished by World Marrow Donor Association (WMDA) that is currently working on establishing ethical and practical guidelines or standards to protect donors. All registries including Asian registries are strongly encouraged to participate in this project.