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The World Marrow Donor Association: Twenty Years of International Collaboration for the Support of Unrelated Donor and Cord Blood Hematopoietic Cell Transplantation

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Abstract

The transplantation of hematopoietic stem cells from unrelated volunteer donors and cord blood units is made possible through an international collaboration of registries and cord blood banks. The World Marrow Donor Association (WMDA) is a non-profit association based in Leiden, The Netherlands, whose mission it is to assure that high quality stem cell products are available for all patients in need, while maintaining the health and safety of the volunteer donors, This goal is accomplished through the work of six working groups and six board committees, in which issues of global significance to the clinical hematopoietic cell transplantation community are identified and guidelines are established. In this special issue of *Bone Marrow Transplantation*, the activities of the WMDA and a vision for future directions in the field are presented.

Keywords

World Marrow Donor Association (WMDA); unrelated donor; cord blood; hematopoietic cell transplantation

Hematopoietic cell transplantation was first performed in the animal model over 40 years ago. [1] The first successful transplants in humans were performed with bone marrow from sibling donors and this experience was instrumental in the development of the transplant procedure using stem cells from donors outside the family. [2, 3] The widespread availability of volunteer donors was made possible by the establishment of registries. Enthusiasm for the recruitment of donors and the systematic collection of donor tissue typing was ignited by Shirley Nolan in the 1970s in the United Kingdom. When her son Anthony was diagnosed with Wiskott-Aldrich syndrome and transplantation was the only known cure, Shirley directed her energy towards creating a system to record the tissue type of volunteers, and catalogue the information in an accessible format in the event that the donor's type might match that of a patient in need of a transplant. This was the birth of The Anthony Nolan Trust, established in London in 1975. [4] The Anthony Nolan Trust paved the way for donor recruitment and was the first donor registry to promote access to HLA-matched donors

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worldwide. The success of the Anthony Nolan Trust energized similar projects in the United States[5] and worldwide. Efforts to facilitate donor searches at the international level were launched by Jon J. van Rood at the Europdonor Foundation in Leiden, The Netherlands. This collection and global catalogue of HLA phenotype data became known as the Bone Marrow Donors Worldwide (BMDW). [6] To this day, transplant centers from around the world can perform preliminary searches by accessing BMDW through the internet for a preliminary view of the availability of potential suitable donors in worldwide registries and cord blood banks. [7]

In 1988, three pioneers, John Goldman, Hammersmith Hospital, London, UK; E Donnell Thomas, Fred Hutchinson Cancer Research Center, Seattle, USA and Jon J. van Rood, organized the Cooperative Marrow Donor Program, an informal group whose primary objective was to establish guidelines for the promotion of volunteer donors for clinical transplantation involving patients and donors residing in different countries. This program provided critical early impetus in the founding of the World Marrow Donor Association (WMDA) in 1994 to formalize the international activities under an umbrella association to promote the exchange of donors across international borders. [8, 9] It is in this spirit that the mission of the WMDA - to work towards making high quality and secure hematopoietic stem cell products available for all patient worldwide while maintaining the health and welfare of the stem cell donors – has led to a global effort.

In 1982, a landmark paper by John Goldman and colleagues, described the successful treatment of patients suffering from chronic myeloid leukemia through bone marrow transplantation, and was the earliest demonstration of the role of allogeneic transplantation as a curative modality for blood disorders. [10] Today, the practice of transplantation from donors other than a relative, reaches far beyond the classical indication of leukemia to encompass both benign and malignant blood disorders; matched and mismatched adult donor and umbilical cord blood stem cells; bone marrow, peripheral blood stem cells sources, and many different approaches for the conditioning of the patient, the prevention and treatment of post-transplant complications, and post-transplant monitoring. Since it is now estimated that only 20% of patients in the United States in need of a transplant have a genotypically HLA-identical sibling to serve as a donor, largely as a result of the smaller average family size the demand for unrelated donors has grown proportionately. The means through which a patient can receive life-saving stem cells from an unrelated donor or umbilical cord blood unit, is a well-orchestrated process coordinated by donor registries which collaborate with a worldwide network of collection centers, donor centers, cord blood banks, transplant centers and laboratories for tissue typing and other specialized testing, necessary for the evaluation of the donor and unit. The mechanisms by which a stem cell product from a donor or umbilical cord blood unit physically located in a different country than the patient’s, can be identified, collected, transported for clinical use, is the primary concern of the WMDA. In this special issue of *Bone Marrow Transplantation*, the activities of the WMDA that make it possible to carry out unrelated and umbilical cord blood transplants are highlighted, and the issues faced by the community to broaden the use of stem cells for all patients in need of a transplant, are discussed.

How global is the coordination of activities for unrelated donor and umbilical cord blood transplantation? As described in Monitoring the International Use of Unrelated Donors for Transplantation – the WMDA Annual Report, there are now over 14.6 million registered adult volunteer donors and 450 000 cord blood units banked worldwide (Figure 1). These figures describe activity in all regions of the world: Africa, the Americas, Europe, the Western Pacific, Southeast Asia, and the Eastern Mediterranean region. These statistics are important not only for measuring growth of transplantation in general, but to identify ways to improve the availability of transplantation to every patient in need. If 1.7 million new donors were recruited and almost 78,000 umbilical cord blood units added to the worldwide inventory in 2008, how might future recruitment be directed to assure that every patient has one suitable stem cell source? The *Annual Report* of the WMDA is a product of the Donor Registries Working Group whose mission is to develop guidelines for donor recruitment and maintenance of donor confidentiality, track the efficiency of donor searches and develop consensus standards for the logistics of transporting stem cell products across international borders. The Report highlights regional differences in the export and import of stem cell products, emphasizing the need for continued research on how the genetics of the volunteer donor pool may influence the extent of worldwide sharing of donors and to identify potential barriers to the exchange of stem cell products. These data are of importance in the recruitment of new donors and umbilical cord blood units, and aid in determining the optimal size and composition of registries and banks.

With almost half of all transplants involving a product originating outside of the patient's country of residence, the need for standardized practice in the collection of the product is of critical importance. To ensure the quality of international donations, standards have been developed to assure that the highest quality product is delivered with safety of both the donor and patient of paramount importance. As described in Standards, Regulations, and Accreditation for Registries Involved in the Worldwide Exchange of Hematopoietic Stem Cell Donors and Products, the standards by which stem cell products are collected and transported result from the collaborative efforts of several organizations represented within the Worldwide Network for Blood and Marrow Transplantation (WBMT). [11] The WMDA's Accreditation program remains one of the most important mechanisms by which registries and banks maintain the highest standards in the field for stem cell collection with donor safety of paramount importance. Its broad goals are to promote harmonisation between worldwide stem cell donor registries and cord blood banks and encourage uniformity of practice based on internationally accepted standards. These goals are accomplished through a set of standards that include donor recruitment; donor characterization; information technology; facilitation of search requests; second/subsequent donations; the collection, processing and transplant of the product; follow-up of the recipient and the donor and issues pertaining to financial and legal responsibilities. The continued sharing of stem cell products brings new challenges in meeting regulatory standards both nationally and internationally; future directions include the need for coordinated efforts among organizations with expertise in this area.

Since 1999 cord blood banks worldwide have provided the platform for the systematic data collection of umbilical cord blood units for altruistic public donation. Their efforts ignited

international efforts in support of umbilical cord blood transplantation, and today, over 450,000 units are currently stored in banks worldwide for any patient in need of a cord blood transplant. The geography of sharing umbilical cord blood units increasingly mirrors that of the adult volunteer donor pool: over 40% of units are used for patients who reside in a country that is different to where the umbilical cord blood unit was banked. This level of activity necessarily requires international collaboration in the establishment of standards for collection, processing, typing, and storage. In International Exchange of Cord Blood Units – The Registry Aspects.

The activities of the Cord Blood Working Group of the WMDA highlight the complex nature and the requirements for good practice in the collection of maternal medical history and confirmatory testing of the umbilical cord blood unit. The WMDA's focus is on the development of best practice and standards to support and promote the safe and effective international exchange of unrelated cord blood units. To meet these goals, the newly formed Cord Blood Working Group gathers and shares information concerning cord blood registry activities, through various instruments including comprehensive questionnaires, and by establishing relationships with organizations active in umbilical cord blood transplantation. As with the donation of bone marrow and peripheral blood stem cells from adult volunteer donors, the sharing of umbilical cord blood units internationally requires regulatory oversight, and is a high priority activity for the WMDA. Another critical area is the emerging data on the immunobiology of umbilical cord blood transplantation and the role of many genetic and non-genetic factors that influence transplant outcome after single and double cord blood unit transplantation. These factors include the definition of confirmatory testing and extended tissue typing, standardized forms to facilitate communication, definition of ethnicity and conditions in the family medical history that are pertinent to the transplantation of blood and cellular products.

Exemplified by the adult volunteer blood and marrow experience, tissue typing guidelines for the selection of unrelated donors significantly impact the activities of registries vis-à-vis their recruitment efforts and the loci and level of resolution for typing recruited donors. For cord blood transplantation, current recommendations for the selection of the optimal unit to meet individual patient needs are summarized from the Eurocord experience. The longitudinal follow-up of outcomes by the WMDA will continue to be an important arena for the refinement of criteria used by transplant centers for cord blood unit selection, as well as for registries and banks to help them to meet clinical needs in the future. Guidelines for the donation of adult unrelated blood and marrow stem cells are very well-developed but the continued high level of international sharing of donors requires on-going oversight of standards of practice including indications for the use of an unrelated donor graft and the health and welfare of the donor. The activities of two WMDA working groups, Clinical Working Group and Ethics Working Group, are highlighted in this issue and include development of criteria for donor activation and formulation of guidelines for subsequent donations including the standardization of stem cell and donor lymphocyte infusions. As described in Donor Safety: The Role of the WMDA in Ensuring the Safety of Volunteer Unrelated Donors – Clinical and Ethical Considerations, the welfare of the volunteer donor in the donation process is one of the most important missions of the WMDA. These needs include indications for use of growth factors for mobilization of stem cells, of harvest

procedures and monitoring immediate, short-term and long-term donor outcomes. A comprehensive data collection system permits the formal tracking of events in the donor and product: the serious events and adverse effects registry (SEAR) for events experienced by donors, and the serious product events and adverse effects registry (SPEAR) related to the product that is infused into the patient. The tracking of SEAR and SPEAR events is an important mechanism for alerting the transplant community to donor-related issues, and serves as a platform to review, modify and apply standards for best practice. Although the focus of the WMDA is on the health and welfare of the volunteer unrelated donor, the information is also pertinent and beneficial to the related donor, and efforts to disseminate information gleaned from the international unrelated experience will continue to be important in the future to optimize donor care in the allogeneic transplant setting.

The initiation of a search for a volunteer donor and/or umbilical cord blood unit for transplantation triggers a worldwide network of communications that depends on a common language for HLA nomenclature and matching standards. In Information Technology and the Role of the WMDA in Promoting Standards for International Exchange of Hematopoietic Stem Cell Donors and Products, two fundamental needs for the electronic exchange of HLA typing information are described: 1) a logical approach to catalogue human variants which is also flexible to accommodate continued discovery of novel alleles and their functional properties, and 2) search systems to accurately identify potential donors for a given recipient. The former need is met through guidelines on the application of HLA nomenclature for matching and selection of suitable stem cell sources based on the World Health Organisation (WHO) Nomenclature Committee for Factors of the HLA System. [12] Use of a common language minimizes ambiguities and errors in the transmission of tissue typing data. The latter feature requires technology that can be applied to datafiles containing heterogeneous information with respect to the number of HLA genes with available typing information, as well as the kind of information specified for the locus (methodology and resolution of the HLA determinant). Beyond the communication of donor match grades, tools for prioritizing the donors and units that are most likely to be matched to the recipient, require constant development and remain a high priority area of research and development for the WMDA's Information Technology Working Group. Additional projects include the development of encrypted e-mail security standards and biostatistical tools for analysis of genetic variation encoded in registry donors and umbilical cord blood units.

The vision of the founding members of the WMDA in 1992 was that the search and provision of stem cells from unrelated donors would eventually become an international effort, and therefore would require standardized practice to ensure the high quality of stem cells no matter where the donor or recipient reside. This vision has been realized not only for adult volunteer donors, but also for umbilical cord blood units. Through these global efforts, over 100,000 patients have received a stem cell transplant for the treatment of a benign or malignant blood disorders worldwide. What does the future hold? As described by John Goldman and Jon J. van Rood in *Future Perspectives*, continued research in several areas is mandatory in order to fully meet the needs of our patients. From a genetic standpoint, understanding the circumstances in which HLA disparity can and cannot be tolerated is a key to broadened application of hematopoietic cell transplantation as a life-saving

procedure. With substantial progress in the elucidation of the genetic diversity, organization and function of the natural killer (NK) receptors, particularly application of donor selection based on killer immunoglobulin-like receptors (KIR) and KIR ligands, is on the horizon. The powerful effect of the non-inherited maternal antigen (NIMA) on outcome after haploidentical related transplantation and cord blood transplantation, provides a model for extending selection to NIMA-matched umbilical cord blood units and maternal donors, opening new options for patients who lack HLA identical siblings or HLA matched unrelated donors. Continued collection of information concerning the properties of the stem cell graft that most strongly associate with optimal clinical outcome, will provide the community with the data needed to refine the requirements of an “optimal” stem cell graft. New understanding will only be achieved through both comprehensive real-time data collection and active participation in clinical studies. Finally, a successful transplant comes about through expertise at each stage of the process; education and training serve as the backbone to the continued growth of centers of excellence. To this end, the WMDA looks forward to maintaining and extending high quality international standards for registries, umbilical cord blood banks and their stem cell products; to participating in research trials related to optimizing the stem cell product, and to integrating new findings from clinical research into practice to fit the individual needs of patients worldwide.

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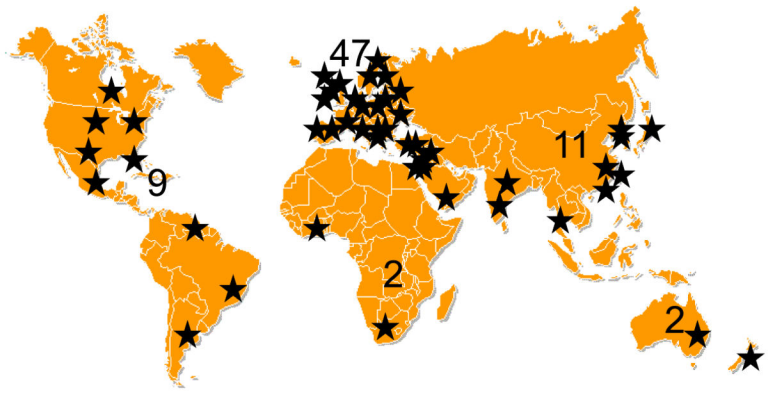

Figure 1.

Worldwide location of unrelated donor registries. Registries are indicated by a star. As of January 1, 2010, there are a total of 9 donor registries in North America, 47 in Europe, 2 in Africa, 11 in Asia and 2 in Australia.