Hematopoietic stem cell transplantation (HSCT) has been used for decades to cure blood diseases, especially leukemia. In the everyday medical practice more than 70 diseases can be treated using this procedure. The one millionth stem cell transplantation performed at the end of 2012, has drawn attention to this little-known type of intervention. The first stem cell transplantation was performed in 1957, by returning the patient’s own stem cells (autologous transplantation). It is since 1968 that clinicians have been carrying out transplantations using the healthy stem cells of a tissue matching family member, and in 1973, the stem cell transplantation became possible among total strangers. Nowadays, more than 50,000 patients undergo stem cell transplantation annually, among them a decreasing proportion with their own cells, and a growing part, with the cells of unrelated stem cell donors. This process is largely due to the worldwide registered, nearly 25 million volunteer donors, who are willing to donate their stem cells for HSCT of patients unknown to them.

Knowledge required for successful hematopoietic stem cell transplantation is based on the fundamental discoveries concerning the human immune system at the end of the 1950s. The tissue identification antigens, named Human Leukocyte Antigens (HLA) that can be found on the surface of most cells of the human body were described for the first time. Their role in the transplantation comparable to that of blood groups AB0 in transfusions, as the donor selection on the basis of the HLA matching is essential to carry out the procedure safely.

Stem cells come always from live donors, like in blood donation. The recipient’s immune system has to accept donor cells for successful stem cell transplantation. This can be achieved if we make sure that the HLA antigens on the donated cells are the same as, or very similar to the antigens in the cells of the recipient. The sibling of the patient has the highest chance to be the suitable donor, because of the 25% chance to match the patient HLA antigens. Majority of the patients, 70%, however, can get help only from a stranger, a volunteer stem cell donor for healing.

A need to create volunteer stem cell donor registries was formulated in 1970, as it had been turned out that for a large part of the patients need no suitable donor (sibling) was available. The first registry was set up by a foundation (Anthony Nolan) in 1974, while the first public cord blood bank was registered in 1993 (Cord Blood Bank, New York).

The international stem cell donor registry (BMDW) was started in 1988; the first edition in 1989 contained a total of 155,000 volunteer stem cell donors of 8 registries. Seventy stem cell donor registries of 53 countries and 49 cord blood banks of 33 countries report today to the BMDW. Despite the fact that the number of registered donors has already reached 25 million, and the number of stored umbilical cord blood units exceeds 630 thousand, the further increase is undiminished. Among them a preliminary search can be done for patients in need of stem cell transplantation with no family donors.

However, there are still many patients without suitable donor in the registries with whom the transplantation can be performed with high hope of recovery. Therefore, most of the countries’ ongoing effort seeks to develop its own national registry and enhance the typing level and the number of the donors.

Our purpose is to promote treatment of Hungarian and foreign patients that could not be envisaged without the help of voluntary donors. We need to increase the number of Hungarian donors to increase the chances of recovery of all patients who need them.

Staff of the Hungarian Stem Cell Donor Registry
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Introduction

Definitions and abbreviations

**Aphaeresis:** any procedure in which blood is obtained from a donor, a portion (such as plasma, leukocytes), is separated and retained, and the remainder is retransfused into the donor.

**Allele:** alternative forms of a gene at the same site in a chromosome, which determines alternative characters in inheritance.

**Allogeneic:** individuals (or tissues) that are from the same species but antigenically distinct.

**Antigen:** any substance capable of inducing a specific immune response.

**Autograft/autologous transplantation:** a tissue or organ regrafted in or on the body of the same individual.

**BMDW (Bone Marrow Donors Worldwide):** BMDW is a voluntary collaborative effort of stem cell donor registries and cord blood banks whose goal is to provide centralized information on the HLA phenotypes and other relevant data of unrelated hematopoietic progenitor cell donors and cord blood units and to make this information easily accessible to the physicians of patients in need of a HPC transplantation.

**CBU:** Cord Blood Unit.

**CMV:** cytomegalovirus.

**BM:** bone marrow: in particular bone contains hematopoietic stem cells. The hematopoietic stem cells can develop into any type of specialized blood cells, red blood cells, white blood cells and platelets. Bone marrow stem cells can obtain in general anesthesia or spinal anesthesia from the back from hip thorns, or the breastbone.

**Donation:** donation of human tissues and cells intended for human use.

**Donor centre:** An organization responsible for donor recruitment, consenting, testing, management and the collection of donor personal, genetic, medical data.

**Donor:** term used mainly in connection with the blood donation and transplantation.

**EBMT:** European Group for Blood and Marrow Transplantation.

**EDS:** European Donor Secretariat.

**EMDIS (European Marrow Donor Information System):** A system that facilitates electronic communication between registries.

**G-CSF:** granulocyte colony-stimulating factor induces hematopoietic stem cell mobilization.

**Genotype:** the entire genetic constitution of an individual, also, the alleles present at one or more specific loci.

**Graft:** any tissue or organ for implantation or transplantation.

**GVHD:** graft versus host disease, a life threatening complication of bone marrow transplantation in which the donated stem cells cause an immune reaction against the recipient’s body.

**Hematopoietic stem cells:** progenitor cells that can replicate itself as well as produce precursor cells of the various blood cell lineages. They are found in the bone marrow, peripheral blood and cord blood. After transplantation, in the micro-environment of the bone marrow, they are capable of the development of all hematopoietic cell line.

**Haplotypes:** a set of linked genetic markers on a chromosome which are usually inherited as a unit.

**HLA:** Human Leukocyte Antigen.

**HSCT:** Hematopoietic stem cell transplantation.
HUB: a computer networking hardware device.

IDM: infectious disease marker.

Locus: the position that a gene occupies on a chromosome.

MUD: matched unrelated donor.

NHBTS: National Hungarian Blood Transfusion Service.

OVSZ: National Hungarian Blood Transfusion Service.

OEP: National Health Insurance Fund of Hungary.

PBSC: peripheral blood stem cells, found in the peripheral blood. Their numbers can be artificially increased by exposure to hematopoietic growth factors. The collection of stem cells suitable for transplantation occurs from the circulating blood after the treatment.

Phenotype: the observable characteristics at the physical, morphologic, or biochemical level of an individual, as determined by the genotype and the environment.

Recipient: a person who receives a blood transfusion, tissue graft or organ, whose genetic properties and the status of the immune system determines the degree and type (tolerance or rejection response) of the immunological reaction against the graft.

Registry: an organization responsible for coordination of the search for hematopoietic stem cells from donors (including cord blood) unrelated to the potential recipient.

SOP: Standard Operational Procedure.

Transplantation Committee: a scientific committee required by law and run by the OVSZ making decisions about the position of patients (enrollment, keeping or deletion) on the transplant waiting list, donor eligibility and transplantation.

Transplant centre (TC): a medical facility where the complex process of stem cell transplantation (examination, transplantation, aftercare) carried out for adult and / or pediatric patients.

Waitlist: a patient appointment list required by law to determine the temporal sequence of the transplants.

Verification typing: this HLA typing includes the tests carried out on a fresh sample of a specific donor or on an attached-segment of a cord blood unit with the purpose of verifying the identity and concordance of an existing HLA assignment. This stage used to be referred to as "confirmatory typing (CT)".

WMDA (World Marrow Donor Association): A non-profit association that fosters international collaboration to facilitate the exchange of high quality HPC for clinical transplantation worldwide and to promote the interests of donors.
Establishment of the Hungarian Stem Cell Donor Registry

The Hungarian Bone Marrow Donor Registry was established in 1991 by the National Institute for Hematology and Blood Transfusion, Department of Immunogenetics, building up a link between clinical bone marrow transplantation program and the worldwide voluntary donor organizations.

In 1992, the Hungarian Bone Marrow Donor Registry joined the International Organization (WMDA). Since 1992, Hungary has been providing donor data to the international database (BMDW).

The operation of the Hungarian Bone Marrow Donor Registry was inserted officially into the Deed of Foundation in 1994, parallel to the reorganization of the Institute of Hematology. Since 2007 the registry has been functioning as a subunit of the National Hungarian Blood Transfusion Service.

For keeping the donor records and performing donor search a selection program developed by the French registry (EDS) and a self-developed database program were used from 1991. With the help of funding sources our own program was developed, and from 2012 Prometheus software developed by a Czech company is used. This software makes it possible to use the EMDIS connection system to run donor search online, which significantly accelerated the process of selecting suitable donor.

At the time of establishment a foundation did, while since 2003 the Ministry of Health has been ensuring direct financial support for the operation of the Registry. The Department for International and European Union Affairs of the National Health Insurance Fund Administration is financing cross-border activities of the Registry for the Hungarian patients.

Legislation defining the operation of the registry, and international guidelines

As mentioned, the operation of the Hungarian Bone Marrow Donor Registry was inserted officially into the Deed of Foundation of the National Institute of Hematology and Blood Transfusion in 1994. As Hungarian Stem Cell Donor Registry, currently works within the framework of the National Blood Transfusion Service, an independent organizational unit as defined in the bylaws.

In Hungary, the XI. Chapter of the Health Care Law regulates issues related to organ and tissue transplantation. DIRECTIVE 2004/23/EC (*) was implemented in Hungary in 2008, in a specialized ministerial implementing Regulation (**), which is the regulation of stem cell transplantation in Hungary at the European level.

National and international regulation determining the operation of the Hungarian Stem Cell Donor Registry:

- Act CLIV of 1997 on Health,
- **Decree 18/1998 of the Ministry of Health on implementing the Act CLIV of 1997 on Health as Regards Organ- and Tissue Transplantation, Storage and Testing,
- Decree 287 of Government on 2006 on the detailed rules of offerable services based on the waitlist,
- Decree 323 of Government on 2006 about the National Hungarian Blood Transfusion Service,
- Decree 340 of Government on 2013 about the application of patients’ rights in cross-border healthcare,
- * DIRECTIVE 2004/23/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells,
Main activity and tasks of the registry

The Hungarian Stem Cell Donor Registry is part of the international network (BMDW). Hungarian donors are added to the international donor pool to be selectable, and for the Hungarian patients the most suitable donor can be selected among the nearly 25 million registered voluntary donors worldwide.

Our tasks are:

- to recruit Hungarian donors in cooperation with the HNBTS regional and local centers; promote the registration of younger and healthy volunteers,
- to select the best fitting donor in the national and international database for the Hungarian patients, and coordinate further testing and the final request of the donor,
- to activate the Hungarian donor selected for a foreign patients; to arrange performing the requested tests or sending blood samples for confirmatory HLA typing,
- to send Hungarian donor data necessary for donor selection to the international database,
- to organize training courses for professionals involved in stem cell donor recruitment, stem cell donation and transplantation,
- to inform registered donors and people interested in donor enrollment, donation, donor selection,
- to support the work of the Pediatric and Adult Bone Marrow Transplant Committee,
- to send annual report about the activity of the registry to the international organization (WMDA).

Structure and relations of the stem cell donor registry

The Hungarian Stem Cell Donor Registry cooperates within the National Hungarian Blood Transfusion Service (OVSZ) with:

- coordinators of the donor centers,
- Laboratory of Transplantation Immunogenetics,
- Central Donor Laboratory,
- Serology Laboratory of Blood Typing,
- Financial Department,
• Information Technology Department.

Cooperates within the country with:
• Adult and Pediatric Bone Marrow Transplantation Committee,
• hematological clinics and departments,
• The Stem Cell Transplant Centers,
• The National Health Insurance Fund,
• The National Health Insurance Fund for International Relations and Legal Relationship Records Department.

Cooperates at international level:
• National registries of other countries,
• The operator of Prometheus (Steiner, Ltd.)
• Bone Marrow Donors Worldwide (BMDW)
• Word Marrow Donor Association (WMDA).

Organizational Structure

Organizations participating in the preparatory process of stem cell transplantation

Figure 1 Organizations participating in the preparatory process of stem cell transplantation
Employees of the Hungarian Stem Cell Donor Registry

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Registration of stem cell donors
General guidelines of Stem Cell Donor Registries, which was accepted by Hungarian Stem Cell Donor Registry when it was established.

- The donor must securely be healthy to protect the patient as well as the donor.
- The stem cell donation is voluntary and unpaid, but expenses of the donor will be refunded.
- The donor at his/her registration accepts that in case she/he is chosen for donation (bone marrow or peripheral blood stem cell) she/he will donate for anyone in the world without considering race, gender and religion.
- The donation is anonymous.
- The donor has right of withdrawal at any time.
- The donor and the patient could exchange messages or even low value gifts through the registry or TC without personal identification already at the time of transplantation.
- Two years after transplantation direct contact can be initiated in case the donor as well as the patient wants it (in accordance with the partner registry’s rules).
- Registration with the intention of a directed stem cell donation is not permissible.
- Conditions (age, health state, exclusion criteria) for unrelated donation can be much stricter than for a related one.

Since 2007 Hungarian Stem Cell Donor Registry has been functioning as a subunit of the National Hungarian Blood Transfusion Service. Since then, the stem cell donor should be a registered blood donor and she/he should have had a blood donation within the preceding 56 days.
Who can be a stem cell donor?

The donor should be at least 18 years old and under 45 when joining the HSCDR. Registration is available at the nearest blood transfusion centre. If the donor had never had a blood collection before or if the previous blood collection had been more than 56 days before application, she/he must donate blood concurrently. The donor’s health state and suitability is tested before blood donation.

Before blood donation, the following examinations are necessary:

- medical examination
- serological blood-group test
- infectious disease marker (IDM) test

After the successful blood donation, within 56 days the application for stem cell donor can be performed. The applicant can contact the donor centre for an appointment by phone.

The donor fills out an informed consent form and had a blood sample of 10 ml drawn (with EDTA as anticoagulant) for HLA typing.

At registration the donor declares the will to donate if needed bone marrow or peripheral blood stem cell or both for anyone in the world, and to accept related medical examination.

The HLA typing determines the tissue type of the donor, which is required to compare to the patients in the donor search process. Since 2007, minimum of HLA-A, B and DR loci have been investigated by molecular method. The parameters needed for donor selection will be stored on the national and international database in accordance with the Data Protection Act.

The donor will be notified by letter about her/his enrollment to the registry.

Call for additional tests

In case a donor is selected for a patient further investigations will be necessary. The selected donor will be called in for another blood drawing either for further HLA typing to test additional loci, or sending the blood sample for confirmatory typing to the requesting foreign registry.

In case the donor and patient match known only for 4 or 6 loci, the patient’s registry requests additional typing. If the donor will differ from the patient, the donor will be released to be available for another patient. Most cases (80%) further investigations uncover mismatches.

In case of adequate compatibility the patient’s registry requires blood sample from the donor for confirmation typing (CT) to be sent to the respective laboratories. In this stage the probability for an acceptable match is higher. In these cases the donor centre performs tests for blood groups ABO and Rh and for infectious disease markers (Lues, HBsAg, anti-HBC, anti-HIV, anti-HCV, and anti-CMV).

The donor must be informed about the outcome of the investigations, whether he/she is a match, and was chosen or not for donation as soon as possible by phone and by written form.

In case the donor was selected for stem cell donation, must be informed by a coworker of the registry by phone and ask for the donation. The medical examination before blood stem cell donation will be performed at St. Laszlo Hospital.

Donation of stem cells

Forms of stem cell donation are either directly from the bone marrow or collecting from peripheral blood. Bone marrow donation requires 2-3 days in the hospital, however, at present most of the donation performed by an alternative method. A process called aphaeresis is used to collect stem cells from peripheral blood after several days of medication (G-CSF) which increases the number of
stem cells released into the bloodstream. This procedure does not require neither surgery nor require hospital stay.

The donation is voluntary and unpaid, but all expenses of the donor incurred connected with the donation will be reimbursed.

The informatical background of the registry, data management, network connections

Bone marrow donor registries need a database, which contains the data of volunteer donors, a database, which keeps the data of patients waiting for stem cell transplantation, the newest HLA database, a search algorithm which helps to find the best donor for the patients, and an international network which makes possible the contact with foreign registries to share their donor databases.

The proper IT background is the prerequisite for the safe data management of donors and patients, the donor search process and the tracking of events. The key element of the donor search is the IT background of the donor records and the donor search algorithm.

International historical overview

The European Society for Blood and Marrow Transplantation (EBMT) had a decision in 1988 to collect all of the HLA phenotypes of volunteer stem cell donors.

The first BMDW issue was distributed in 1989 in a printed form, and from 1991 the donor data were submitted and distributed on floppy diskettes. From 1998 the donor data transmission has been sent monthly by encoded e-mail, and donor files and the matching programs were accessible through the Internet on the password-protected webpage of the BMDW.

In 1991 direct computational connection with EDS (European Donor Secretariat) was created among registries via Paris; in 1994 EMDIS was established which was a totally automated system among registries’ HUB.

In 1998 NetCord, a non-profit association of public umbilical cord blood banks was established to provide hematopoietic graft for patients in need for stem cell transplantation.

Hungarian historical overview

In 1991 the Hungarian Bone Marrow Donor Registry had its own donor/recipient data-handling software (developed in-house), while the donor selection program (EDS) was a present from the French Bone Marrow Donor Registry (FGM).

Since this year our Registry has sent the Hungarian donor data to BMDW, and connected to the international organization.

In 1992 we connected to the French EDS to manage donor search with international registries. For the expanding tasks our program was further developed using funding resources, and then from 2012 we have started to use the Czech Prometheus software. The usage of this program has allowed using the EMDIS online search system (replacing EDS) which significantly accelerated the process of finding a suitable donor.

IT background of the Hungarian Stem Cell Donor Registry

Each month, our registry sends the HLA phenotypes of the Hungarian stem cell donors to BMDW, supplemented with other data supporting the donor selection decisions, such blood group, donor’s age and gender. The first estimation of the patients’ chance for a matching donor is carried out using the online BMDW database which is updated monthly.
Since 2007, updating the Hungarian donors’ data has been done by the e-Progesa filing system of the OVSZ.

From 2012 on, all new stem cell donor data are imported once a month from eProgesa system to Prometheus database. All of these systems are operated by ‘Navigátor Informatikai Zrt’, the data transfer and making back up files, being performed in a validated system.

According to an agreement on cooperation with NMDP (National Marrow Donor Program) made in 1999, for American donors we use TRAXIS, the American donor search algorithm online.

Using Prometheus system we are in touch with 21 national registries directly via EMDIS, for example with English and German registries, which ensure the most donations for Hungarian patients.

**The process of selection of the stem cell donor**

**Indications of the allogeneic stem cell transplantation**

Indications of the allogeneic stem cell transplantation are the malignant and non malignant hematologic diseases, immunologic defects and inherited metabolic disorders. There are more than 15.000 such medical interventions annually worldwide.

**Transplantation of the hematopoietic stem cells**

The hematopoietic system of the patient is totally destroyed and later the transplantation is carried out with his/her previously removed and stored stem cells or ones obtained from an appropriate (HLA-matched) donor. Stem cells of the donor are capable of transforming into different kinds of blood cells. This process may result in the reconstruction of healthy hematopoietic system of the patient.

**Process of the stem cell transplantation**

![Diagram of stem cell transplantation process](www.hnbts.hu)
How a patient is getting enrolled on a waiting list for a stem cell transplantation

The Adult Bone Marrow Transplant Committee and the Pediatric Bone Marrow Transplant Committee have monthly meetings where decisions are made on placing a patient with appropriate indications on the transplant waiting list as well as temporary suspension and removal from the list according to professional rules laid down in specific laws.

The diagnosis by the hematologist verifies the need for allogeneic stem cell transplantation as a therapy for the patient.

The first step of the donor search is the HLA test of the family. According to international standards examination of the patient and his/her nearest relatives is necessary. The chance of matching is 25% between siblings, and in this way they can potentially be HLA matched donors, while the parents’ (in some cases the children’) examinations identify the jointly inherited characteristics, the so called haplotype.

The knowledge of the haplotype is a great assistance in the search of an unrelated donor (through comparison with the population database). Besides, members of the family matching in a haplotype can be alternative donors.

According to the family test results, the transplant committee makes a decision about the enrollment of the patient on the waiting list for transplant with sibling or about the permission of unrelated donor search in lack of family donor.

In case of a matching sibling the repeated HLA-typing test is carried out from a newly drawn sample according to the regulations (at least for 6 characteristics) from the patient and potential donor with the goal of exclusion of sample-changing and proving total match of donor and patient.

In absence of fully matching family donor a more accurate determination of HLA-typing is required (10-12 characteristics) from the second blood sample of the patient to initiate the unrelated donor search.

Provided the donor search is successful, the committee makes a decision about the donor acceptance and transplant permission. Following a successful donor selection the committee enrolls the patient on the transplant waiting list.

General criteria for donor selection

Potential allogeneic stem cell donor might be (in decreasing order according to the degree of genetic matching):

- a genetically fully matched sibling (identical twins)
- an HLA- identical sibling (for HLA-genotype)
- other related donor (HLA-matched or with 1 HLA-type mismatched)
- an unrelated donor matched for HLA phenotype (voluntary donor or umbilical cord blood)
- an unrelated donor mismatched for HLA-phenotype (voluntary donor or cord blood)
- a related donor matched for a haplotype

Sources of stem cells:

- bone marrow (BM)
- peripheral blood stem cell (PBSC)
- cord blood unit (CBU)
The degree of HLA matching is major criterion in bone marrow or peripheral stem cell selection (out of the 12 examined characteristics 8 have major importance, among these characteristics only 1 mismatch can be allowed,) while in selection of cord blood units the most important factor is the number of cells divided by body weight (transplantation can be executed if at least 4 characteristics out of 6 are matching). One or two mismatch may be compensated with larger number of nucleated cells, occasionally assured by supplying 2 cord blood units.

**Factors influencing the outcome of HSCT**

- Conditioning regime R
- Original disease, stage and burden R
- Age D/R
- Gender D/R
- HLA matching (A, B, Cw, DR, DQ, DP)
- Other Immune related genes D/R
- Virological status (CMV) D/R
- Timing diagnosis -> transplantation D/R
- Stem cell source D

R= Recipient
D= Donor

In case for a patient with frequent HLA type more matched donor is available, other aspects influencing the outcome of the transplant could be considered during the donor choice.

- the donor’s age: the younger is the better,
- body weight: optimal, when the donor has higher body weight,
- the donor’s gender: male donor is preferable (avoid female donor in case of male patient)
- ABO blood group: it is preferred when the patient and the donor are ABO-compatible,
- CMV status: an asset when the CMV status of the patient and the donor is the same,
- anti-HLA antibodies: in case donor specific antibody detected in the patient, the transplantation is contraindicated,
- donor registry: the closer the better, to shorten the delivery time.

**Unrelated donor search algorithm for Hungarian patients**

For a successful transplantation with the best available donor a continuous and thorough communication is required among the people participating in the process.

Preceding submission, the treating physician initiates the process with building up the accurate diagnosis and requesting the HLA typing of the patient and the core family. Following submission he/she sends a new blood sample of the patient for extended HLA typing and notifies the committee and the registry about the health status of the patient.
During the donor search Registry keeps in touch with the laboratories, donor centers, transplant centers and foreign registries (requests on donors, donor reservation, suspending donor search, stopping international search, information relating to donor/patient health status), and reports on a monthly basis at the committee meeting about the status of the donor selection.

Figure 4. shows the process of donor selection and patient and donor examination before allogeneic stem cell transplantation.

**Process of donor selection**

<table>
<thead>
<tr>
<th>Patient in need of HSCT</th>
<th>HLA typing for patient and family</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matched relative?</td>
<td>YES</td>
</tr>
<tr>
<td>NO</td>
<td>Committee permission for unrelated donor search</td>
</tr>
<tr>
<td></td>
<td>Extended HLA typing of patient from new sample</td>
</tr>
<tr>
<td>Donor search of world-wide registries</td>
<td></td>
</tr>
<tr>
<td>Potential donor available?</td>
<td>YES</td>
</tr>
<tr>
<td>Alternative therapy</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>Committee permission for transplantation</td>
</tr>
<tr>
<td></td>
<td>HLA match confirmed?</td>
</tr>
<tr>
<td></td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>TRANSPLANTATION</td>
</tr>
<tr>
<td></td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>Alternative therapy</td>
</tr>
</tbody>
</table>

Figure 5. shows the simplified scheme of donor selection. In case no HLA matched donor is available, there are alternative options.
Algorithm of donor search

Based on the results of the family investigation, comparing the patient’s HLA type to the 25 million donors in the international donor database (BMDW) the chance to have a donor for the patient can be estimated. The more properties known of the patient (and the donors), the more accurate the preliminary estimation will be.

In case a suitable matched donor has been found in the HSCDR, the donor is asked to visit the closest blood donation center to give a new blood sample. The further donor typing is performed in different levels depending on the existing HLA data until the matching is either proved or excluded. Finding a donor in the national registry has several advantages: length of the donor selection is shortened and the investigation of the donor and the donation occurs faster and more safely.

I. Knowing the patient’s exact HLA-type in the international database (BMDW) can be mapped, in which country’s registry has a potentially matching donor for the patient. In order to make further decisions it is necessary to consider several additional factors, as:

- Donors of the international registries are HLA typed in different level concerning the number of loci tested as well as the resolution of the test. Around 20% of the donors have been typed only for HLA-A and -B loci; and in case of most donors HLA-C, -DQ and -DP type is not known.

- Knowing the characteristics of the HLA system helps to grow efficiency of selection among the donors typed insufficiently (linkage between individual loci, allele and haplotype frequencies in different populations).

- With several registries we have a direct contact through the database management software, while other registries can be contacted only by fax or email.

II. Current availability and other relevant characteristics (age, gender, blood type) of the potential donor found in the BMDW can be clarified through a direct contact with the donor registry.

III. From the selected potential donor, who is identical or very close to identical on allelic level with the patient, a blood sample is requested for confirmatory HLA typing (to verify and/or confirm the donor’s earlier results) performing in the national laboratory at DNA level. The foreign registry performs the donor blood group and virus tests simultaneously, and sends the results. The
comparative result of the patient and the donor is sent by the laboratory to the transplant centre, the registry and the physician requesting the investigation.

**Matching criteria in case of related/unrelated haematopoetic stem cell transplantation (HSCT)**

<table>
<thead>
<tr>
<th>Related</th>
<th>HLA genotypically identical sib (12/12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DP</td>
<td>DQ</td>
</tr>
<tr>
<td>DR</td>
<td>B</td>
</tr>
<tr>
<td>Cw</td>
<td>A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unrelated</th>
<th>HLA haploidentical sib (6/12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DP</td>
<td>DQ</td>
</tr>
<tr>
<td>DR</td>
<td>B</td>
</tr>
<tr>
<td>Cw</td>
<td>A</td>
</tr>
</tbody>
</table>

**Figure 6 Matching criteria in case of related/unrelated hematopoietic stem cell transplantation (HSCT)**

On the basis of the decision of the Transplant Committee the request for the stem cell product can be initiated.

In case the committee does not accept the donor, the donor search process is repeated for finding a better matching donor.

IV. To assess suitability of a potential donor having been investigated in a lower level, further HLA typing can be requested from the foreign registry. High resolution HLA typing or that for additional loci can refine the degree of matching.

V. Depending on the patient's diagnosis and severity of the disease based on the decision of the Commission and according to the selection criteria, investigation of a not fully HLA matched donor, a choice of umbilical cord blood (CBU), or a not fully matched family donor for transplantation, can also be initiated.
The development of the voluntary donor pool in Hungary

The recruitment of voluntary donors has been started in 1990, and the number of registered donors increased depending on the financial support. From the 8000 donors registered today only 6,900 are active: most of the donors were archived reaching the age limit (60 years), but numerous donors were lost because they moved, are no traceable, or leaving for medical or personal reasons.

Donors typed for the Hungarian Stem Cell Donor Registry

Donors deleted from the Registry (n=1130)

- personal reason; 129; 12%
- medical reason; 151; 13%
- other; 205; 18%
- age limit; 641; 57%
There is a rise in the number of active donors in the registry and an upgoing tendency in the thoroughly examined donors: the proportion of sexes is equal, the diversity by ages is characterized by younger generations in the last couple of years especially as the 45 year limit has been introduced in enrollment.

Active donors in the Hungarian Stem Cell Donor Registry

Figure 9 Active donors in the Hungarian Stem Cell Donor Registry

Active donors in the Hungarian Stem Cell Donor Registry by HLA typing level

Figure 10 Active donors in the Hungarian Stem Cell Donor Registry by HLA typing level
The activity of the registry and the quality of donors are featured by the number of requests for further examination of potentially matching donors and by the number of actual examinations.

Blood sample/HLA typing requests from Hungarian donors in 2014

Figure 11 Age and sex distribution of the Hungarian stem cell donors (2014)

Figure 12 Blood sample/HLA typing requests from Hungarian donors in 2014
International data collection and retrospective analyses have shown that besides identity in HLA-type, success of transplantation is subject to the matching of other genetic factors, and that transplantations with donors selected from national registries have greater chance for success. More registered Hungarian donors can give greater recovery chances for Hungarian patients. Moreover, the great altruistic help received by our patient from abroad could be returned more frequently.

**Why is there a need for more Hungarian donors?**

**International registries:**
- 24 million donors
- Hungarian registry: 6900 donors

**Our patients received graft from:**
- 581 international and 12 national donors

16 Hungarian donors donated stem cells
Hematopoietic stem cell transplantation in Hungary

Increasing proportion of patients is in need for allogeneic stem cell transplantation can get help only from unrelated volunteer donors. In 2014, unrelated donor search was initiated for 51% of all pediatric patients, and for 81% of pediatric patients need allogeneic transplantation, while among adult patients these numbers were 28% and 74%.

Among the patients enrolled in 2014, 41% of pediatric patients (n = 18), and 20% of adult patients (n = 24) were transplanted. Some characteristics of this transplant activity shown in the following diagrams.

![Distribution by stem cell source of pediatric patients whose transplantation indication was accepted by the Transplantation Committee](image-url)

Figure 15 Distribution of pediatric patients whose transplantation indication was accepted by the Transplantation Committee (by stem cell source).
Pediatric patients dedicated for unrelated donor search

![Bar chart](image1.png)

**Figure 16** Pediatric patients dedicated for unrelated donor search

Distribution by stem cell source of adult patients whose transplantation indication was accepted by the Transplantation Committee

![Bar chart](image2.png)

**Figure 17** Distribution of adult patients whose transplantation indication was accepted by the Transplantation Committee (by stem cell source)
The number of transplantations with unrelated donor stem cells has increased. The donor selection criteria are the HLA matching, while the choice of stem cell source additional professional aspects are taken into account. There were 6 patients who underwent the second transplant.
Table 1. shows the distribution of altruistic donors donating stem cells to Hungarian patients in 2014 by countries of origin.

<table>
<thead>
<tr>
<th>Donors</th>
<th>number</th>
</tr>
</thead>
<tbody>
<tr>
<td>German</td>
<td>56</td>
</tr>
<tr>
<td>Polish</td>
<td>10</td>
</tr>
<tr>
<td>Czech</td>
<td>3</td>
</tr>
<tr>
<td>Spanish</td>
<td>3</td>
</tr>
<tr>
<td>English</td>
<td>2</td>
</tr>
<tr>
<td>Cyprian</td>
<td>2</td>
</tr>
<tr>
<td>French</td>
<td>2</td>
</tr>
<tr>
<td>Israeli</td>
<td>1</td>
</tr>
<tr>
<td>Canadian</td>
<td>1</td>
</tr>
<tr>
<td>Russian</td>
<td>1</td>
</tr>
<tr>
<td>Swiss</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 1: Donors who donated stem cells to Hungarian patients in 2014 distributed by countries

Unrelated stem cell transplantations in Hungary distributed by stem cell sources in 2014

Figure 20: Unrelated stem cell transplantations in Hungary distributed by stem cell sources in 2014
Figure 21 Unrelated stem cell transplantations distributed by stem cell sources and patient groups in 2014

Unrelated stem cell transplantations distributed by stem cell sources and patient groups in 2014

**Pediatric patients**
- PBSC: 2; 9%
- 2 CBU: 2; 9%
- CBU: 3; 13%
- BM: 16; 69%

**Adult patients**
- PBSC: 57; 98%
- BM: 1; 2%

www.hnbts.hu
Acknowledgements

Transplantations with unrelated donors have been made possible by the coordinated work of a great number of colleagues.

We acknowledge the efficient collaboration of the donor coordinators and other colleagues working in Donor Departments in giving information, tracking and activation of the donors.

Donors’ examinations are executed by the Laboratory of Transplantation Immunogenetics and by the Central Donor Laboratory.

The help of hematological physicians, Transplant Committees, Stem Cell Transplantation Centers’ physicians, transplant coordinators and other fellow-workers guarantees that stem cell products get to all patients who need transplantation.

The financial background of the transplantations is provided by the Financial Department of The Hungarian National Blood Transfusion Service and the Department for International and European Union Affairs of the National Health Insurance Fund Administration.

The stem cell products can be shipped to Hungary by the assistance of fellow-workers at the international registries.

The informatical background is assured by Navigator Informatical Zrt., the Informatical Department of National Hungarian Blood Transfusion Service and the Czech colleagues who run the Prometheus software.

We are obliged to the „Foundation for Life and for Bone Marrow Patients”, who made a contribution to the expenses of the examination of donors and the operation of the Registry in the 1990’s.

We thank the „Association of Cancer Patients” for founding the prize, „Life Giver” and supporting donors’ programs.

We also acknowledge the help of all voluntary donors...

Finally, we are grateful to the 16 Hungarian and several hundred foreign donors for their stem cell donations.

Appendices

Websites and references assuring directives and supporting the operation of the Registry:

TRNSPL-02_V05: Recording, activating, sample drawing and testing of the voluntary stem cell donors. (NHBTS SOP, valid: from 15.02.2015).

World Marrow Donor Association: http://www.worldmarrow.org
Bone Marrow Donor Worldwide: http://www.bmdw.org
HLA database: http://www.ebi.ac.uk/imgt/hla/
HLA allele frequency: http://www.allelefrequencies.net

EBMT - European Group for Blood and Marrow Transplantation http://www.ebmt.org
CIBMTR - Center for International Blood and Marrow Transplant Research http://www.cibmtr.org
NetCord - Netcord Virtual Office http://www.netcord.org