



Canadian Blood Services
Société canadienne du sang

Stem Cell Background Paper

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Introduction

In August 2008, it was officially announced that Canadian Blood Services would assume a new mandate related to organ and tissue donation and transplantation. This included assuming the activities of the former Canadian Council for Donation and Transplantation (CCDT), as well as setting up registries for living donor paired exchange, and urgent status and highly sensitized patients. Canadian Blood Services was also given the responsibility to develop a strategic plan and system design for a national integrated OTDT system.

Stem cells (cord blood, bone marrow and peripheral blood stem cells) were not included in the above mandate, as much of the national structure and integration already exists. There is a national system for the recruitment of bone marrow and peripheral stem cells donors, managed by Canadian Blood Services' OneMatch Stem Cell and Marrow Network, and coordinated within Québec by Héma-Québec. Canadian Blood Services also coordinates the searching, matching and importation of cord blood for Canadian patients. As well, in response to a request by the Provincial/Territorial Governments (excluding Québec), Canadian Blood Services has developed a business proposal for a national public cord blood bank, which is currently under review.

In spite of the difference organizations involved in stem cells and organs and tissues, there are many similar activities, especially in donor recruitment, screening, testing and consent. Therefore, in the establishment of national, integrated OTDT system, it is appropriate to ensure there is harmonization with not only the stem cell systems currently operating in Canada, but also the blood systems. To that end, this document provides background on stem cells and explains the similarities, differences and interactions between the blood, stem cell, organ, and tissue systems in Canada.

Stem Cell Basics

What are Stem Cells?

Stem cells are a primitive type of cell found in all animals and humans that have the potential to differentiate into other types of cell with more specialized function. There are two main types of stem cells:

Embryonic Stem Cells:

Because embryonic stem cells, found in human embryos, can differentiate into any type of cell, they possess enormous potential for development of cell therapies that could treat diseases like Parkinsons or diabetes. They have also been successfully used to develop animal clones. Currently, embryonic stem cells are obtained from excess embryos from in vitro fertilization clinics. Because of the source of these cells and their potential uses, there is much controversy and debate about the ethics of embryonic stem cell research.

Adult Stem Cells:

Adult stem cells are found in the body and serve as a repair system, replacing cells and tissues that degenerate over the life span of the organism. Adult stem cells typically generate the types of the tissue in which they reside. For example, hematopoietic stem cells in the bone marrow give rise to the many types of blood cells such as red blood cells, white blood cells, and platelets.

Stem Cell Transplants

Today, transplantation using hematopoietic stem cells is one of the standard therapies for a variety of diseases, including:

- cancers of the bone marrow, such as leukemia or lymphoma,
- inherited diseases, such as sickle cell anemia and Hurler's syndrome,
- bone marrow failure, such as aplastic anemia.

Depending on the type of disease, the stem cells can be taken from the patient and frozen for their own use (**autologous transplant**) or stem cells can be collected from another person (**allogeneic transplant**). Allogeneic stem cells can come from a family member, usually a sibling (**related donor**), or they can come from someone outside the family (**unrelated donor**).

Before transplantation, the patient receives high dose treatments of chemotherapy and/or radiotherapy. This destroys the patient's cancerous or defective cells, as well as the patient's normal stem cells. The patient is then transfused intravenously with the previously collected stem cells. The donor stem cells migrate to the bone marrow and, after 2-4 weeks, hopefully begin producing normal blood cells.

Rates of success for allogeneic stem cell transplant vary, depending on the type of underlying disease. Major causes of mortality include severe infections, graft-versus-host disease, and recurrence of the initial disease. Patients are very vulnerable from the time their own cells are destroyed to the time the

new blood cells are produced. During this time, they must be given antibiotics and immunosuppressive drugs, and must also be supported with blood transfusions until their new stem cells are functioning properly. However, for most of these patients, transplant is their only option for survival.

Graft versus Host Disease and HLA Typing

One of the more serious complications of a stem cell transplant is **graft-versus-host disease (GVHD)**. The body's immune system, which involves the hematopoietic stem cells, uses markers called **human leukocyte antigens (HLA)** to recognize which cells belong to an individual and which do not. The HLA system is extremely complex, with hundreds of thousands of possible antigen combinations.

In GVHD, the donor's stem cells, which now have become the recipient's new system, do not recognize the HLA antigens on the patient's cells, and will attack cells and tissues in the body. To minimize the risk of graft-vs-host disease, the donor and recipient are matched through HLA typing. The closer the HLA match, the more successful the transplant will be, and the less chance of GVHD. The severity of GVHD can vary; however, serious cases of GVHD can result in death. All transplant patients who receive stem cells from an unrelated donor remain on immunosuppressants for the rest of their lives to prevent and treat GVHD.

Sources of Stem Cells

There are three sources of hemopoietic stems cells that are used:

Bone Marrow (BM):

Stem cells are collected from a large bone of the donor, typically the pelvis. This is performed under general anesthesia or an epidural, because of the hundreds of needle insertions that are required to obtain sufficient material.

Peripheral Blood Stem Cells (PBSC):

Until recently, bone marrow was the most common source of stem cells for transplantation. Now peripheral blood stem cells (PBSC) are used more often. PBSC refers to stem cells that circulate in the blood. In an adult or child, there are too few of these cells to provide a useful quantity for transplant purposes. However, donors are given a drug, granulocyte colony stimulating factor (G-CSF), which increases the number of stem cells in the blood. The donor receives an injection of G-CSF every day for four or five days. The stem cells are then collected using a procedure called apheresis.

Umbilical Cord Blood (UCB):

Stem cells can also be obtained from the blood of the umbilical cord and placenta immediately after delivery of a baby. This blood contains a much higher concentration of stem cells than the blood of a child or adult donor. In addition, umbilical cord stem cells possess different characteristics from bone marrow and PBSC stem cells, that make them particularly attractive for stem cell transplantation. Because the volume of blood that can be collected from the umbilical cord is small, cord blood was initially used only in pediatric patients. It is now

considered standard therapy for pediatric unrelated transplants. In adult patients, recent successes with the use of two or more cord blood units for one patient make this a promising stem cell source for other adult patients as well.

Comparison of Different Stem Cell Types

	Bone Marrow	Peripheral Blood Stem Cells	Cord Blood
HLA Matching Requirements	Strict, at least 5 out of 6 HLA antigens must match	Strict, at least 5 out of 6 HLA antigens must match	More permissive, can use a unit with only 4 antigens matching
Risks to Donor	Surgery required for collection, general anesthesia, back pain	Collected by apheresis, bone pain, muscle pain, fatigue (from G-CSF)	No risk to donor, stem cells collected from umbilical cord/placenta after delivery of baby
Cell Dose Collected	Sufficient dose for adult	Highest number of cells obtained	Smallest number of cells obtained, usually only sufficient for pediatric patient or small adults
Risks to Recipient	Donor tested for infectious diseases prior to collection of stem cells, no risk of transplanting a genetic disease	Donor tested for infectious diseases prior to collection of stem cells, no risk of transplanting a genetic disease	Lower potential for transmission of infectious diseases; however, small risk that a genetic disease can be given with the transplant
Incidence of Graft-vs-Host Disease	High	High	Lower
Risk of Infection After Transplantation	High, approx. 3 - 4 weeks before cells engraft and start producing white cells	High, approx. 2 weeks before cells engraft and start producing white cells	Highest, longest time to engraftment (~8 weeks)
Shelf-Life of Stem Cell	Usually used fresh	Usually used fresh	Can be frozen for 20+ years
Availability	Weeks to months (need to locate and test donor, and collect cells)	Weeks to months (need to locate and test donor, and collect cells)	Less than 2 weeks (cells are already collected and stored)

Stem Cell Registries

Since HLA groups are inherited, the most likely place to find a close HLA match is within the patient's own family. However, only about 25 - 30% of patients have an HLA-identical sibling. For other patients, there are many stem cell registries worldwide that assist in finding a compatible donor. These registries maintain HLA information of potential volunteer donors. If there is a HLA match, and the donor can be found and is still interested in donating, a blood sample is taken for confirmatory typing and infectious disease testing. If the donor is confirmed as a match and both the patient and donor agree to proceed, the bone marrow is harvested or the PBSCs are collected by apheresis and transfused into the patient.

Notwithstanding their success, unrelated stem cell registries are often not able to find compatible donors for patients in need. Several factors contribute to this:

- The probability of finding a match is highly dependent on the patient and donor being from the same ethnic group. Most registries are located in Western countries and are composed of predominantly Caucasian donors. Therefore, non-Caucasians have greater difficulties in finding a match. As well, certain ethnic groups, e.g. African Americans, have a wider variability of HLA antigens and have more difficulty finding a match.
- People who are of mixed ancestry may have unique or rare HLA types and will be unable to find matches, regardless of the number of donors on the registries.
- Many patients are severely ill, and are unable to survive long enough to obtain bone marrow cells from a donor. It can take up to 4 months from the start of a search to the actual transplant.
- In many cases, the identified donor is no longer available: the donor may not be able to be found or is deceased, they may have changed their mind about donating, or they may have had changes to their physical health that make them no longer eligible.

Cord Blood Banks

As a result of the limitations with donor registries, cord blood banks have been developed to provide an alternative source of stem cells to patients. Blood is collected from the umbilical cord/placenta after delivery and is processed and stored in liquid nitrogen. If testing is acceptable, the HLA results are listed on a searchable registry. The unit can be quickly made available if a match is found. Because of the advantages of more immediate access and more lenient matching, cord blood stem cell use has increased exponentially in recent years, especially for pediatric patients.

Stem cell registries and cord blood banks provide complementary services. A physician will order a search of all types of registries to find the best match for the patient, in order to ensure the highest probability of a successful transplant.

Canadian Registries and Cord Blood Banks

Donor Registries

Canadian Blood Services operates the OneMatch Stem Cell and Marrow Network for all provinces and territories, except Quebec. OneMatch recruits registrants, coordinates testing and HLA typing, coordinates the actual donation and provides post donation follow up for Canadian donors. (Hema-Quebec provides similar services for the province of Quebec.) OneMatch also operates the national donor registry for the entire country, including Quebec. It initiates searches for all Canadian patients through its own registry (the 9th largest in the world) as well as through international registries. Through its affiliation with Bone Marrow Donors Worldwide, Canadians have access to donors and cord blood in 59 registries and 40 cord blood banks throughout the world, and international patients have access to Canadian donors.

Cord Blood Banks

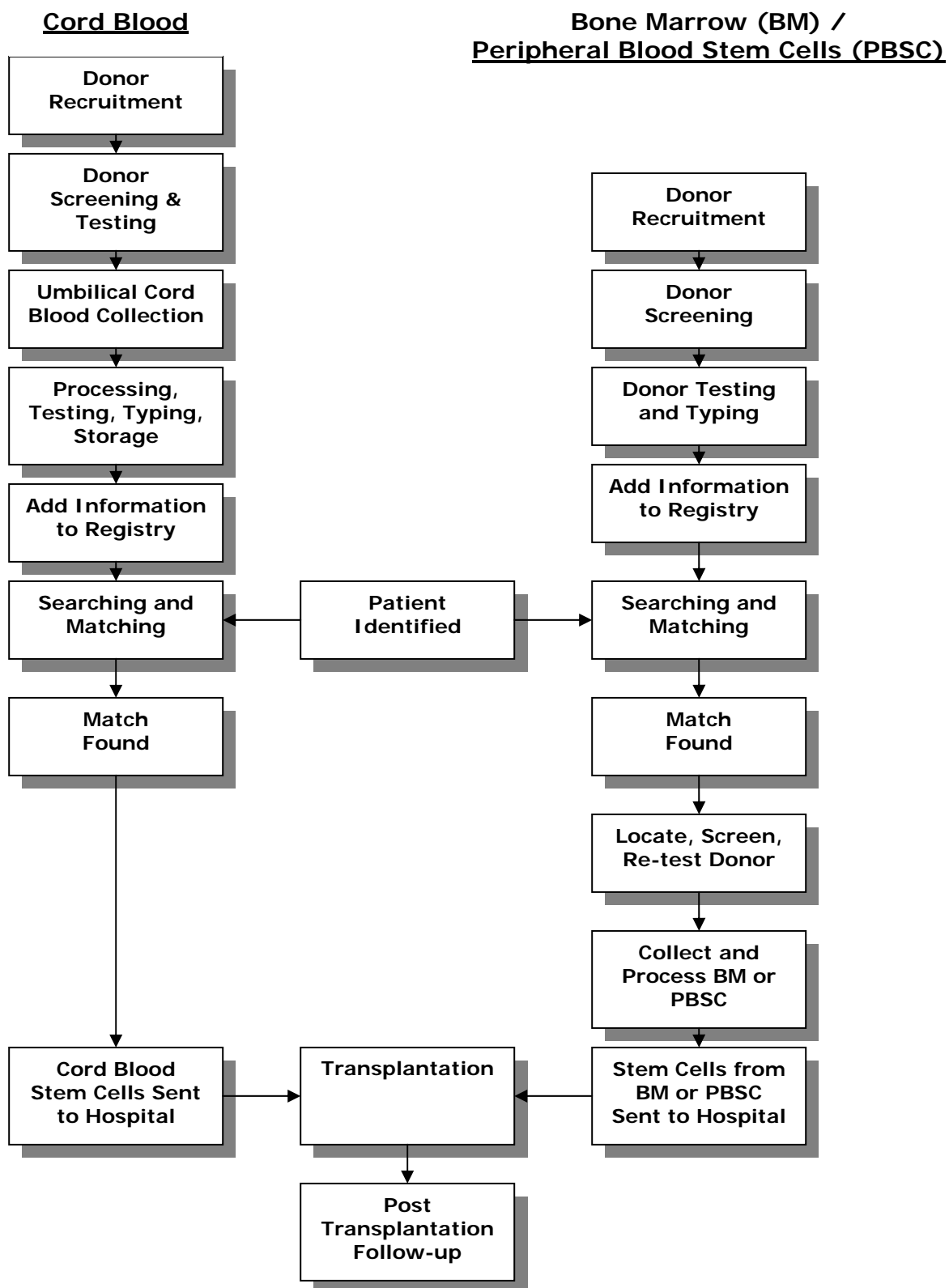
There are currently three public cord blood banks operating in Canada:

- **Héma-Québec's** cord blood bank, located in Montreal, currently houses approximately 400 cord blood units. Its inventory is not currently available through any registry, however, Hema-Quebec is currently in the process of developing a database, so that units can be searched and matched for patients.
- **Alberta Cord Blood Bank**, located in Edmonton, is a non-profit organization dedicated to the collection and storage of cord stem cells for public use. The ACBB was founded in 1996, and currently lists its inventory on the Caitlin Raymond International Registry in the United States.
- In 2004, Cells for Life, a private cord blood bank operating out of Markham, Ontario, established a publicly accessible cord bank, **The Victoria Angel Registry of Hope**, as an adjunct to their private bank. Cells for Life uses some of its profit and accepts public donations to process, test and store stem cells from Canadian donors. Its inventory is not currently accessible through any registry.
- **Canadian Blood Services** has submitted a business case to the Provincial and Territorial Deputy Ministers of Health (except Quebec) to establish a national public cord blood for Canada. The proposal is currently working through the approval process.

Future Potential of Stem Cells

While stem cell therapy has become established treatment for certain diseases, researchers are actively investigating new areas of cellular therapy. Clinical trials are underway to examine the use of stem cells for treatment of multiple sclerosis and other autoimmune diseases, as well as neurological diseases such as Parkinsons disease and Huntingtons disease, or to treat spinal cord injury. Scientists have grown pancreatic beta cells, which secrete insulin, from umbilical cord stem cells, which could be used to treat diabetes. Clinical trials are underway to examine myocardial regeneration with stem cells in patients after acute myocardial infarction or in congestive heart failure. It remains to be seen whether the promising results from current research translate into safe and effective therapies.

Stem Cell Process Flow



Comparison of Blood, Stem Cells, Tissues and Organs Processes

Donor Recruitment and Registration

- All use marketing and recruitment campaigns to build public awareness and recruit donors/registrants.
 - Blood and cord blood donors register at the time they wish to / are able to donate.
 - Bone marrow (BM), peripheral stem cell (PBSC), tissue and organ donors indicate their intent to donate if they should have the opportunity, by listing their names on registries, where available.

Informed Consent

- All donations require similar informed consent.
 - Consent for living donor (blood, stem cells, and living organ and tissue donors) is given by the donor.
 - Consent for deceased donor generally is given by the family, though previous consent by the donor is considered legally binding.

Donor Screening and Testing

- All donations require a health screening assessment, which includes review of potential high risk behaviours. Similar questions are used, though there are some differences in questions based on donation type.
- All donations require similar transmissible disease testing, though there are variations in some tests and methodologies, based on donation type.

Collection and Recovery

- Methods for collection varies significantly:
 - Collection by needle (Blood, Cord Blood, Bone Marrow)
 - Apheresis (Blood, PBSC)
 - Surgical removal (tissues, organs)

Processing

- Processing varies significantly by product type:
 - Separation into components (Blood, PBSC, cord blood)
 - Minimal manipulation and sterilization (some tissue products, e.g. corneas)
 - Freezing (cord blood, some blood and tissue products)
 - Extensive processing, e.g. plasma protein products and demineralized bone products
- All donations must follow regulations for proper packaging and labeling.

Storage

- Organs must be used immediately and cannot be stored.
- Other products can be stored for variable lengths of time, e.g. cornea can be stored for several days, while frozen stem cells, blood and tissue products can be stored as long as 20 years.

Matching and Allocation

- Matching requirements vary:
 - Stem cells must be HLA matched as closely as possible for successful transplantation.
 - Blood products are matched based on ABO and Rh typing. Sensitized patient (to either other blood antigens or HLA antigens) receive closely matched blood products.
 - Tissue products are generally not matched for either ABO/Rh or HLA.
 - Organs are initially matched by ABO/Rh. Kidney patients are also HLA matched.

Transfusion/ Transplantation

- Blood and stem cells are transfused by needle into patients.
- Tissues and organs are surgically implanted.

Regulations

- Cells, tissues, and organs (including assisted reproductive tissues) are regulated under the Food and Drug Act, through the *Safety of Human Cells, Tissues, and Organs for Transplantation Regulations*
- Dura mater and heart valves are regulated as medical devices by Health Canada's Therapeutic Products Directorate and are subject to the *Medical Devices Regulations* under the *Food and Drugs Act*.
- Blood and blood products are regulated by Health Canada's Biologics and Genetic Therapies Directorate and are subject to the Health Products and Food Branch Inspectorate's *Good Manufacturing Practices Guidelines (Schedule D Drugs, Part 1 Biological Drugs* for fractionated blood products, and *Schedule D Drugs, Part 2, Human Blood and Blood Components)* and *Annex to GMP Guidelines*, under the *Food and Drugs Act*.

Responsibilities for the Blood, Stem Cells, Tissues and Organs Supply Chains in Canada

	BLOOD	STEM CELLS		ORGANS	TISSUES
		Proposed Cord Blood Bank*	BM and PBSC		
Donor Recruitment	CBS	CBS** & Hospitals	CBS**	Hospital programs, Organ Procurement Organizations (OPO), NGOs (i.e. Kidney Foundation)	Hospital programs, Organ Procurement Organizations, Tissue Banks
Donor Registries	CBS	CBS	CBS	Donor intent/consent captured by registries, donor cards, driver's licenses (varies provincially)	
Donor Referral	-	-	-	Donor identified in hospitals by ICU, ER staff and referred to OPOs	Donor identified by ICU, ER staff, medical examiners, funeral directors and referred to OPOs or tissue bank
Informed Consent	Obtained from donor by CBS	Obtained from mother by CBS	Obtained from donor by CBS and collection hospitals	Obtained from donor (living donations) or family (deceased donations) by OPO or hospital staff	Obtained from donor (living donations) or family (deceased donations) by OPO, hospital or tissue bank staff
Donor Care Throughout Donation Process	CBS	Hospital	CBS and hospital	ICU, ER staff clinically manage donor to ensure optimal organ donation	-
Donor Screening	CBS	CBS	CBS and collection hospitals	Screening by OPO or hospital staff	Screening by OPO, tissue bank or hospital staff
Donor Testing	CBS	CBS	CBS and transplant hospitals	Provincial or hospital labs	Provincial, hospital or private labs
Collection / Recovery	At CBS blood donor clinics	CBS or hospital staff	Collection hospital	At hospital by recovery team	At hospitals or tissue banks by tissue bank staff
Processing	CBS; Plasma fractionated by third-party fractionators	CBS	Collection hospital	-	Processed by Canadian and US tissue banks
Matching and Allocation	Hospital blood banks	Coordinated through CBS OneMatch program		Organ matching managed by transplant programs and OPOs (varies provincially and by organ type)	No matching required
Storage and Distribution	Products stored and distributed by CBS	Cord blood to be stored and distributed by CBS	CBS (logistics) and hospitals	Organs are sent directly to transplant hospitals for specific patients	Tissue banks and distributors for imported tissue products
Transfusion/ Transplantation	Hospitals	Transplant hospitals	Transplant hospitals	Transplant hospitals	Transplant hospitals or in dental surgeons offices

* Refers to Canadian Blood Services' proposal for a national public cord blood bank, which is currently working through the approval process with the provincial deputy ministers of health and their representatives

** Canadian Blood Service activities for stem cell managed under its OneMatch Stem Cell and Marrow Network