

# Cancer Association of South Africa (CANSA)



Research • Educate • Support

## Fact Sheet on Stem Cells and Stem Cell Transplant

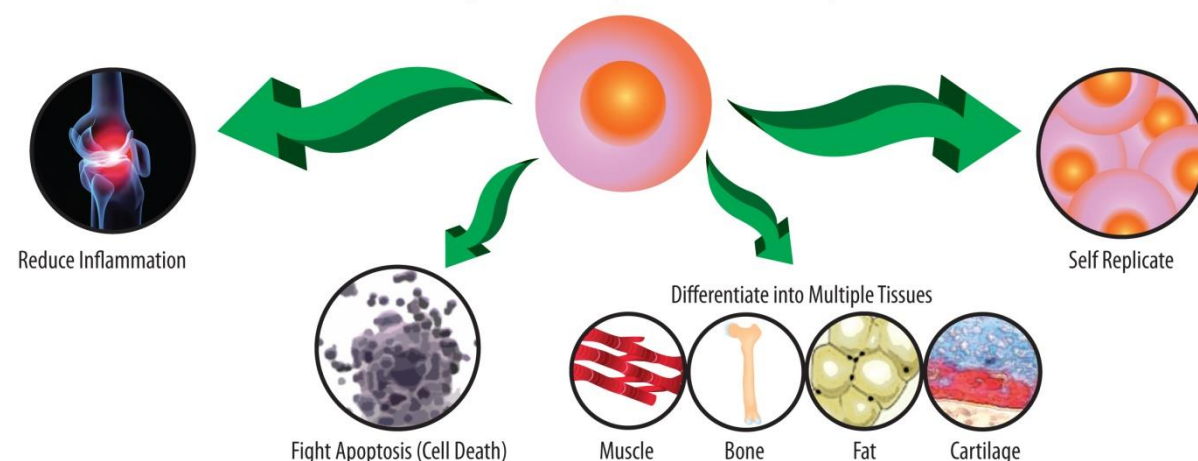
### Introduction

Stem cells are undifferentiated biological cells that can differentiate into specialised cells. They divide through mitosis, a type of cell division that results in two daughter cells each having the same number and kind of chromosomes as the parent nucleus, typical of ordinary tissue growth to produce more stem cells.

In mammals, there are two broad types of stem cells, namely: embryonic stem cells, which are isolated from the inner cell mass or blastocysts (a thin-walled hollow structure in early embryonic development that contains a cluster of cells called the inner cell mass from which the embryo arises), and adult stem cells, which are found in various tissues. In adult organisms, stem cells and progenitor cells (a biological cell that, like a stem cell, has a tendency to differentiate into a specific type of cell, but is already more specific than a stem cell and is pushed to differentiate into its 'target' cell) act as a repair system for the body, replenishing adult tissues.

### What is a Stem Cell?

A mesenchymal stem cell is a primitive cell with the ability to:



[Picture Credit: Stem Cell]

In a developing embryo, stem cells can differentiate into all the specialised cells - ectoderm, endoderm and mesoderm but also maintain the normal turnover of regenerative organs, such as blood, skin, or intestinal tissues.

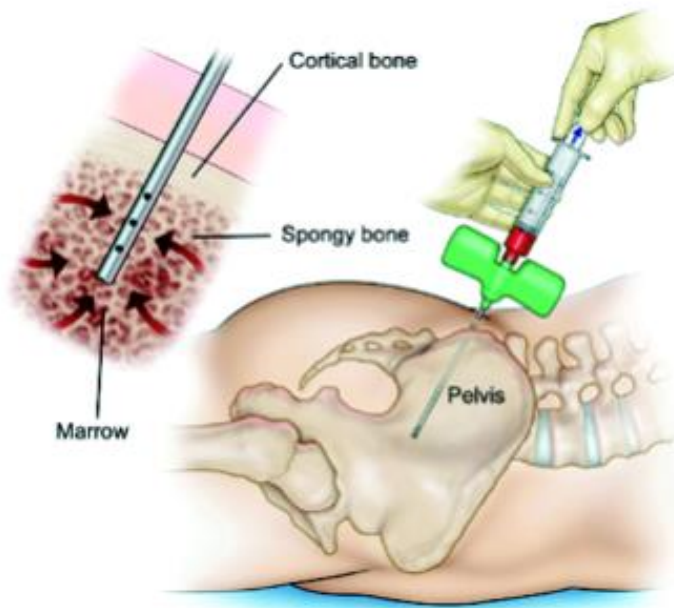
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There are several known accessible sources of autologous (a patient's own blood-forming stem cells) adult stem cells in humans:



[Picture Credit: Stem Cell Harvest]

- Bone marrow, which requires extraction by *harvesting*, that is, drilling into bone (typically the femur (thigh bone) or iliac crest (pelvic bone)).
- Adipose tissue (lipid cells), which requires extraction by liposuction.
- Blood, which requires extraction through apheresis, wherein blood is drawn from the donor (similar to a blood donation), and passed through a machine that extracts the stem cells and returns other portions of the blood to the donor.
- Stem cells can also be taken from umbilical cord blood just after birth.

Of all stem cell types, autologous harvesting involves the least risk. By definition, autologous cells are obtained from one's own body, just as one may bank his or her own blood for elective surgical procedures.

### Stem Cells and Their Importance

Stem cells have the remarkable potential to develop into many different cell types in the body during early life and growth. In addition, in many tissues they serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person is still alive. When a stem cell divides, each new cell division has the potential either to remain a stem cell or become another type of cell with a more specialised function, such as a muscle cell, a red blood cell, or a brain cell.

Stem cells are distinguished from other cell types by two important characteristics. First, they are unspecialised cells capable of renewing themselves through cell division, sometimes after long periods of inactivity. Second, under certain physiologic or experimental conditions, they can be induced to become tissue- or organ-specific cells with special functions. In some organs, such as the gut and bone marrow, stem cells regularly divide to repair and replace worn out or damaged tissues. In other organs, however, such as the pancreas and the heart, stem cells only divide under special conditions.

Stem cells are important for living organisms for many reasons. In the 3- to 5-day-old embryo, called a blastocyst, the inner cells give rise to the entire body of the organism, including all of the many specialised cell types and organs such as the heart, lungs, skin, sperm, eggs and other tissues. In

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some adult tissues, such as bone marrow, muscle, and brain, discrete populations of adult stem cells generate replacements for cells that are lost through normal wear and tear, injury, or disease. Given their unique regenerative abilities, stem cells offer new potentials for treating diseases such as diabetes, heart disease, and various cancers.

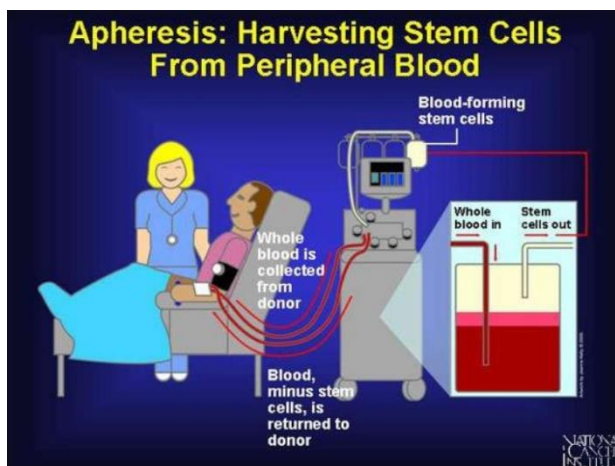
### Stem Cell Harvesting

In autologous transplantation, physicians usually collect, or “harvest,” stem cells that circulate in the bloodstream, called peripheral blood stem cells (PBSCs).

Autologous transplantation is commonly used in treatment of multiple myeloma and some forms of lymphoma.

Peripheral blood stem cell harvesting is similar to giving blood and easier than taking cells from a person’s bone marrow, which is sometimes done for allogeneic transplants. It can take place outside of an operating room and does not require general anaesthesia.

A few days before the blood collection, the patient will receive a medication called G-CSF (filgrastim), which forces the stem cells to leave the bone marrow and move into the circulating blood. This may cause flu-like symptoms in the days preceding and following stem cell harvest. The patient may also experience aches and pain from the medication.



Stem cells are collected in a blood donor room using an apheresis or leukopheresis machine. Over the course of one to five days, blood is withdrawn from a vein and circulated through the machine, which collects the stem cells; the other components of the blood are then returned to the patient.

[Picture Credit: Apheresis]

Most patients experience no side effects from harvesting and can go back to their regular activities. The stem cells are cryopreserved (frozen) until they are given to the patient.

**Mohammadi, S., Jalili, M., Malek Mohammadi, A., Nikbahht, M., Aminian, P., Bagherian, M., Mousavi, S.A. & Heshmati, F. 2020.**

“Daily CD34+ cells enumeration as a success indicator of stem cell pheresis procedure using flow cytometry is costly, lengthy, and labor-intensive. Thus, finding a simpler method to achieve the optimum time for harvesting the minimum required stem cells for transplantation could be helpful. The aim of this study was to evaluate the predictive value of reticulocytes fractions and their sensesity and specificity in guiding CD34+ cell harvesting by G-CSF mobilization strategy. In this study, 49 candidates for autologous peripheral blood stem cell transplantation were enrolled. Before leukapheresis, the immature reticulocytes fraction (IRF) and CD34+ cell count were measured. Moreover, patients were evaluated for leukapheresis outcomes in two MNC and cMNC groups. Here we demonstrated that IRF, LFR, and MFR with the associated criterion of >17.3, ≤82.5, and >15.9,

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respectively, earned 100 % specificity and 47.2 %, 47.22 %, and 41.46 % sensitivity to predict the minimum required CD34+ cell count. Furthermore, IRF-V (Value) and MFR-V with the associated criterion of >0.77 and >0.55, respectively, earned 58.33 %, 66.67 % sensitivity and 84.62 %, 69.23 % of specificity, separately. As only MFR-V was able to predict the platelet engraftment (P-value = 0.014), none of the other above mentioned factors were not able to predict the neutrophil engraftment. Likewise, it was shown that patients who underwent MNC leukapheresis had a statistically significantly higher total WBC, harvested CD34+ cells, MNCs/ kg, and lower apheresis durations (P-values<0.05). Taken together, using IRF and its maturity stages seems to be a compelling predictor of minimal required CD34+ cells in autologous peripheral blood stem cell transplantation.”

**Rajabzadeh, N., Fathi, E. & Farhzadi, R. 2019.**

“Recent developments in the stem cell biology provided new hopes in treatment of diseases and disorders that yet cannot be treated. Stem cells have the potential to differentiate into various cell types in the body during age. These provide new cells for the body as it grows, and replace specialized cells that are damaged. Since mesenchymal stem cells (MSCs) can be easily harvested from the adipose tissue and can also be cultured and expanded in vitro they have become a good target for tissue regeneration. These cells have been widespread used for cell transplantation in animals and also for clinical trials in humans.”

### **How Donor Stem Cells are Matched**

One can also receive stem cells from another person. These are donor stem cells. They are collected from the donor as described above.

If one is going to receive donated stem cells they need to closely match one’s own stem cells. A brother or sister is most likely to be a close match. Sometimes, if one does not have a brother or sister (a sibling donor) who is a match, one can have stem cells from a donor who is not related but whose stem cells are similar to one’s own. This is called a matched unrelated donor (MUD) transplant.

First, laboratory staff check the surface of one’s blood cells and the donor blood cells for certain proteins. The proteins are called HLA markers or histocompatibility antigens. Everyone has their own set of proteins. The cells in the blood samples are compared to see if the HLA markers are the same or very similar. Usually 10 HLA markers are checked. The results of the test informs the doctor how good the HLA match is. Members of one’s close family are most likely to have similar proteins to one’s own.

One can have a transplant without a perfect match. This is known as a mismatch. If one has a mismatched transplant, one will be more likely to have a reaction after the transplant called graft versus host disease (GVHD).

In some cases, the doctor may consider a half matched transplant (haplo identical transplant). With this, the donor is at least a 50% match with the recipient. These transplants are generally between brothers and sisters or a parent and their child.

**Fürst, D., Neuchel, C., Tsamadou, C., Schrezenmeier, H. & Mytilineous, J. 2019.**

“Unrelated hematopoietic stem cell transplantation (HSCT) has evolved from an experimental protocol to a potentially curative first-line treatment in certain disease instances. Factors enabling this transformation were the optimization of treatment protocols and supportive care as well as the availability of a large number of donors worldwide along with the higher quality and reliability of HLA typing. The main criterion for donor selection is HLA compatibility. In this review we discuss the current clinical evidence of HLA matching in unrelated HSCT. In this context, we address methodical aspects of transplantation immunobiology research and discuss the impact of locus and resolution of HLA differences. Furthermore, we address special constellations such as unidirectional mismatches or the presence of nonexpressed alleles as well as HLA alloimmunization and describe the perspective for HLA typing and matching strategies in the future, given the implementation of novel complete or near-complete gene typing approaches using next-generation sequencing short read technology, which are now entering the standard of clinical care.”

### **Stem Cell Transplant**

Stem cell transplant (also called peripheral blood stem cell transplant) is a treatment to try to cure some types of cancer, such as leukaemia, lymphoma and myeloma. Patients receive very high doses of chemotherapy, sometimes with whole body radiation. This has a good chance of killing the cancer cells but also kills the stem cells in the bone marrow.

Patients are given injections of growth factors before, and sometimes after, the stem cell transplant.

Infusing the stem cells usually takes several hours. The patient will be checked frequently for signs of fever, chills, hives, a drop in blood pressure or shortness of breath.

**Kongtim, P. & Ciurea, S.O. 2019.**

“Recent advances in haploidentical stem cell transplantation have enabled the use of human leukocyte antigen-half matched related donors for allogeneic stem cell transplantation and helped overcome one of the most important limitations in transplantation, which is donor availability, especially for the non-Caucasian population and mixed race individuals, extending allogeneic stem cell transplant for almost all patients in need. As many multiple potential related donors may now be available, it is increasingly clear that not all of these donors can provide equivalent transplant outcomes. Here we review the current available evidence of donor characteristics known to be associated with transplant outcomes for different types of haploidentical transplants using unmanipulated grafts (with post-transplant cyclophosphamide-based graft-vs-host prophylaxis and G-CSF and anti-thymocyte globulin approach) as well as modified grafts (with either selective or complete T-cell depletion). While various platforms use haploidentical donors, graft manipulation and approach to prevent graft-vs-host post-transplant may impact on donor selection and transplant outcomes.”

### **Types of Stem Cell Transplant**

If one is a candidate for a stem cell transplant, one's doctor will usually recommend one of three types of transplant:

- Autologous transplant - the stem cells come from one's own body.

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- Allogeneic transplant - the stem cells are from a healthy person (the donor).
- Reduced-intensity stem cell transplant - like allogeneic transplant, the stem cells are from a healthy person (the donor), but the chemotherapy given is less intensive.

**Khaddour, K., Hana, C.K. & Mewawalla, P. 2020.**

“Bone marrow transplant (hematopoietic stem cell transplant) (HSCT) involves the administration of healthy hematopoietic stem cells in patients with dysfunctional or depleted bone marrow. This helps to augment bone marrow function and allows, depending on the disease being treated, to either destroy tumor cells with malignancy or to generate functional cells that can replace the dysfunctional ones in cases like immune deficiency syndromes, hemoglobinopathies, and other diseases.

“**History and Evolution** Hematopoietic stem cell transplantation (HSCT) was first explored in humans in the 1950s and was based on observational studies in mice models which showed that infusion of healthy bone marrow components into a myelosuppressed bone marrow could induce recovery of its function in the recipient. These animal-based studies soon found their clinical application into humans when the first successful bone marrow transplant was performed in monozygotic twins in New York in 1957 (syngeneic transplant) in a patient with acute leukemia. As a result, the physician Dr. Thomas who performed the procedure continued his research on the development of bone marrow transplantation and later received the Nobel Prize of physiology and medicine in appreciation of his work. The first successful allogeneic bone marrow transplant was reported in Minnesota in 1968 for a pediatric patient with severe, combined immunodeficiency syndrome. Since then, allogeneic and autologous stem cell transplant has increased in the United States and worldwide. The Center for International Blood and Marrow Transplant Research (CIBMTR) reported over 8000 allogenic transplants performed in the United States in 2016 with a higher number of autologous transplants with a steady and higher increase of autologous compared to allogenic.

“**Definitions Major Histocompatibility Complex (MHC)** The group of genes on the short arm of chromosome 6 (p6) that encodes human leukocyte antigens (HLA) which are considered being highly polymorphic leading to a large difference in the resultant expressed proteins on human cells. They are divided into MHC I and MHC II

“**Human Leukocyte Antigens (HLA)** These are the proteins expressed on the cellular surface and play an important role in alloimmunity. HLA can be divided into (HLA-A, B, and C) which are encoded by class I MHC and are expressed on all cell types and present peptides derived from the cytoplasm and are recognized by CD8+ T cells. The other HLA type is classified as (HLA- DP, DQ, and DR) which are encoded by MHC II and can be found on antigen-presenting cells (APCs) and this class is recognized by CD4+ T cells.

“**Syngeneic Bone Marrow Transplantation** The donor and the recipient are identical twins. The advantages include no graft versus host disease (GVHD) and no graft failure. However, only a tiny number of transplant patients will have the ability to have an identical twin for transplantation.

“**Autologous Bone Marrow Transplantation** The bone marrow products are collected from the patient and are reinfused after purification methods. The advantages include no GVHD. The disadvantage is that the bone marrow products may contain abnormal cells that can cause relapse in the case of malignancy hence; theoretically, this method cannot be used in all cases of abnormal bone marrow diseases.

“**Allogenic Transplantation** The donor is an HLA matched family member, unrelated matched donor or mismatched family donors (haploidentical).

“**Engraftment** The process of which infused transplanted hematopoietic stem cells produce mature progeny in the peripheral circulation

“**Preparative Regimen** This is a regimen that comprises high-dose chemotherapy and/or total body irradiation (TBI) which are administered to the recipient prior to stem cell infusion to eliminate the

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largest number of malignant cells and to allow for immunosuppression in the recipient so that engraftment can occur.

### **Loss of Immunity to Conditions which Recipient was Previously Vaccinated Against**

Patients who have undergone a haematopoietic stem cell transplant (HSCT) usually lose the immunity they had acquired through vaccination. Studies have shown that the levels of antibodies to diseases that can be prevented by vaccination decrease during the first few years after a stem cell or bone marrow transplant. It is standard practice to revaccinate these patients with standard childhood vaccines, the so-called baby shots, although this should not be done without previous consultation with one's treating oncologist.

Vaccinations to be avoided – It is important that patients NOT receive the measles, mumps, and rubella (MMR) vaccine until two years post-transplant and at least one year after discontinuing immunosuppressive therapy. The same is true for other live-virus vaccines, such as BCG, oral (Sabine) polio, yellow fever, and typhoid. The Varicella-zoster (chickenpox/shingles) vaccine is currently not generally recommended, pending further research. If the benefits outweigh the risks, it may be given to help prevent chickenpox if the patient doesn't already have antibodies to the chickenpox virus.

Recommended vaccinations – it is recommended that patients receive the most common vaccinations one year after their transplant. These include: diphtheria, tetanus, Haemophilus influenzae type B, Streptococcus pneumoniae, Salk poliovirus (inactive virus) and influenza (annually).

Vaccination of family members and close contacts - it is strongly recommended that the patient's family members and close contacts be current on vaccinations to help protect the patient from exposure to infectious diseases.

### **How Stem Cell Transplants Work against Cancer**

Stem cell transplants do not usually work against cancer directly. Instead, they help one recover one's ability to produce stem cells after treatment with very high doses of radiation therapy, chemotherapy, or both.

However, in multiple myeloma and some types of leukaemia, the stem cell transplant may work against cancer directly. This happens because of an effect called graft-versus-tumour that can occur after allogeneic transplants. Graft-versus-tumour occurs when white blood cells from one's donor (the graft) attack any cancer cells that remain in one's body (the tumour) after high-dose treatments. This effect improves the success of the treatments.

### **Total Body Irradiation Before Stem Cell Transplant**

Total-body irradiation (TBI), when given as part of bone marrow transplantation (BMT), works by enhancing immune suppression and by exerting a tumoricidal effect. Total-body irradiation has continued to play a pivotal role in the conditioning regimens for BMT, which has become a common modality in the treatment of both acute and chronic leukaemias and myelodysplastic disorders, as well as relapsed Hodgkin's and non-Hodgkin's lymphomas.

Transplantation is also gaining favour in the treatment of aggressive multiple myeloma, breast cancer (autologous transplantation), neuroblastoma, Ewing's sarcoma, and relapsed testicular carcinoma. In addition, BMT has a role in benign but fatal diseases, such as refractory aplastic anaemia, some congenital deficiency disorders, and, experimentally, in some autoimmune disorders.

### **Side Effects of Total Body Irradiation Treatment (TBI)**

One will not feel any pain during the treatment, but TBI has side effects. Some occur right away or during the four days of treatment. Some occur days or weeks after treatment. And some occur months after TBI.

During the treatment, the most common side effects include:

- Headache
- Nausea and vomiting
- Diarrhoea
- Fatigue
- A skin reaction

Less common is swelling of the salivary glands. This causes pain in front of the ear and in the jaw.

During the days of treatment, one may not use any:

- Lotions.
- Creams.
- Ointment.
- Deodorants.

Some patients develop a mild reddening of the skin during the first few days of treatment. After radiation is completed, one's skin may feel dry and itchy. If one received a boost to the testes, the reaction may be more severe in the scrotal area.

There are a number of side effects one may get during the days and weeks after TBI. These also may be from the chemotherapy one has received. They include:

- Hair loss.
- Discomfort in the throat and mouth.
- Change in taste.
- Mouth sores.
- Nausea and vomiting.

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- Diarrhoea.
- Bone marrow suppression (low blood counts).
- Patients are at a high risk of infections for a while after the treatment and may be in a single room (isolation) in hospital.

These usually goes away over time.

### **A Shortage of Black Donors in South Africa**

According to the South African Bone Marrow Registry (SABMR), 60% of cancer deaths are among Black South Africans, while only 10% are registered as stem cell donors.

Each year, an estimated 3 762 new cases of blood disorders, such as leukaemia and lymphoma occur in South Africa. For most patients, the best chance of a cure is a bone marrow transplant, also termed a stem cell transplant.

“Only about 2.8% of black leukaemia patients who require a stem cell transplant and haven’t secured a match within their family, are lucky enough to find an unrelated donor match. Sadly, the remainder go without a transplant and eventually succumb to the disease. Some of them are still babies,” said Jane Ward, SABMR’s Deputy Director.

Despite the SABMR having access to the World Bone Marrow Donor Registry (WDMA) that has over 39 million registered donors, only a small percentage of them are Black.

“The lack of Black donors is a worldwide concern causing a serious under-representation of ethnic populations in the global donor pool. There are currently about 7 600 Black donors on our data base, only 1% more compared to four years ago. Finding a match is highest among donors of a patient’s own ethnic group,” added Ward.

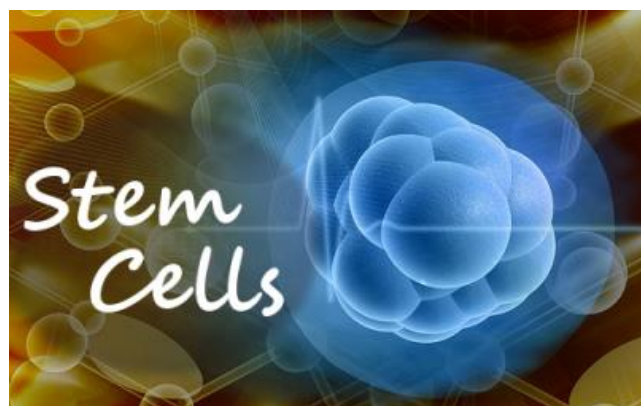
The SABMR said that the likelihood of Black people finding a successful match is only 37%, compared to patients of European descent whose chances are 72%.

### **Stem Cell Banking**

Cryo-Save South Africa offers both local and international storage options in either Pretoria or Belgium, for both cord blood and cord tissue.

[Picture Credit: Stem Cells]

Stem cells that are present in cord blood are ‘younger’ than those in bone marrow and have a significantly greater capacity to multiply and grow (proliferate) and to differentiate into different types of cells.




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Stem cells with this high proliferative potential are present in greater numbers in cord blood (more than eight times higher than in bone marrow).

Umbilical cord blood stem cells have a higher expression of certain 'adhesion' molecules which enables them to 'home-in' to where they are needed.

They have 'younger' DNA and are, therefore, able to continue to form the elements of blood for longer.

Stem cells in cord blood which belong to the immune system have not yet been exposed to outside factors (i.e. they are more immunologically 'naïve').

Blood-forming stem cells are less likely to cause complications (graft-versus-host disease) in allogeneic (donor to patient) transplants than other adult stem cells.

Increasing the number of umbilical cord blood haematopoietic stem cells prior to transplantation (stem cell 'expansion') is proving to be successful in clinical trials.

Cord tissue stem cells are able to transform into numerous types of cell including muscle, bone, cartilage and nerve cells.

Contact Details of Cryo-Save, South Africa:

**Telephone**  
+27 (0) 87 8080 170

**Facsimile**  
+27 (0) 86 219 9157



**Address**

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**Shortage of Black Donors**

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