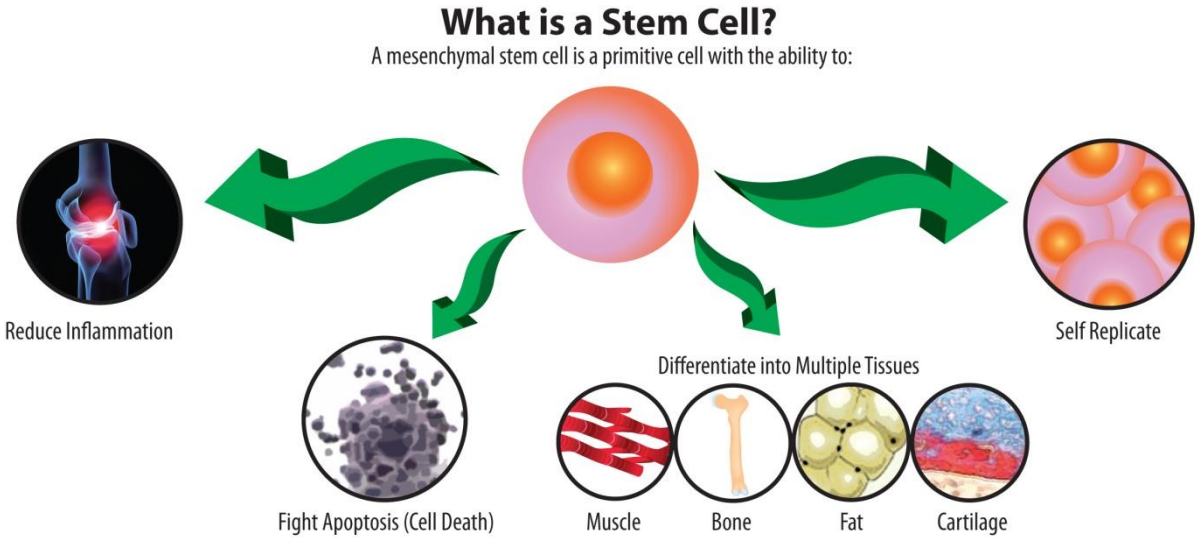
Cancer Association of South Africa (CANSA)

CANSA 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.



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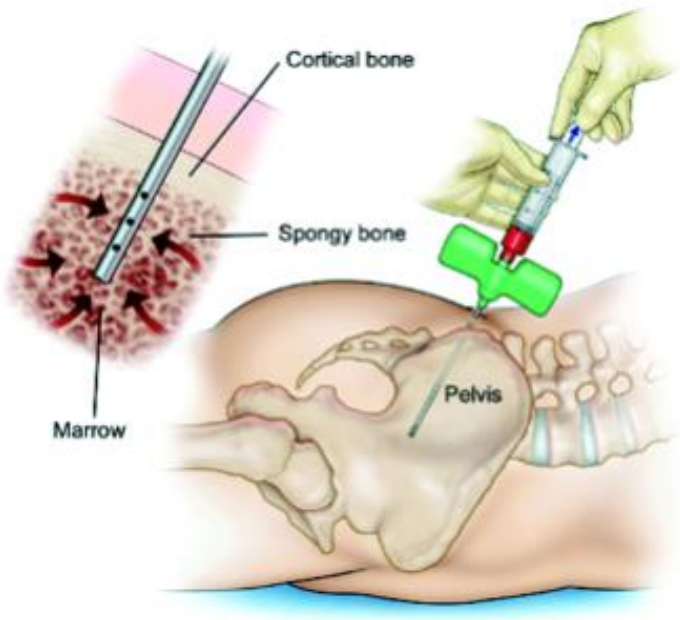
There are several known accessible sources of autologous (a patient's own blood-forming stem cells) adult stem cells in humans:



- 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.

[Picture Credit: Stem Cell Harvest]

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.

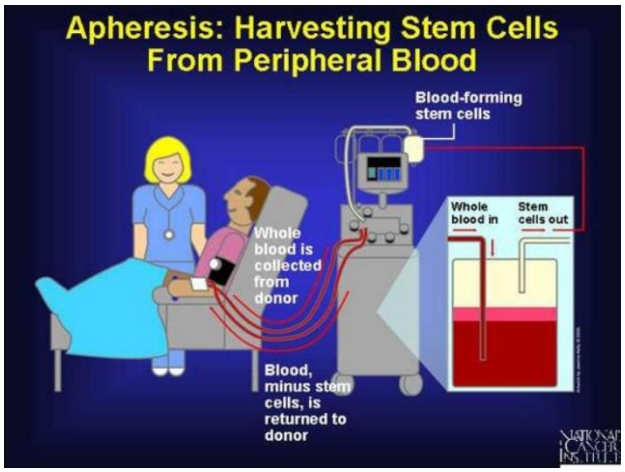
Stem cells are important for living organisms for many reasons. In the 3- to 5-day-old embryo, called a blastocyst, the inner cells give rise to the entire body of the organism, including all of the many specialised cell types and organs such as the heart, lungs, skin, sperm, eggs and other tissues.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

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.

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 a 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.

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.
- 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.

History and Evolution of Stem Cell Transplant

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 leukaemia. 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 paediatric patient with severe, combined immunodeficiency syndrome. Since then, allogeneic and autologous stem cell transplant has increased in the United States and worldwide. The Centre for International Blood and Marrow Transplant Research (CIBMTR) reported over 8 000 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 transplants.

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 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.

<u>Vaccinations to be avoided</u> – 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.

Wang, Y.H., Hsieh, C.Y., Hsiao, L.T., Lin, T.L., Liu, Y.C., Yao, M., Tan, T.D. & Ko, B.S. 2022.

"Mantle cell lymphoma (MCL) is a B-cell lymphoma featuring an aggressive course and a progressive relapsing pattern. International guidelines recommend early consolidative autologous stem cell transplant (auto-SCT) for eligible patients while reserving allogeneic SCT (allo-SCT) as therapy for refractory cases. Since data describing the implementation of transplants in the Asian population with MCL are limited, we aimed to analyze post-SCT outcomes of 99 MCL patients from the Taiwan Bone Marrow Transplant Registry database. The median age was 56 years, and 11% of the patients had blastoid variant MCL. Ninety-four patients received auto-SCT, while 13 patients received allo-SCT, eight of which received allo-SCT after failing auto-SCT. Before auto-SCT, 52% of the patients were in their first complete remission (CR1). Overall, 37 patients (39%) relapsed after auto-SCT. The median post-auto-SCT progression-free survival and overall survival (OS) were 43.6 months and not reached, respectively. Blastoid variant MCL, transplant not received in CR1, and disease progression within 12 months post-auto-SCT independently predicted inferior OS in multivariable analysis. The median post-allo-SCT OS was 74 months. Two patients (15%) died of MCL recurrence post-allo-SCT. Three patients with refractory diseases were salvaged with ibrutinib or venetoclax to allo-SCT. Treatment strategies incorporating novel agents warrant further optimization."

Cashen, A.F. & Bartlett, N.L. 2022.

The Center for International Blood and Marrow Transplant Research (CIBMTR) registry, provide a retrospective outcomes analysis of 285 patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) who underwent autologous hematopoietic cell transplantation (autoHCT) after achieving complete (CR) or partial response (PR) to their *third or higher line* of chemotherapy.

Prakash, V.S., Malik, P.S., Sahoo, R.K., Pramanik, R., Choudhary, P., Varshney, A.N. & Kumar, L. 2022.

Background: We used plerixafor in 'a risk adapted approach' for stem cell mobilization for multiple myeloma (MM) patients prior to autologous stem cell transplantation (ASCT).

Patients and methods: Between January, 2017 and December, 2019 105 consecutive patients of MM were recruited (Study Cohort). Patients received inj G-CSF 10 µg/kg in 2 divided doses for 5 days. Day 4 peripheral blood (PB) CD34+ count was used as a guide; if count was < 20 cells/µl, patients received plerixafor. For those with ≥ 20 cells/µl apheresis was commenced on day 5. We compared their outcome with 156 MM patients transplanted between 2012 and 2016 with G-CSF mobilized PB stem cells (Control Cohort). Primary end point was to collect ≥2.0 × 10^6 CD34+ cells/kg (minimal harvest). Secondary end points were: no of apheresis sessions, percentage of patients with optimal stem cell harvest (≥4.0 × 10^6 CD34+ cells/kg) and cost analysis. An intent to treat analysis was done.
Result: 96.2% of patients achieved ≥ 2.0 × 10^6 CD34+ cells/kg in the study cohort vs. 87.2% in the control cohort, P < .01. Mean apheresis sessions were 1.5 vs. 1.7 respectively, P < .014 . Optimal stem cell harvest was 29.5% vs. 16%,P = .23. Days for neutrophil engraftment (P < 0.025) and for IV antibiotics (P < .0017) were favorable for the study cohort. Incremental cost effectiveness ratio was $ 15.80/- and $ 10.56/- per 1% increase to achieve a minimal and optimal harvest.
Conclusion: Plerixafor in this risk adapted strategy resulted in successful mobilization, decreased time to engraftment and was cost effective.

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.
- 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.

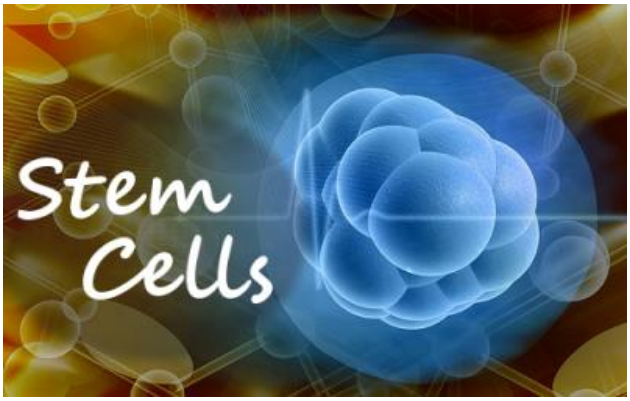
Despite the SABMR having access to the World Bone Marrow Donor Registry (WDMA) that has over 39 million registered donors, only a small percentage of them are Black.

"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.

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:

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CryoSave
The Family Stem Cell Bank

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