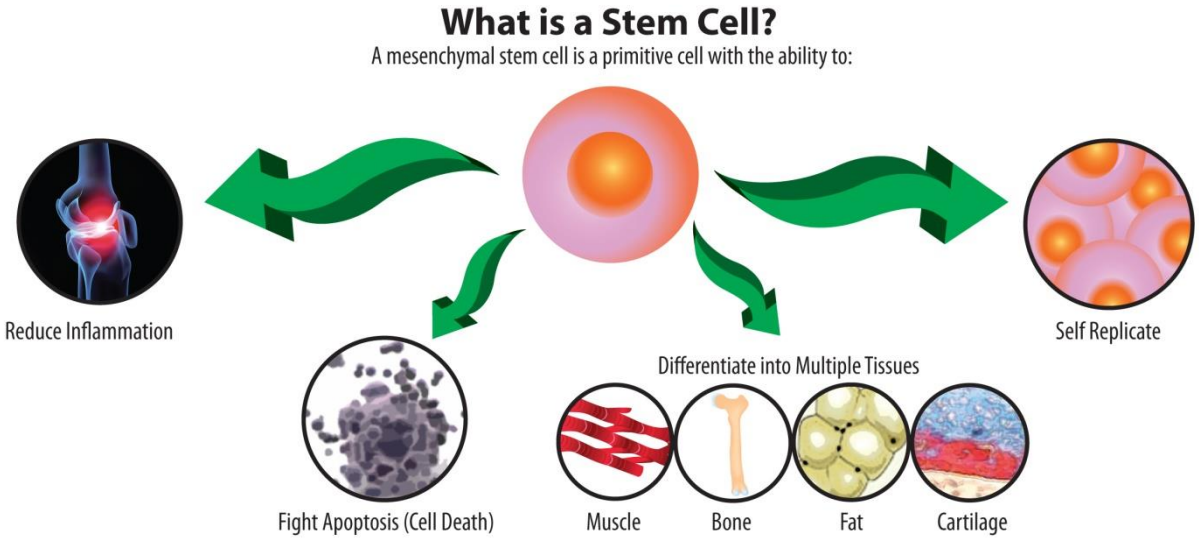
Cancer Association of South Africa (CANSA)

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 and can 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.

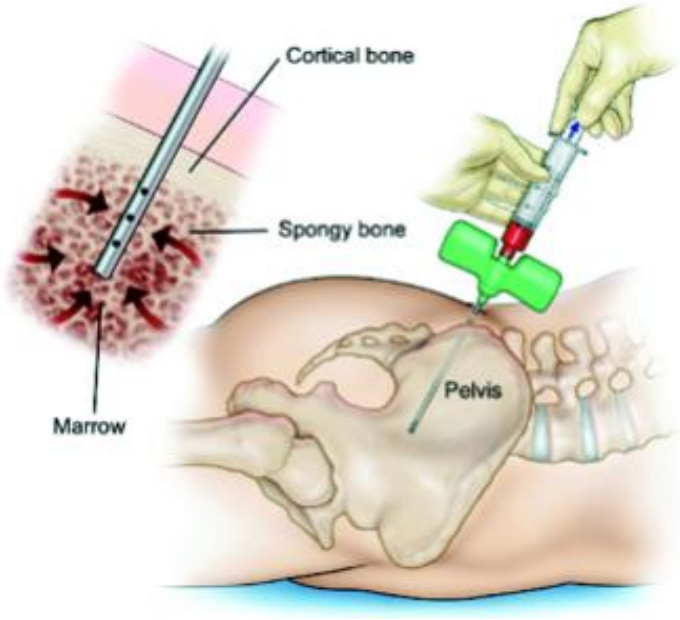


[Picture Credit: Stem Cell]

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.

Researched and Authored by Prof Michael C Herbst
[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Diagnostic Radiographer; Dip Audiometry and Noise Measurement]
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

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.
(Wikipedia; Dictionary.com; MedicineNet).

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.

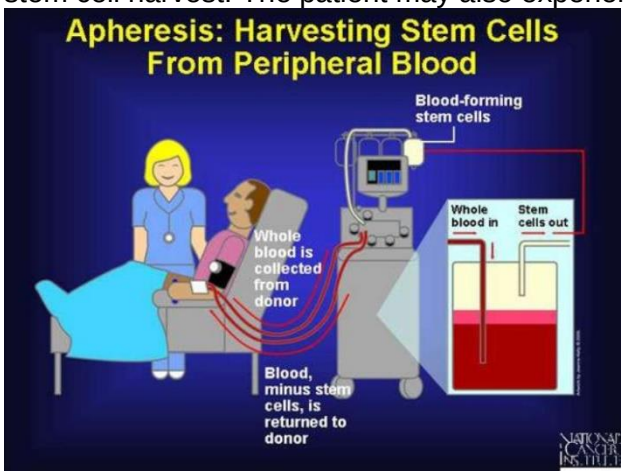
Given their unique regenerative abilities, stem cells offer new potentials for treating diseases such as diabetes, heart disease, and various cancers.
(National Institutes of Health; MedlinePlus).

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.
(Memorial Sloan Kettering cancer Center).

How Donor Stem Cells are Matched
Some people have 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. 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. Staff compare the proteins on the cells in the blood samples to see if the HLA markers are the same or very similar. Usually 10 HLA markers are checked. The results of one's blood test and the donor's test tells 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).. This means the immune cells from the donated stem cells attack some of one's body cells. GVHD typically causes skin rashes, diarrhoea and liver damage. One will receive antirejection drugs to help stop it developing. GVHD can be severe and even life threatening in some people. But mild GVHD is not always a completely bad thing. As it is an immune system reaction, GVHD can help to kill off any cancer cells that are left after one's treatment.

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. In the past these transplants have been difficult to do due to the increased risk of severe GVHD and infection. But doctors are finding new ways of improving this type of transplant and reducing the risk of GVHD.
(Cancer Research UK).

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.

Stem cell transplant means that patients can have higher doses of treatment. So there may be more chance of curing the cancer than with standard chemotherapy.

Patients are given injections of growth factors before, and sometimes after, the stem cell transplant. Growth factors are natural proteins that make the bone marrow produce blood cells. It is administered as small injections under the skin.

Sometimes patients may have low doses of a chemotherapy drug alongside the growth factor injections. The chemotherapy and growth factor injections help the bone marrow to make lots of stem cells. These stem cells then spill out of the bone marrow into the bloodstream. One may have blood tests every day to see if there are enough stem cells in the bloodstream. When there are enough stem cells, the stem cells are collected (harvested).

Growth factor injections can cause some side effects. Some people have itching around the injection site. Some people get a high temperature (fever). One may also have some pain in the bones after having had a few injections. This is because there are a lot of blood cells being made inside the bones.

Donor stem cells are transferred to patients by infusion, a procedure similar to a blood transfusion. Blood is delivered through a catheter - a thin flexible tube - into a large blood vessel, usually in the chest.

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. Recipients may experience side effects such as headache, nausea, flushing and shortness of breath from the cryopreservative used to freeze the stem cells. If so, the person will be treated and then the infusion will be continued.
(Leukemia and Lymphoma Society; Cancer Research UK).

Types of Stem Cell Transplant
If you're a candidate for a stem cell transplant, your doctor will usually recommend one of three types:

- Autologous - the stem cells come from one's own body.
- Allogeneic - the stem cells are from a healthy person (the donor).
- Reduced-intensity stem cell transplantation - like allogeneic transplant, the stem cells are from a healthy person (the donor), but the chemotherapy given is less intensive.

A fourth type of stem cell transplant, syngeneic transplant, is much less common than the other three.

Syngeneic transplantation is rare for the simple reason that it is only used on identical twins. In addition, the donor twin and the recipient twin must have identical genetic makeup and tissue type. (Leukemia and Lymphoma Society).

[Picture Credit: Stem Cell Transplants]

Loss of Immunity to Conditions which Recipient was Previously Vaccinated Against
Patients who have undergone a haematopoietic stem cell transplant (HSCT) for a haematological cancer 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. The immunities acquired by the patient prior to the transplant are generally lost. This can occur after both allogeneic and autologous transplantation. In addition, while some immunity may be transferred from a donor, this is generally limited and can't be relied upon to prevent infection. Chronic graft-versus-host disease (GVHD) increases the likelihood that immunity will be lost. Transplant patients are at a higher risk of infection until their immune systems become stronger. Vaccination can protect the transplant patient from infections such as childhood diseases, influenza and pneumococcal pneumonia.

The underlying disease, radiation therapy and chemotherapy conditioning regimens, the transplant itself, and immunosuppressive drugs given after the transplant all contribute to the loss of previously acquired immunity in patients who have undergone autologous or allogeneic HSCT.

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 – stem cell transplant patients should definitely NOT receive the smallpox vaccine because it is made from a live virus (vaccinia) and can cause vaccinia infection. It is also 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). Children less than 7 years of age should also receive the pertussis vaccine. Hepatitis A and B vaccines may be recommended for certain patients. If blood tests show that immunity has waned, additional vaccination doses may be recommended. Other vaccinations may be recommended on an individual basis by one's healthcare provider.

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. However, if a family member or other close contact receives a vaccine using a live virus, the patient may need to take additional precautions. For the first year after transplant, or while a patient is receiving immunosuppressive therapy they are at risk of contracting the disease from a person who received a live-virus vaccine within the previous few months.

In some patients, vaccination is withheld or delayed intentionally, usually due to graft-versus-host disease treatment with certain drugs, such as corticosteroids or the anti-CD20 antibody rituximab. But a minority of patients who would benefit from post-HSCT vaccines do not receive them because of breakdowns in communication among clinicians or between clinicians and patients.
(MD Anderson Cancer Center; Fred Hutch; UpToDate; Cancer Network).

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.
(National Cancer Institute).

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. The modality has been made less toxic because of new approaches to delivering TBI, such as fractionation, and partial organ shielding.

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.

Stem-cell transplantation also looks promising in the treatment of primary progressive multiple sclerosis (MS). Patients qualifying for the experimental protocols are bed-bound and likely to die of their disease within 2 years. In half a dozen or so patients who have received this therapy, disease status has substantially improved and lesions have regressed, as measured on magnetic resonance imaging (MRI). In laboratory models of an MS-like syndrome, TBI prior to transplantation decreases the likelihood of disease progression to a greater extent than does transplantation without TBI. Therefore, TBI may have an adjunctive role in this new approach.
(CancerNetwork).

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.

Medicines can decrease nausea and vomiting. These side effects are most severe during the first day of radiation. They usually begin one to two hours after the first treatment. If one

vomits, it usually becomes less frequent as the treatment proceeds. It often stops by the third day. One may also have diarrhoea during the first few treatment days.

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 will go away over time.

TBI can cause long-term side effects. They can occur months or years after transplant:

- Sterility is an expected side effect.
- Sexual function and pleasure will not be affected.
- One should talk to a doctor or nurse about any concerns.

Other long-term side effects are rare, but can occur.
They include:

- Inflammation of the sac that surrounds the heart.
- Inflammation of the lungs.
- Cataracts.
- Second malignancies or new cancers.

One should discuss these side effects with a doctor.
(Memorial Sloan Kettering Cancer Center).

Researchers Develop Novel Treatment to Prevent Graft-Versus-Host-Disease
Graft-versus-host-disease (GVHD) is the leading cause of non-relapse associated death in patients who receive stem cell transplants. In a new study published in *Science Translational*

Medicine, Moffitt Cancer Center researchers show that a novel treatment can effectively inhibit the development of GVHD in mice and maintain the infection- and tumour-fighting capabilities of the immune system.

Stem cell transplants can be used to treat patients who have certain types of cancer, such as leukaemia or lymphoma. Many patients who have stem cell transplants receive an allogeneic transplant - stem cells donated by another person. One risk associated with allogeneic stem cell transplants is GVHD during which the donated immune cells fail to recognise the patient's own tissues and organs. The symptoms of GVHD vary and can be life-threatening. Common symptoms include rash, nausea and vomiting, diarrhoea, and occasionally jaundice and liver failure.

The researchers discovered that combined inhibition of Aurora kinase A and JAK2 promotes the differentiation of potent regulatory T cells, specialised immune cells that prevent GVHD. Aurora kinase A and JAK2 also significantly reduced GVHD in mice and allowed for the development of anti-cancer immune cells. This was best demonstrated by a drug developed at Moffitt that inhibits both Aurora kinase A and JAK2 simultaneously, eliminating the need to use two different medications.

This novel prevention strategy requires further investigation because of its potential to reduce the risk of GVHD and possibly be more effective and selective than commonly used GVHD treatments currently available today.
(Science Daily).

Advantages and Disadvantages of Stem Cell Research
The advantages of stem cell research include:

1. Immense Medical Benefits - The main purpose of researching stem cells is to assess their use in the medical field. It has been shown that they can be extremely beneficial in therapeutic cloning to treat chronic illnesses. They have also been a wonderful stepping stone into the advancement of regenerative medicines.

2. A Better Knowledge of Human Growth - By studying the very foundation of human growth, stem cells, in depth, scientists have been able to gain a much better understanding of how human bodies work. This is vital for advancing medicine, medical processes, and even cures for degenerative illnesses.

3. The Key To Reversing Aging - Stem cells are the key to regenerative processes, which could possibly be age reversal. By reviving organs in one’s body that have become old or worn out, one could essentially live forever or at least greatly prolong the lives of humans.

4. Cure Development Defects Before They Happen - Stem cell research does not just benefit the people walking around the earth, but also the ones that have not been born yet. The effects of these cells on embryos could change the way that birth defects are treated. They could possibly be corrected before the child is even born, greatly improving their quality of life and chance of survival.

The disadvantages of stem cell research include:

1. High Uncertainties - One of the largest issues that people have with stem cell research is just how risky and unknown it truly is. Major advancements still need to be made and new technology must be developed before it can be used in an efficient and safe way.

2. Unknown Side Effects - Since stem cells are still in their research phase, the true long term effects of their use is not known or understood. Using them could cause new illnesses and disease to develop, or even interfere with the natural functions of the body.

3. Playing God - The moral argument is another big one when it comes to this topic. Many people believe that altering the basic structure of a human's genes is putting hands somewhere they should not be. The moral issue is the most frequently argued.

4. Perpetuates Cloning of Humans - Cloning is the process of making an exact genetic copy of a living organism. Stem cell research also aids the research into human cloning. Human cloning has been widely reviewed as a detriment to society with many negative benefits.
(The Next Galaxy).

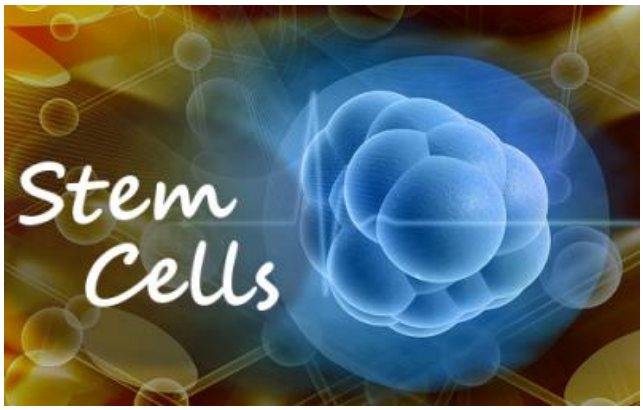
Important Facts About Stem Cell Research

- Parkinson's disease, spinal cord injuries, birth defects, damaged organs, and cancer could all be possibly treated with the use of stem cells.
- Bone marrow transplantation is the only form of stem cell research that has been proven to be effective and safe.
- Manipulating cells and their functions in a clinical setting or laboratory can hinder their normal functions and render them dangerous for use.
- Stem cells can copy themselves for an unlimited period of time.
- The reason that they have gained so much attention, is because stem cells are 'blank' cells that can be turned into almost anything that the body needs.
- Therapeutic cloning is a type of stem cell research.

(The Next Galaxy).

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:

Telephone
+27 (0) 87 8080 170

Facsmile
+27 (0) 86 219 9157

Address
Ground Floor, Acacia House, Green Hill Village Office Park, Cnr Botterklapper & Nentabos Street, The Willows, 0041, Pretoria, South Africa.
(Cryo-Save South Africa).

Medical Disclaimer
This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet.

Whilst the Cancer Association of South Africa (CANSA) has taken every precaution in compiling this Fact Sheet, neither it, nor any contributor(s) to this Fact Sheet can be held responsible for any action (or the lack thereof) taken by any person or organisation wherever they shall be based, as a result, direct or otherwise, of information contained in, or accessed through, this Fact Sheet.

Sources and References

Apheresis
http://www.slideshare.net/98567/presentation-of-stem-cell-and-bone-marrow-tranplan-tation

CancerNetwork
http://www.cancernetwork.com/review-article/total-body-irradiation-bone-marrow-transplantation
http://www.cancernetwork.com/hematologic-malignancies/vaccinations-against-infectious-diseases-hematopoietic-stem-cell-transplant-recipients

Cancer Research UK
http://www.cancerresearchuk.org/about-cancer/cancers-in-general/treatment/transplant/stem-cell-transplants

Cryo-Save South Africa
https://www.cryo-save.co.za/

Dictionary.com
http://www.dictionary.com/browse/mitosis

Fred Hutch
https://www.fredhutch.org/en/treatment/long-term-follow-up/FAQs/vaccination.html

Leukemia and Lymphoma Society
https://www.lls.org/treatment/types-of-treatment/stem-cell-transplantation

MD Anderson Cancer Center
https://www.mdanderson.org/publications/oncolog/july-2016/vaccination-after-stem-cell-transplant.html

MedicineNet
http://www.medicinenet.com/script/main/art.asp?articlekey=18258

MedlinePlus
https://medlineplus.gov/stemcells.html

Memorial Sloan Kettering Cancer Center
https://www.mskcc.org/cancer-care/treatments/cancer-treatments/blood-stem-cell-transplantation/approach/autologous-transplantation
https://www.mskcc.org/cancer-care/patient-education/total-body-irradiation

National Cancer Institute
https://www.cancer.gov/about-cancer/treatment/types/stem-cell-transplant#2

National Institutes of Health
https://stemcells.nih.gov/info/basics/4.htm

Science Daily
https://www.sciencedaily.com/releases/2017/01/170111184513.htm

Stem Cell
http://www.tsaog.com/our-specialties/joint-preservation/orthopedic-stem-cell-therapy/

Stem Cells
https://www.heatherwood.co.za/stem-cell-banking/

Stem Cell Harvest
http://cvilleortho.com/services/regenerative-therapy/

Stem Cell Transplant
http://healthlove.in/health/stem-cells/stem-cell-transplant/

UpToDate
http://www.uptodate.com/contents/immunizations-in-hematopoietic-cell-transplant-candidates-and-recipients

Wikipedia
https://en.wikipedia.org/wiki/Stem_cell
https://en.wikipedia.org/wiki/Progenitor_cell