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REVIEW ARTICLE

Clinical Indications of Hematopoietic Stem Cell Transplantation: A Clinical Review

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ABSTRACT

Hematopoietic stem cells (HSCs) are multipotent, self-renewing progenitor cells that develop from mesodermal hemangioblast cells. All differentiated blood cells from the lymphoid and myeloid lineages arise from HSCs. HSCs can be found in adult bone marrow, peripheral blood, and umbilical cord blood. Classic studies in mice describe two populations of Hematopoietic Stem Cells, Long Term and Short Term. Long term HSCs are capable of self renewal, while short term HSCs do not have this capacity. Short term HSCs, also called progenitor or precursor cells, can differentiate into all types of blood cells, which can be characterized by specific markers. Hematopoietic stem cell transplantation (HSCT) involves the intravenous infusion of autologous or allogeneic stem cells collected from bone marrow, peripheral blood, or umbilical cord blood to reestablish hematopoietic function in patients with damaged or defective bone marrow or immune systems. HSCT is used throughout this article as a general term covering transplantation of progenitor/stem cells from any source (e.g., bone marrow, peripheral blood, and cord blood). Interpretation of the results of trials of bone marrow transplantation is always complicated by the problem of patient selection. The efficacy of transplantation can be underestimated if only patients with the worst prognoses are studied, or it can be overestimated if only those with the best prognoses are studied. HSCT has led to the cure of diverse forms of cancer, bone marrow failure, hereditary metabolic disorders, and severe congenital immunodeficiency's that would otherwise have been fatal. The indications for HSCT vary according to disease categories and are influenced by factors such as cytogenetic abnormalities, response to prior therapy, patient age and performance status, disease status (remission vs. relapse), disease-specific prognostic factors, and, most importantly, availability of a suitable graft source. The aim of present article is to provide in depth knowledge about Hematopoietic stem cell transplantation (HSCT) as well as various clinical indications of HSCT.

KEYWORDS: Hematopoietic stem cells, HSCs, HSCT, Stem Cells, Stem Cell Treatments.

INTRODUCTION:

1. STEM CELLS:

Stem cells are biological cells found in all multicellular organisms, that can divide (through mitosis) and differentiate into diverse specialized cell types and can self-renew to produce more stem cells. In mammals, there are two broad types of stem cells: embryonic, which are isolated from the inner cell mass of blastocysts, and adult stem cells, which are found in various tissues. In adult organisms, stem cells and progenitor cells act as a repair system for the body, replenishing adult tissues. In a developing embryo, stem cells can differentiate into all the specialized cells (these are called pluripotent cells), but also maintain the normal turnover of regenerative organs, such as blood, skin, or intestinal tissues.

There are three accessible sources of autologous adult stem cells in humans:

1. Bone marrow, which requires extraction by *harvesting*, that is, drilling into bone (typically the femur or iliac crest),

2. Adipose tissue (lipid cells), which requires extraction by liposuction, and

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3. Blood, which requires extraction through pheresis, wherein blood is drawn from the donor (similar to a blood donation), 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. Highly plastic adult stem cells are routinely used in medical therapies, for example in bone marrow transplantation. Stem cells can now be artificially grown and transformed (differentiated) into specialized cell types with characteristics consistent with cells of various tissues such as muscles or nerves through cell culture. Embryonic cell lines and autologous embryonic stem cells generated through therapeutic cloning have also been proposed as promising candidates for future therapies **(**1**)**. Research into stem cells grew out of findings by Ernest A. McCulloch and James E. Till at the University of Toronto in the 1960s **(**2, 3**)**.

1.1 CLINICAL APPLICATIONS OF STEM CELLS AND STEM CELL TREATMENTS:

Stem cell treatments are a type of intervention strategy that introduces new adult stem cells into damaged tissue in order to treat disease or injury. Many researchers believe that stem cell treatments have the potential to change the face of human disease and alleviate suffering (4**)**. The ability of stem cells to self-renew and give rise to subsequent generations with variable degrees of differentiation capacities (5), offers significant potential for generation of tissues that can potentially replace diseased and damaged areas in the body, with minimal risk of rejection and side effects. A number of stem cell therapies exist, but most are at experimental stages or costly, with the notable exception of bone marrow transplantation. Medical researchers anticipate that adult and embryonic stem cells will soon be able to treat cancer, Type 1 diabetes mellitus, Parkinson's disease, Huntington's disease, Celiac Disease, cardiac failure, muscle damage and neurological disorders, and many others . Nevertheless, before stem cell therapeutics can be applied in the clinical setting, more research is necessary to understand stem cell behavior upon transplantation as well as the mechanisms of stem cell interaction with the diseased/injured microenvironment (6). Medical researchers believe that stem cell therapy has the potential to dramatically change the treatment of human disease. A number of adult stem cell therapies already exist, particularly bone marrow transplants that are used to treat leukemia (7). In the future, medical researchers anticipate being able to use technologies derived from stem cell research to treat a wider variety of diseases including cancer, Parkinson's disease, spinal cord injuries, Amyotrophic lateral sclerosis, multiple sclerosis, and muscle damage, amongst a number of other impairments and conditions (8). However, there still exists a great deal of social and scientific uncertainty surrounding stem cell research, which could possibly be overcome through public debate and future research, and further education of the public. One concern of treatment is the risk that transplanted stem cells could form tumors and become cancerous if cell division continues uncontrollably. Stem cells are widely studied, for their potential therapeutic use and for their inherent interest.

2. HEMATOPOIETIC STEM CELLS

Blood cells are responsible for constant maintenance and immune protection of every cell type of the body. This relentless and brutal work requires that blood cells, along with skin cells, have the greatest powers of self-renewal of any adult tissue. The stem cells that form blood and immune cells are known as hematopoietic stem cells (HSCs). They are ultimately responsible for the constant renewal of blood—the production of billions of new blood cells each day. Physicians and basic researchers have known and capitalized on this fact for more than 50 years in treating many diseases. The first evidence and definition of blood-forming stem cells came from studies of people exposed to lethal doses of radiation in 1945. Basic research soon followed. After duplicating radiation sickness in mice, scientists found they could rescue the mice from death with bone marrow transplants from healthy donor animals. In the early 1960s, Till and McCulloch began analyzing the bone marrow to find out which components were responsible for regenerating blood (9). They defined what the two hallmarks of an HSC remain: it can renew itself and it can produce cells that give rise to all the different types of blood cells. A haematopoietic stem cell is a cell isolated from the blood or bone marrow that can renew itself, can differentiate to a variety of specialized cells, can mobilize out of the bone marrow into circulating blood, and can undergo programmed cell death, called apoptosis—a process by which cells that are detrimental or unneeded self-destruct. A major thrust of basic HSC research since the 1960s has been identifying and characterizing these stem cells. Because HSCs look and behave in culture like ordinary white blood cells, this has been a difficult challenge and this makes them difficult to identify by morphology (size and shape). Even today,

scientists must rely on cell surface proteins, which serve, only roughly, as markers of white blood cells. Identifying and characterizing properties of HSCs began with studies in mice, which laid the groundwork for human studies. The challenge is formidable as about 1 in every 10,000 to 15,000 bone marrow cells is thought to be a stem cell. In the blood stream the proportion falls to 1 in 100,000 blood cells. To this end, scientists began to develop tests for proving the self-renewal and the plasticity of HSCs. The "gold standard" for proving that a cell derived from mouse bone marrow is indeed an HSC is still based on the same proof described above and used in mice many years ago. That is, the cells are injected into a mouse that has received a dose of irradiation sufficient to kill its own blood-producing cells. If the mouse recovers and all types of blood cells reappear (bearing a genetic marker from the donor animal), the transplanted cells are deemed to have included stem cells. These studies have revealed that there appear to be two kinds of HSCs. If bone marrow cells from the transplanted mouse can, in turn, be transplanted to another lethally irradiated mouse and restore its haematopoietic system over some months, they are considered to be long-term stem cells that are capable of self-renewal. Other cells from bone marrow can immediately regenerate all the different types of blood cells, but under normal circumstances cannot renew themselves over the long term, and these are referred to as short-term progenitor or precursor cells. Progenitor or precursor cells are relatively immature cells that are precursors to a fully differentiated cell of the same tissue type. They are capable of proliferating, but they have a limited capacity to differentiate into more than one cell type as HSCs do. For example, a blood progenitor cell may only be able to make a red blood cell (Figure 1.). The Haematopoietic stem cell differentiation may also be illustrated in Figure 2. The Hematopoietic Stem Cell Pathway is illustrated in Figure 3 while Figure 4, Signifies Assays Used to detect Hematopoietic Stem Cells.

3. HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

Hematopoietic stem cell transplantation (HSCT) (Figure 5, 6) is the transplantation of multipotent hematopoietic stem cells, usually derived from bone marrow, peripheral blood, or umbilical cord blood. It is a medical procedure in the fields of hematology and oncology, most often performed for patients with certain cancers of the blood or bone marrow, such as multiple myeloma or leukemia. In these cases, the recipient's immune system is usually destroyed with radiation or chemotherapy before the transplantation. Graft-versus-host disease is a major complication of HSCT. Hematopoietic stem cell transplantation remains a dangerous procedure with many possible complications; it has traditionally been reserved for patients with life-threatening diseases. While occasionally used experimentally in nonmalignant and nonhematologic indications such as severe disabling auto-immune disease and cardiovascular disease, the risk of fatal complications appears too high to gain wider acceptance (10, 11). Georges Mathé, a French oncologist, performed the first European bone marrow transplant in 1959 on five Yugoslavian nuclear workers whose own marrow had been damaged by irradiation caused by a Criticality accident at the Vinča Nuclear Institute, but all of these transplants were rejected. Mathé later pioneered the use of bone marrow transplants in the treatment of leukemia. Stem cell transplantation was pioneered using bone-marrow-derived stem cells by a team at the Fred Hutchinson Cancer Research Center from the 1950s through the 1970s led by E. Donnall Thomas, whose work was later recognized with a Nobel Prize in Physiology or Medicine. Thomas' work showed that bone marrow cells infused intravenously could repopulate the bone marrow and produce new blood cells. His work also reduced the likelihood of developing a life-threatening complication called graft-versus-host disease (12). The first physician to perform a successful human bone marrow transplant on a disease other than cancer was Robert A. Good at the University of Minnesota in 1968.

3.1. CLINICAL INDICATIONS OF HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT):

Many recipients of HSCTs are multiple myeloma (13) or leukemia patients (14) who would not benefit from prolonged treatment with, or are already resistant to, chemotherapy. Candidates for HSCTs include pediatric cases where the patient has an inborn defect such as severe combined immunodeficiency or congenital neutropenia with defective stem cells, and also children or adults with aplastic anemia (15) who have lost their stem cells after birth. Other conditions treated with stem cell transplants include sickle-cell disease, myelodysplastic syndrome, neuroblastoma, lymphoma, Ewing's Sarcoma, Desmoplastic small round cell tumor, chronic granulomatous disease and Hodgkin's disease. More recently non-myeloablative, or so-called "mini transplant," procedures have been developed that require smaller doses of preparative chemo and radiation. This has allowed HSCT to be conducted in the elderly and other patients who would otherwise be considered too weak to withstand a conventional treatment regimen. Some

Important Clinical Indications of Haematopoietic Stem Cell Transplantation are listed as follows-:

3.1 a. LEUKAEMIA AND LYMPHOMA:

Among the first clinical uses of HSCs were the treatment of cancers of the blood—leukemia and lymphoma, which result from the uncontrolled proliferation of white blood cells. In these applications, the patient's own cancerous hematopoietic cells were destroyed via radiation or chemotherapy, then replaced with a bone marrow transplant, or, as is done now, with a transplant of HSCs collected from the peripheral circulation of a matched donor. A matched donor is typically a sister or brother of the patient who has inherited similar human leukocyte antigens (HLAs) on the surface of their cells. Cancers of the blood include acute lymphoblastic leukemia, acute myeloblastic leukemia, chronic myelogenous leukemia (CML), Hodgkin's disease, multiple myeloma, and non-Hodgkin's lymphoma.

Thomas and Clift describe the history of treatment for chronic myeloid leukemia as it moved from largely ineffective chemotherapy to modestly successful use of a cytokine, interferon, to bone marrow trans-plants—first in identical twins, then in HLA-matched siblings (16). Although there was significant risk of patient death soon after the transplant either from infection or from graft-versus-host disease, for the first time, many patients survived this immediate challenge and had survival times measured in years or even decades, rather than months. The authors write, "In the space of 20 years, marrow transplantation has contributed to the transformation of [chronic myelogenous leukemia] CML from a fatal disease to one that is frequently curable. At the same time, experience acquired in this setting has improved our understanding of many transplant-related problems. It is now clear that morbidity and mortality are not inevitable consequences of allogeneic transplantation that an allogeneic effect can add to the anti-leukemic power of conditioning regimens.

3.1 b. INHERITED BLOOD DISORDERS:

Another use of allogeneic bone marrow transplants is in the treatment of hereditary blood disorders, such as different types of inherited anemia (failure to produce blood cells), and inborn errors of metabolism (genetic disorders characterized by defects in key enzymes need to produce essential body components or degrade chemical byproducts). The blood disorders include aplastic anemia, beta-thalassemia, Blackfan-Diamond syndrome, globoid cell leukodystrophy, sickle-cell anemia, severe combined immunodeficiency, X-linked lymphoproliferative syndrome, and Wiskott-Aldrich syndrome. Inborn errors of metabolism that are treated with bone marrow transplants include: Hunter's syndrome, Hurler's syndrome, Lesch Nyhan syndrome, and osteoporosis. Because bone marrow transplantation has carried a significant risk of death, this is usually a treatment of last resort for otherwise fatal diseases.

3.1 c. HAEMATOPOIETIC STEM CELL RESCUE IN CANCER CHEMOTHERAPY:

Chemotherapy aimed at rapidly dividing cancer cells inevitably hits another target—rapidly dividing hematopoietic cells. Doctors may give cancer patients an autologous stem cell transplant to replace the cells destroyed by chemotherapy. They do this by mobilizing HSCs and collecting them from peripheral blood. The cells are stored while the patient undergoes intensive chemotherapy or radiotherapy to destroy the cancer cells. Once the drugs have washed out of a patient's body, the patient receives a transfusion of his or her stored HSCs. Because patients get their own cells back, there is no chance of immune mismatch or graft-versus-host disease. One problem with the use of autologous HSC transplants in cancer therapy has been that cancer cells are sometimes inadvertently collected and rein fused back into the patient along with the stem cells. One team of investigators finds that they can prevent reintroducing cancer cells by purifying the cells and preserving only the cells that are $CD34^+$, Thy-1^+ (17).

3.1 d. GRAFT-VERSUS-TUMOUR TREATMENT OF CANCER:

One of the most exciting new uses of HSC transplantation puts the cells to work attacking otherwise untreatable tumors. A group of researchers in NIH's intramural research program recently described this approach to treating metastatic kidney cancer (18). Just under half of the 38 patients treated so far have had their tumors reduced. The research protocol is now expanding to treatment of other solid tumors that resist standard therapy, including cancer of the lung, prostate, ovary, colon, esophagus, liver, and pancreas. This experimental treatment relies on an allogeneic stem cell transplant from an HLA-matched sibling whose HSCs are collected peripherally. The patient's own immune system is suppressed, but not totally destroyed. The donor's cells are transfused into the patient, and for the next three months, doctors closely monitor the patient's immune cells, using DNA fingerprinting to follow the engraftment of the donor's cells and regrowth of the patient's own blood cells. They must also judiciously suppress the patient's immune system as needed to deter his/her T cells from attacking the graft and to reduce graft-versus-host disease.

3.1 e. OTHER APPLICATIONS OF HAEMATOPOIETIC STEM CELLS:

Substantial basic and limited clinical research exploring the experimental uses of HSCs for other diseases is underway. Among the primary applications are autoimmune diseases, such as diabetes, rheumatoid arthritis, and system lupus erythematosis. Here, the body's immune system turns to destroying body tissues. Experimental approaches similar to those applied above for cancer therapies are being conducted to see if the immune system can be reconstituted or reprogrammed. The use of HSCs as a means to deliver genes to repair damaged cells is another application being explored.

3.2 COMPLICATIONS OF HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT):

HSCT is associated with a high treatment -related mortality in the recipient (10% or higher), which limits its use to conditions that are themselves life-threatening. Major complications are veno-occlusive disease, mucositis, infections (sepsis), graft-versus-host disease and the development of new malignancies.

3.2 a. INFECTION:

Bone marrow transplantation usually requires that the recipient's own bone marrow be destroyed ("myeloablation"). Prior to "engraftment" patients may go for several weeks without appreciable numbers of white blood cells to help fight infection. This puts a patient at high risk of infections, sepsis and septic shock, despite prophylactic antibiotics. However, antiviral medications, such as acyclovir and valacyclovir, are quite effective in prevention of HSCT-related outbreak of herpetic infection in seropositive patients (19). The immunosuppressive employed in allogeneic transplants for the prevention or treatment of graft-versus-host disease further increase the risk of opportunistic infection. Immunosuppressive drugs are given for a minimum of 6-months after transplantation, or much longer if required for the treatment of graft-versus-host disease. Transplant patients lose their acquired immunity, for example immunity to childhood diseases such as measles or polio. For this reason transplant patients must be re-vaccinated with childhood vaccines once they are off immune -suppressive medications.

3.2 b. VENO-OCCLUSIVE DISEASE:

Severe liver injury can result from hepatic veno-occlusive disease (VOD). Elevated levels of bilirubin, hepatomegaly and fluid retention are clinical hallmarks of this condition. There is now a greater appreciation of the generalized cellular injury and obstruction in hepatic vein sinuses, and hepatic VOD has lately been referred to as sinusoidal obstruction syndrome (SOS). Severe cases of SOS are associated with a high mortality rate. Anticoagulants or defibrotide may be effective in reducing the severity of VOD but may also increase bleeding complications. Ursodiol has been shown to help prevent VOD, presumably by facilitating the flow of bile.

3.2 c. MUCOSITIS:

The injury of the mucosal lining of the mouth and throat is a common regimen-related toxicity following ablative HSCT regimens. It is usually not life-threatening but is very painful, and prevents eating and drinking. Mucositis is treated with pain medications plus intravenous infusions to prevent dehydration and malnutrition.

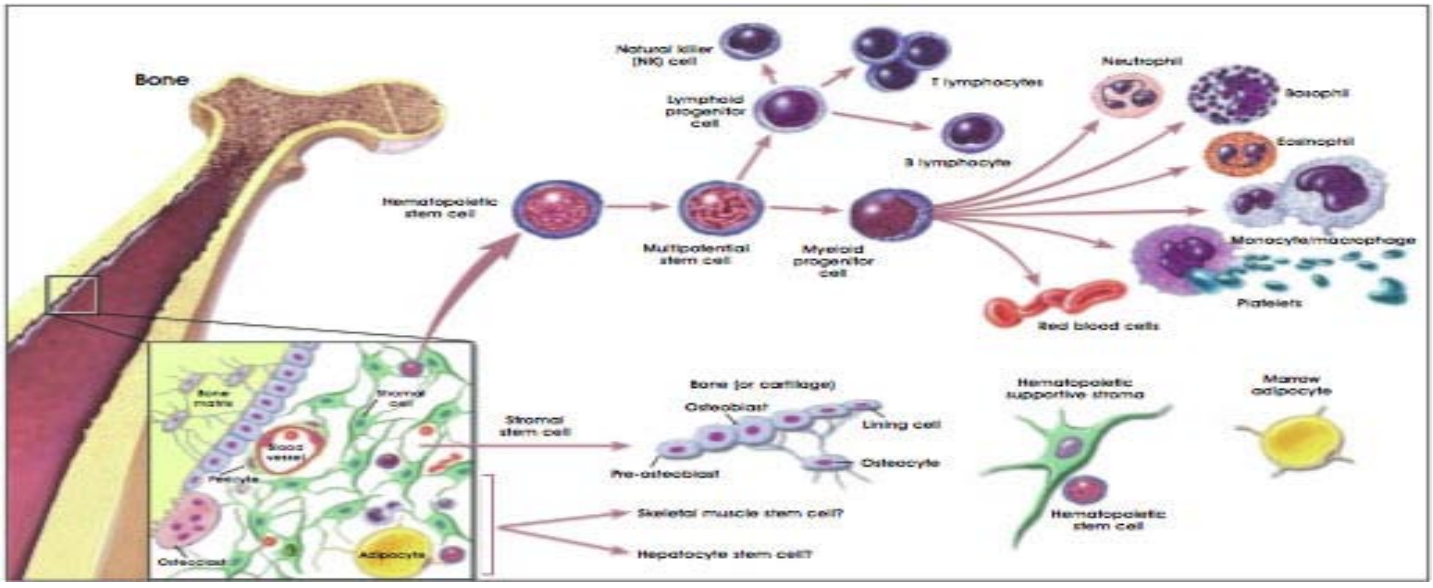

Figure No. 01: Hematopoietic and Stromal Stem Cell Differentiation.

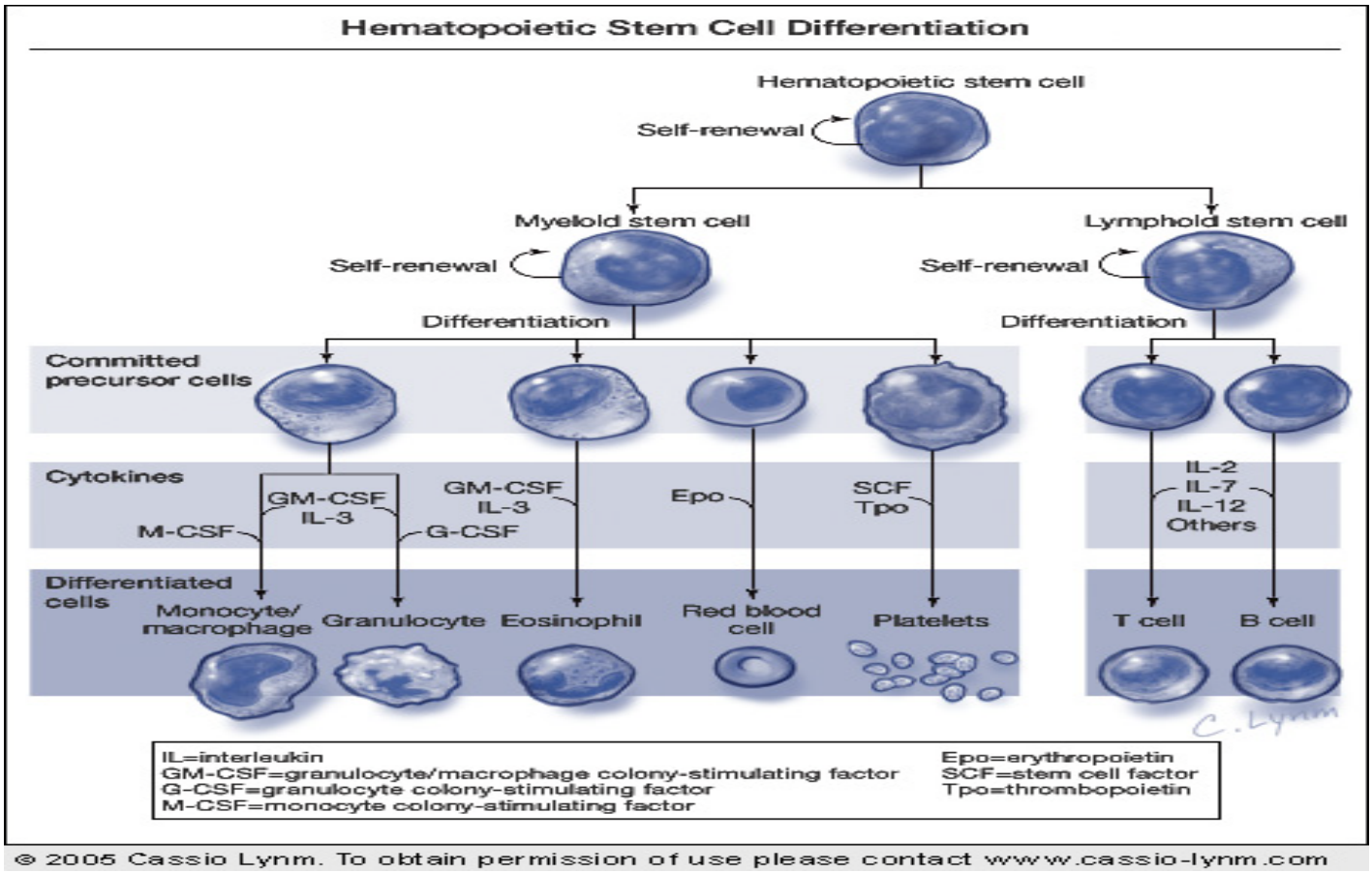

Figure No. 02: The Haematopoietic Stem Cell Differentiation

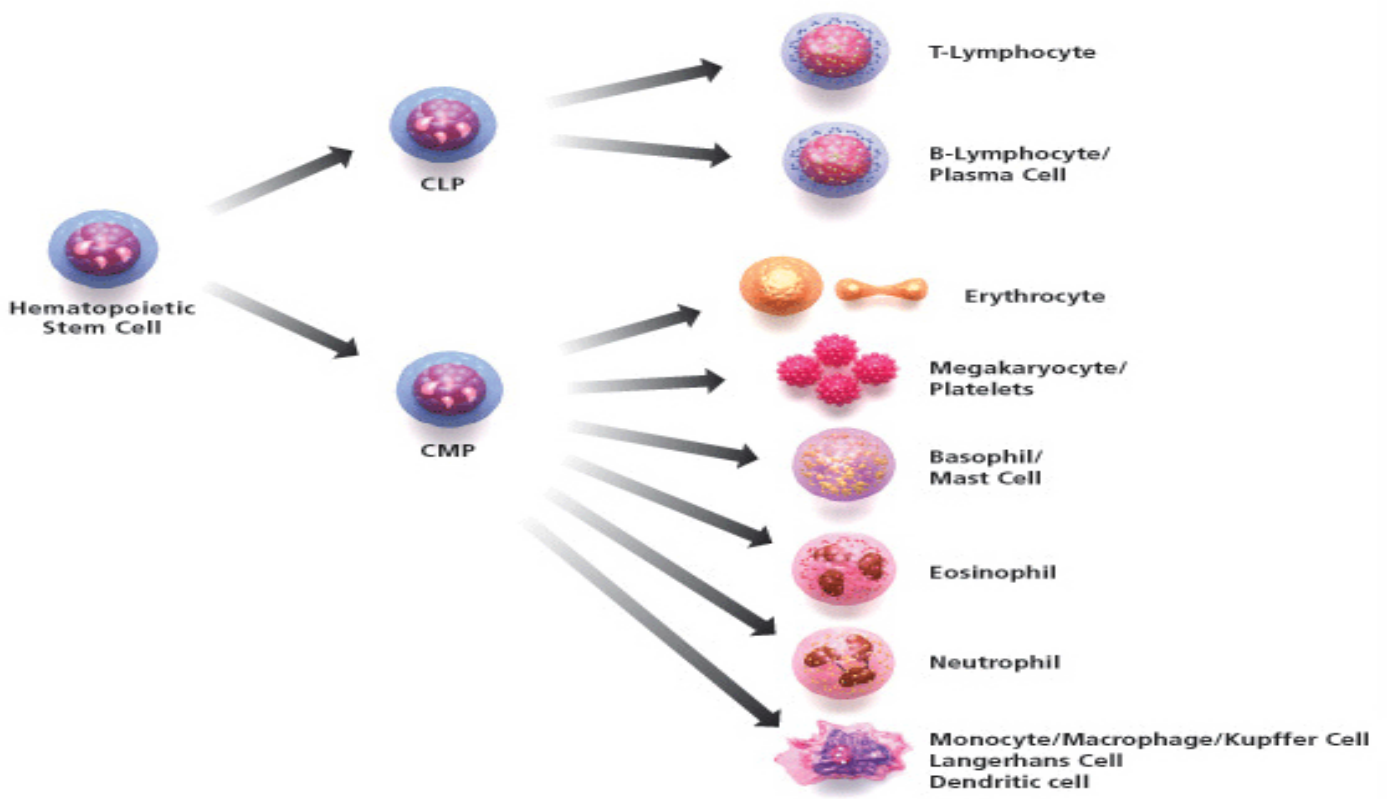

Figure No. 03: The Haematopoietic Stem Cell Pathway

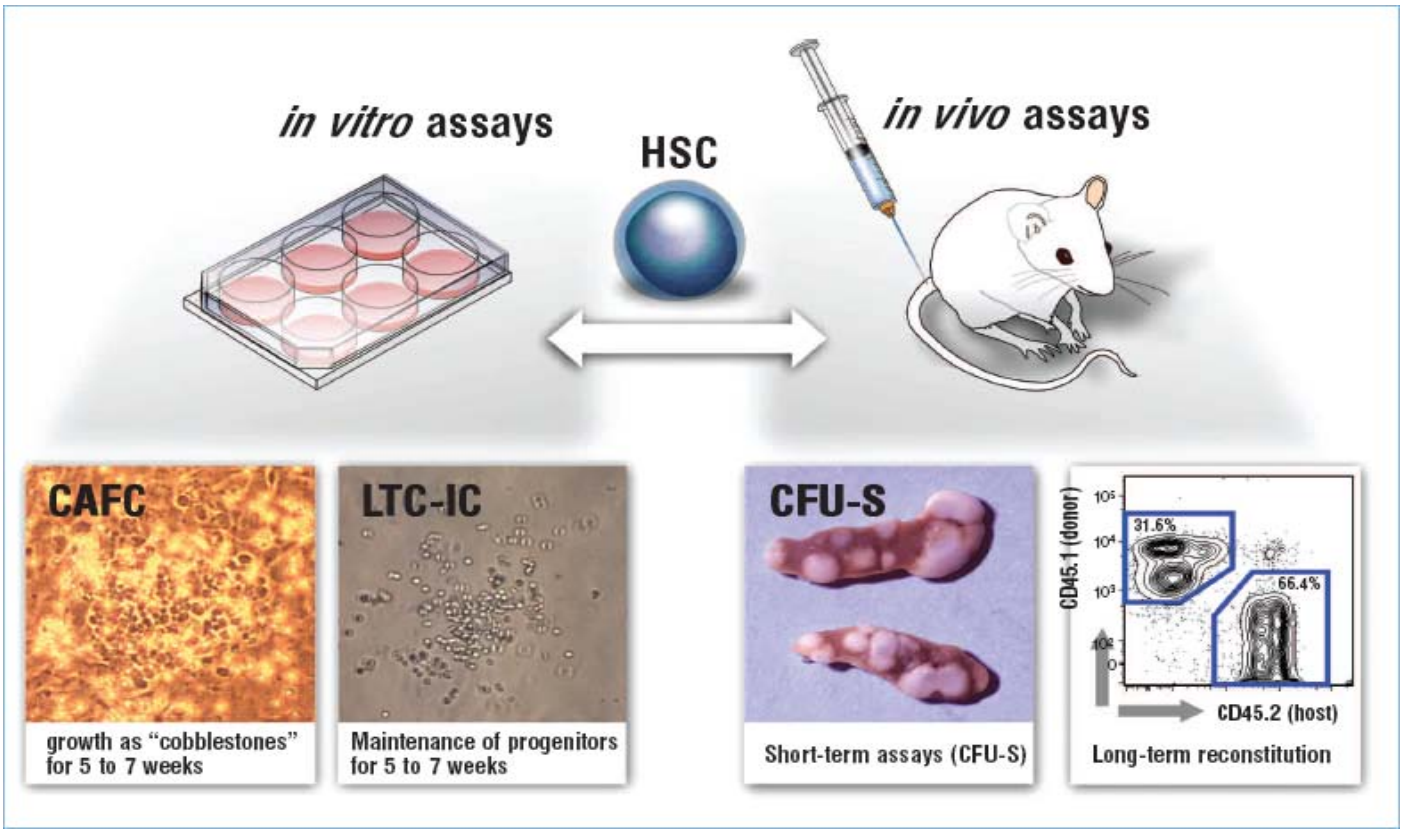

Figure No. 04: Assays Used To Detect Hematopoietic Stem Cells

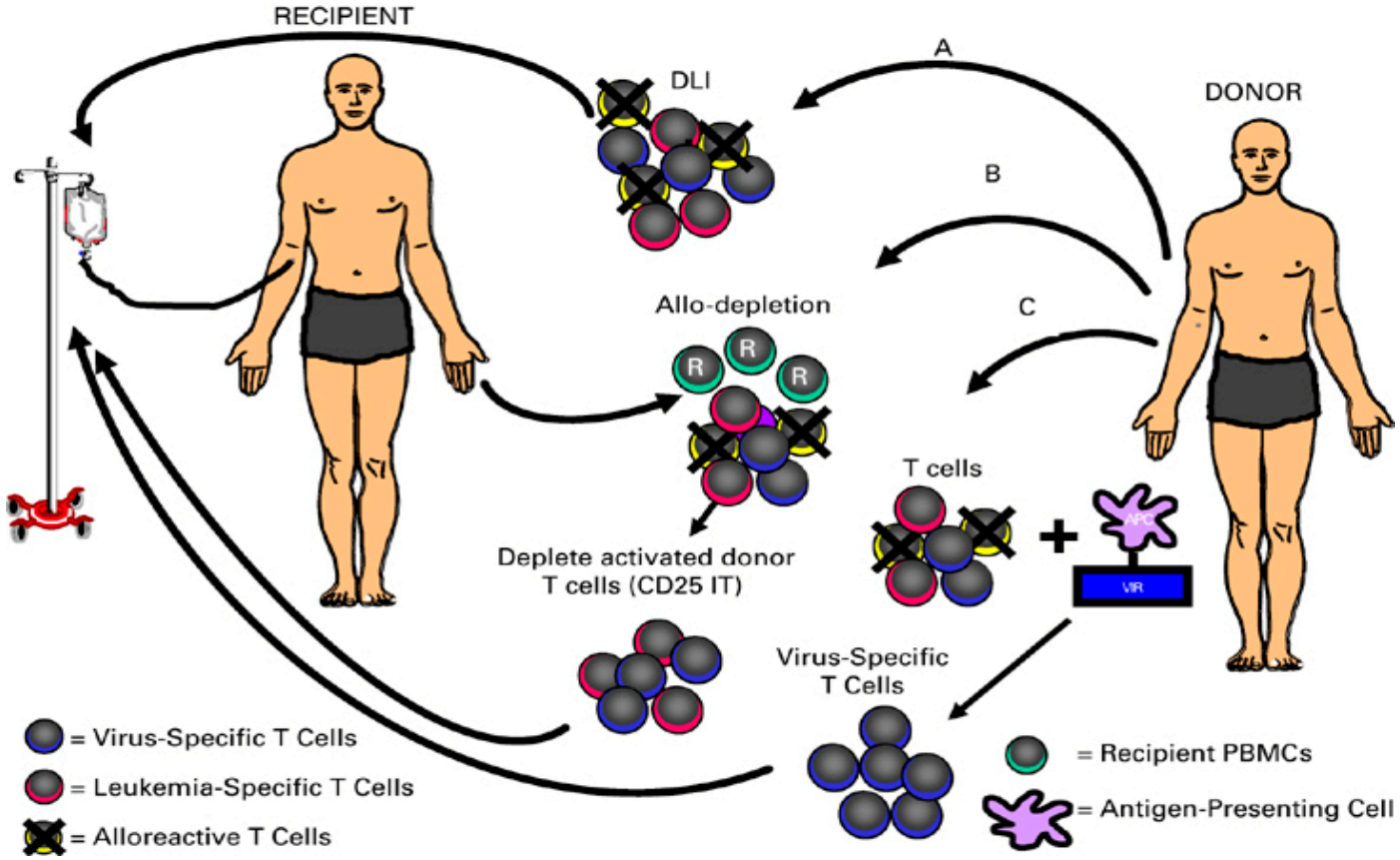

Figure No. 05: Hematopoietic Stem Cell Transplantation Process

Figure No. 06: Hematopoietic Stem Cell Transplantation (Bone Marrow Transplant)

4. CONCLUSION:

With more than 50 years of experience studying blood-forming stem cells called hematopoietic stem cells, scientists have developed sufficient understanding to actually use them as a therapy. Currently, no other type of stem cell, adult, fetal or embryonic, has attained such status. *Hematopoietic stem cell* transplants are now routinely used to treat patients with cancers and other disorders of the blood and immune systems. Recently, researchers have observed in animal studies that hematopoietic stem cells appear to be able to form other kinds of cells, such as muscle, blood vessels, and bone. If this can be applied to human cells, it may eventually be possible to use hematopoietic stem cells to replace a wider array of cells and tissues than once thought. HSCT was undoubtedly one of the most important medical advances in the second half of the 20th century. Worldwide, approximately 30,000-40,000 transplantations are performed yearly, and the number continues to increase by 10-20% each year. More than 20,000 people have now survived 5 years or longer after HSCT. Despite the vast experience with hematopoietic stem cells, scientists face major roadblocks in expanding their use beyond the replacement of blood and immune cells. First, hematopoietic stem cells are unable to proliferate (replicate themselves) and differentiate (become specialized to other cell types) in vitro (in the test tube or culture dish). Second, scientists do not yet have an accurate method to distinguish stem cells from other cells recovered from the blood or bone marrow.

Until scientists overcome these technical barriers, they believe it is unlikely that hematopoietic stem cells will be applied as cell replacement therapy in diseases such as diabetes, Parkinson's disease, spinal cord injury, and many others.

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