



IJPPR

INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals

ISSN 2349-7203




Human Journals

Review Article


December 2016 Vol.:8, Issue:1

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Stem Cell: A Review



IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals

ISSN 2349-7203

HUMAN

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Submission: 10 December 2016
Accepted: 15 December 2016
Published: 25 December 2016

Keywords: Stem cells, substantial, application, emerging field

ABSTRACT

Stem cells are undifferentiated or 'blank' cells found in the human body that have the potential to develop into many different cell types that carry out different functions. In recent years, research advancement in stem cell therapy has been rapid. Accordingly, general clinical, scientific, and public attention to the application of stem cell therapy has been substantial. Promises are great, most notably with regard to the application of stem cell therapy for diseases that are currently difficult to treat or incurable. It is in the best interest of patient care for diagnostic and interventional radiologists to be actively involved in the development of these therapies. In recent years, clinical trials with stem cells have taken in many new directions. While numerous teams continue to refine and expand the role of bone marrow and cord blood stem cells for their vanguard uses in blood and immune disorders.



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INTRODUCTION

The human body is made up of about 200 different kinds of specialized cells such as muscle cells, nerve cells, fat cells and skin cells. All specialized cells originate from stem cells. A stem cell is a cell that is not yet specialized. The process of specialization is called differentiation and once the differentiation pathway of a stem cell has been decided, it can no longer become another type of cell.^[1]

Different types of stem cells have different levels of *potential*. A stem cell that can become every type of cell in the body is called pluripotent and a stem cell that can become only some types of cells is called multipotent.^[1]

Stem cells are the foundation cells for every organ and tissue in our bodies. The highly specialized cells that make up these tissues originally came from an initial pool of stem cells formed shortly after fertilization. Throughout our lives, we continue to rely on stem cells to replace injured tissues and cells that are lost every day, such as those in our skin, hair, blood and the lining of our gut.^[2]

Stem cells are undifferentiated cells from which other cells originate. Stem cells have the ability either to divide indefinitely or to differentiate into other cell types. Their ability to differentiate varies. Some stem cells differentiate only into cells of certain tissues, while others can differentiate into many cell types. Stem cells are grouped according to their ability to differentiate and their origin. The stem cell that is most able to differentiate is the fertilized ovum. It is the origin of all tissue types and the developing human body. Other stem cells embryonic, fetal and adult stem cells are much more limited in their ability to differentiate.^[2]

Stem cells are found in the early embryo, the fetus, amniotic fluid, the placenta and umbilical cord blood. After birth and for the rest of life, stem cells continue to reside in many sites of the body, including skin, hair follicles, bone marrow and blood, brain and spinal cord, the lining of the nose, gut, lung, joint fluid, muscle, fat, and menstrual blood, etc. In the growing body, stem cells are responsible for generating new tissues, and once growth is complete, stem cells are responsible for repair and regeneration of damaged and aging tissues.^[1]

Stem cells are different from other cells in the body in three main ways:

1. Stem cells are unspecialized. They have not developed into cells that perform a specific function.

2. Stem cells can differentiate. This means they can divide and produce cells that have the potential to become other more specific cell types, tissues or organs. These new cells and tissues are used to repair or replace damaged or diseased cells in the body. Once cells have differentiated, they have less capacity to form multiple different cell types and become 'committed' to becoming a particular cell type. Skin stem cells, for example, give rise to new skin cells when needed, to assist regeneration after damage and as part of the normal aging process.

3. Stem cells are capable of self-renewal. Stem cells are able to divide and produce copies of themselves which leads to self-renewal. Once a cell has become specialized (has differentiated) to a particular tissue or organ, it has a very limited capacity to self-renew (produce new stem cells) but instead, produces only cells relevant to that organ.^[1]

Until recently, scientists primarily worked with two kinds of stem cells from animals and humans: embryonic stem cells and non-embryonic "somatic" or "adult" stem cells. Scientists discovered ways to derive embryonic stem cells from early mouse embryos nearly 30 years ago, in 1981. The detailed study of the biology of mouse stem cells led to the discovery, in 1998, of a method to derive stem cells from human embryos and grow the cells in the laboratory. These cells are called human embryonic stem cells. The embryos used in these studies were created for reproductive purposes through *in vitro* fertilization procedures. When they were no longer needed for that purpose, they were donated for research with the informed consent of the donor. In 2006, researchers made another breakthrough by identifying conditions that would allow some specialized adult cells to be "reprogrammed" genetically to assume a stem cell-like state. This new type of stem cell called induced pluripotent stem cells (IPSCs).^[3]

Over the past 60 years, evidence has accumulated supporting the existence of a multipotent adult stem cell population in the body that has the potential to differentiate into bone, cartilage, tendon, ligament, adipocytes, dermis, muscle, and connective tissue. These cells are now collectively grouped under the term mesenchymal stem cells (MSCs) or multipotent mesenchymal stromal cells. A large proportion of the studies on MSCs has involved the role of these cells in the development and repair of bone and cartilage, heightening interest in the clinical orthopedic community. In 1966, intraperitoneal diffusion chambers implanted with mouse bone marrow cells demonstrated that undifferentiated "stem" cells were present and

resulted in osteogenic foci of cells producing alkaline phosphatase (AlkP) and fibroblasts while hematopoietic cells were lost.^[4]

Stem cells are a pervasive component of embryonic and fetal development, of tissue maintenance and of regeneration and repair. Accordingly, stem cells are central to normal human growth and development and are also a potential source of new cells for the therapeutic regeneration of diseased or damaged tissue. The body is made up of a large number of diversely functioning specialized (i.e. differentiated) cells that are organized into specific tissues and organs. During development and also throughout life, many of these tissues are able to repair themselves after damage. This regeneration and repair depend on reserve populations of cells that divide slowly to maintain their own population but can also proliferate to provide the committed precursors for specific cell differentiation. These stem cell populations are specialized in (that is, committed to) specific directions of differentiation.^[5]

Given their unique regenerative abilities, stem cells offer new potentials for treating diseases such as diabetes and heart disease. However, much work remains to be done in the laboratory and the clinic to understand how to use these cells for cell-based therapies to treat disease, which is also referred to as regenerative or reparative medicine. Laboratory studies of stem cells enable scientists to learn about the cells' essential properties and what makes them different from specialized cell types. Scientists are already using stem cells in the laboratory to screen new drugs and to develop model systems to study normal growth and identify the causes of birth defects.^[3]

Research on stem cells continues to advance knowledge about how an organism develops from a single cell and how healthy cells replace damaged cells in adult organisms. Stem cell research is one of fascinating areas of contemporary biology, but, as with many expanding fields of scientific inquiry, research on stem cells raises scientific questions as rapidly as it generates new discoveries.^[3]

Types of stem cells

Embryonic stem (ES) cells-

Embryonic stem cells have been derived from a variety of species, including humans, and are described as “pluripotent,” meaning that they can generate all the different types of cells

in the body. Embryonic stem cells can be obtained from the blastocyst, a very early stage of development that consists of a mostly hollow ball of approximately 150-200 cells and is barely visible to the naked eye. At this stage, there are no organs, not even blood, just an “inner cell mass” from which embryonic stem cells can be obtained.^[2]

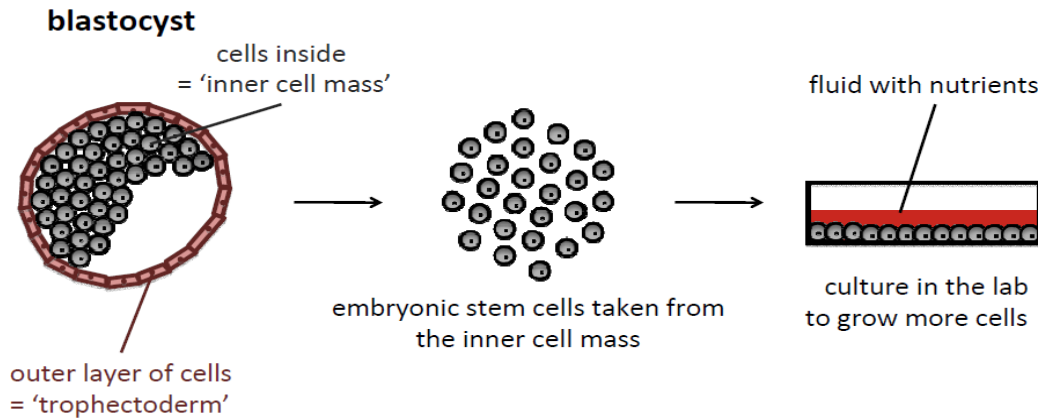


Fig no 1: Origin of Embryonic stem (ES) cells.

Induced pluripotent stem (iPS) cells-

These are adult cells (e.g., skin cells) that are engineered, or “reprogrammed,” to become pluripotent, i.e., behave like an embryonic stem cell. While these iPS cells share many of the same characteristics of embryonic stem cells, including the ability to give rise to all the cell types in the body.^[2]

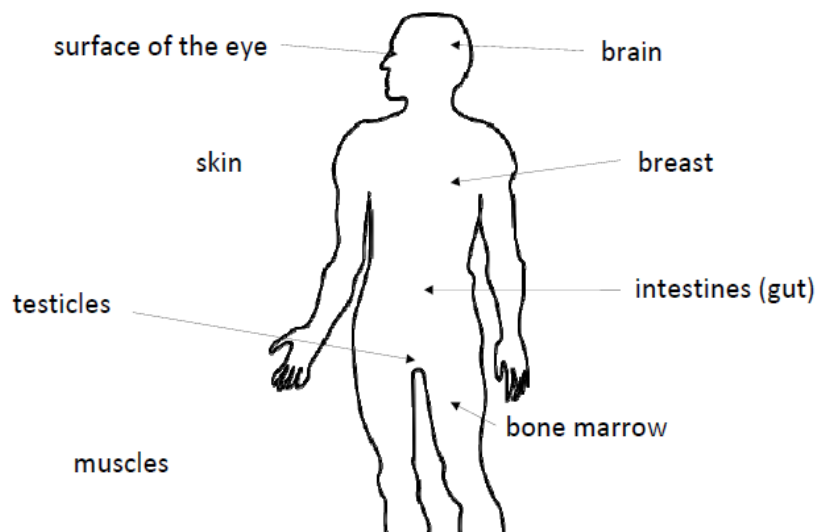


Fig no 2: Origin of Induced pluripotent stem (iPS) cells.

Stem Cell Therapies in Phase III Clinical Trials

Cardiac repair

The use of patient's own bone marrow aspirates, hematopoietic stem cells and mesenchymal stem cells (MSCs), for heart muscle tissue repair, can be puzzling because these cells do not normally contribute to the cardiac lineage types that are desired. There is some preclinical data in support of umbilical cord blood for improved cardiac function for myocardial infarction^[6] but sustained patient recovery has not been clearly demonstrated. It has been shown, that these blood and stromal cells may, *in vitro*, form sarcomeric structures typical of cardiomyocytes with expression of some genes expected of these cell types: atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and contractile proteins including myosin heavy chain, myosin light chain, and alpha-actin^[7]. There is little evidence, however, of myocardial regeneration *in-vivo*, despite 3% to 4% (range 2% to 7%) improvement in the global left ventricular function and cardiac ejection fraction (contractility), but not left ventricular remodeling, in meta-analyses following intracoronary infusions for myocardial infarction^[7-9] In comparative studies of MSCs and cardiac (c-kit+) stem cells and cardiosphere derived cells,^[10] the cardiomyogenic differentiation capacity was clearly more effective with the cardiac derived cells than with MSCs. there is a distinct possibility that procedure-related variables influence the positive outcomes for patients. So there is a need to optimize treatment timing, cell type and dose, and delivery methods. Also, research needs to determine the potential tropic influence of stem cell secretions or cytokines released at the site of injury and the degree of cardio repair that may be clinically relevant^[11]. A recent study by Lee and colleagues at Harvard found a subset of marrow cells that was able to stimulate endogenous adult cardiac stem cells, offering a possible mechanism for the effect seen^[12]. It is possible that protein based rather than cell-based therapies may evolve from these studies. It is pretty clear that for the ventricular remodeling required, more effective cell types with significant populating capacity will be needed to replace the severely damaged infarct area of the heart.

Neurological applications

Studies involving umbilical cord blood for neurological indications have been promoted as a result of preclinical data on the apparent formation of neurons *in-vitro*^[13] but there is little evidence of their trans-differentiation to functional neurons or glial cells *in-vivo*. Mobilized

peripheral blood cells (CD34+) delivered into the femoral artery has been used in safety studies for chronic spinal cord injury without adverse effects but with very little evidence of efficacy in follow-up^[14]. Clinical trials involving use of MSCs for the treatment of neurological disorders is also relatively common, despite little evidence for their conversion to neural cells *in-vivo*. Autologous MSCs isolated from bone marrow and injected intrathecally into spinal cord cerebrospinal fluid, allowing access to the brain and spinal column, can be accomplished safely in patients with multiple sclerosis and amyotrophic lateral sclerosis (ALS). Karussis *et al.* (2010)^[15] provided some evidence of immunomodulatory effects of MSCs within 24 hours of intrathecal injection but claims of ferumoxides labeled MSCs persisting after three to six months was less persuasive.

Immunological applications

Multiple sclerosis is currently treated with steroids, immunomodulating agents, immunosuppression and humanized monoclonal antibodies (*Natalizumab*) and more recently by immunosuppression followed by transplantation of autologous CD34+ hematopoietic stem cells (HSCs) aimed to reconstitute the immune system following the removal of active autoreactive T cells. This would enable the establishment of tolerance to autoantigens and a period of remission in diseases such as multiple sclerosis. With more than 400 patients treated in Phase I/II trials there is benefit seen in inflammatory parameters and disease progression, particularly in rapidly evolving severe multiple sclerosis^[16]. Whether these early improvements in clinical parameters of disability will translate into long-term benefits and sustained remission is as yet unclear. There are strong recommendations to undertake randomized comparative trials of HSC transplantation versus non-transplantation with a large target patient population to validate any benefit for HSC therapy^[17]. Given the need for strong immunosuppression as part of the strategy, the benefits need to substantially outweigh the risks inherent in the treatment. There have been some studies using allogenic HSCs but none are currently reported active. This approach is only considered in advanced nonmalignant disease because of unfavorable risk to benefit ratio^[17]. Further study is warranted for HSC therapy in these patients. Systemic sclerosis, systemic lupus erythematosus and Crohn's Disease as well as multiple sclerosis, are major disease targets for multinational randomized clinical trials. Improvements are observed in dermal fibrosis and pulmonary dysfunction in systemic sclerosis patients following lymphoablative conditioning and HSC therapy up to 8 years^[18]. There are also trials evaluating HSC therapy in rheumatoid

arthritis and juvenile idiopathic arthritis^[19]. These approaches all focus on transient depletion of active immune cell numbers followed by qualitative changes in the immune cell repertoire that enable the resetting of a modified adaptive immune system that is tolerant to self-antigens, previously targeted in autoimmune disease. While present clinical trial approaches using autologous HSCs will be informative, it remains speculative whether long-term remission will be achieved in the variety of diseases under examination and improvements in therapeutic strategies are expected to evolve in time. The potential use of MSCs in resetting immune homeostasis as a therapeutic approach is being explored because of their ability for cytoprotection and immunosuppression. However, their long-term usefulness and exact role in the treatment of autoimmune diseases remains to be determined.

Chronic Graft Versus Host Disease (GVHD) has also been a target for HSC and MSC cell therapies and is usually observed after allogenic HSC or tissue transplants. This very serious condition may manifest in the peripheral or central nervous systems, and in multiple organs of the body^[20]. At least ten clinical trials with MSC have been reported with mixed results, but many show a significant level of positive response. One company, Osiris, has completed patient enrollment in Phase 3 trials for steroid refractory acute GVHD and for newly diagnosed acute GVHD^[21].

Genetic blood diseases

Hematopoietic stem cells (HSC) therapies are in clinical trials for genetic diseases such as sickle cell disease and b-thalassemia. In sickle cell disease, curative high levels of T-cell chimerism (>50%) using HLA-matched sibling allogenic CD34+ HSC transplantation can be achieved without myeloablation^[22]. New developments in stem cell gene therapy offer a potentially safer therapy for sickle cell disease in the future^[23].

Long-term mixed chimerism with allogenic HSCs can be achieved in b-thalassemia but it is recommended that the donor chimerism is >25% for robust therapeutic effects in these patients^[24]. However, gene therapy models involving the transduction of CD34+ HSCs with lentiviral vectors indicate that only 10% to 15% chimerism of functional thalassemic cells can be achieved which is below the therapeutically curative level^[24]. Even the recovery of CD34+ cells for gene therapy, using granulocyte-colony stimulating factor (G-CSF) stem cell mobilization may be harmful in b-thalassemia patients and may cause severe side effects in

sickle cell anemia patients. This needs careful evaluation and additional consideration to minimize these adverse risks^[25].

Allogenic HSC therapy in cases of inherited genetic disease may be associated with death or severe complications after transplantation making autologous gene therapy for blood and immune disease an important strategy. Boztug *et al.*^[26], have shown that HSC gene therapy for Wiskott-Aldrich syndrome, a severe X-linked recessive immunodeficiency disorder, can be largely corrected by autologous HSC gene therapy. CD34+ cells from two patients were transduced with a retroviral vector incorporating a construct expressing the correct gene (*WASP*) after transient myelosuppression with busulfan. Stable chimerism of 9% and 20% of donor hematopoietic progenitors were sufficient to effect correction of the primary disease phenotype, including hemorrhagic diathesis, eczema, autoimmunity, and severe infection. These types of clinical studies lay the foundation for stem cell gene therapy in human disease. This will likely include the potential cure of HIV/AIDS by targeted disruption of the CCR5 gene in autologous CD34+ HSCs^[27].

Adipose stem cells

Adipose stem cells are plentiful and relatively easily accessed. They have been shown to be useful for soft tissue repair [28]. They consist of adipose-derived stem cells (ASCs) (CD31-/CD34+/CD45-/CD90+/CD105-/CD146-), endothelial progenitor cells and pericytes. Autologous ASCs and the stromal vascular fractions are being used for soft tissue engineering with a range of scaffolds, particularly for breast augmentation, fistulas in Crohn's disease and tissue damaged by radiation^[28].

In addition to soft tissue repair, ASCs are also in clinical trial for myocardial infarction and graft versus host disease, with outcomes equivalent to MSCs^[29]. They have also been used in clinical trials for tracheomediastinal fistula, Calvarial bone defect, skin ulcer and stress-induced urinary incontinence.

The relative advantage of ASCs over MSCs remains to be determined for the variety of applications envisaged and further studies may demonstrate the merits of ASCs. Meanwhile, soft tissue repair and fistula repair will remain a primary application of ASCs for the immediate future.

Endothelial stem cells

Endothelial progenitor cells (CD34+/CD133+/KDR+ or VEGFR2+) may be sourced from several sources including bone marrow, umbilical cord blood and adipose tissue. They are effective in the stimulation of angiogenesis and in clinical studies requiring revascularization and remodeling of collaterals in atherosclerotic cardiovascular disease. The result desired is the regeneration of damaged tissues, preventing amputation of ischemic limbs and other areas, and recovery after myocardial infarction. While efficacy in preclinical trials and safety in Phase I studies has been demonstrated, unequivocal evidence for patient benefit in placebo-controlled trials has not been obtained^[30]. The role of endothelial progenitor cells (EPCs) in neoangiogenesis of plexiform lesions remains uncertain and there is continuing debate about the function of EPCs in the regenerative processes that are the target of EPC therapy. These matters require careful consideration in future clinical trials^[31].

Pancreatic β islet cells

Transplantation of pancreatic β Islet cells has been recently reviewed by Matsumoto^[32]. Approximately 70% of Type I diabetes patients can achieve insulin independence but may have difficulty in maintaining this. They also have problems due to immunosuppression and generally, there is a shortage of donors (patients need multiple donors). Xenotransplants of pig islets using encapsulation to address immune rejection are moving towards the clinic but concerns still exist for transmission of porcine endogenous retrovirus. The use of embryonic stem cell-derived β Islets in special subcutaneous capsules that induce minimal fibrosis may evolve into clinical trials shortly^[33].

Myoblasts

Regeneration of skeletal muscle in cases of muscular dystrophy depends on satellite cells or myogenic progenitors that are localized between the basal lamina and muscle fiber membrane^[34]. Transplant trials of satellite cells or expanded myocytes, injected into muscles of patients with muscular dystrophy were shown to be safe and in some cases new dystrophin production was observed but clinical benefits were not demonstrated^[35]. The problem appears to be in the need for massive numbers of injections because satellite cells distribute at local injection sites, with rapid cell loss. Also, immune responses were seen even with compatible cells, resulting in patients requiring immunosuppression^[36].

The use of myoblasts for cardiac repair has been disappointing because skeletal muscle doesn't integrate functionally with cardiomyocytes, leading to a high incidence of arrhythmias^[37].

Hepatocytes

Hepatocyte transplantation is currently most successful for liver-based metabolic disorders, for example, to replace a deficient enzyme. This includes familial hypercholesterolemia, where autologous hepatocytes transduced with the low-density lipoprotein (LDL) receptor gene showed engraftment and 20% reduction in LDL cholesterol in three of five patients^[38]. Allogenic hepatocyte transplantation has also been undertaken with some partial success for metabolic disorders with a few reports of long-term function of transplanted hepatocytes^[38, 39]. Hepatocytes are usually injected into the portal venous system and engraftment is most common in the liver or spleen.

Limbal stem cells

Corneal disease is the second most common cause of blindness. Corneal epithelial stem cells are located in the basal layer of the limbus epithelium and provide for replacement of corneal epithelial cells that are lost or damaged. Limbal cell deficiency can be treated with transplanted limbal stem cells taken as a small biopsy and expanded *ex vivo*. Patients treated with expanded autologous limbal stem cells transplanted on human amniotic membrane had stable corneal epithelium reconstruction in all their eyes with improvement in visual acuity in the majority^[40]. This appears to be a safe and effective way of restoring vision in limbal cell deficiency.

Table 1. Pluripotent Stem Cell Clinical Trials (USA) ^[41].

Trial sponsor	Disease target	Cell therapy
Geron Inc. Phase I: 10 patients enrolled 2010-12	Complete subacute thoracic spinal cord injuries. T3 to T10 segments between seven and 14 days after injury	Human embryonic stem cell- derived Oligodendrocyte progenitor cells (GRNOPC1)
Advanced Cell Technologies (ACT) Phase I/II: 12 patients enrolled 2011	Stargardt's Macular Dystrophy (juvenile macular degeneration)	Retinal Pigment Epithelium- derived from human embryonic stem cells.
Advanced Cell Technologies (ACT) Phase I/II: 12 patients enrolled 2011-12	Age-related Macular Degeneration	Retinal Pigment Epithelium- derived from human embryonic stem cells.
California Stem Cell (CSC) Phase I: Currently on hold 2011	Spinal muscular atrophy (SMA) Type 1	Human motor neuron progenitor cells from human embryonic stem cells

Stem cell therapy market

Stem cells (SCs) have been used in medicine since 1968 when bone marrow transplantation (BMT) was first achieved. Today, BMT is still used for treating cancers and genetic blood disorders, but the transplanted hematopoietic SCs (HSCs) are increasingly sourced from peripheral and umbilical cord blood rather than the bone marrow. Worldwide, ~60,000 BMT operations are performed yearly (~35,000 using autologous HSCs; ~25,000 using allogeneic HSCs). Beyond BMT, there are high near-term expectations for SC therapeutics derived from multipotent mesenchymal SCs (MSCs); in the long term, pluripotent embryonic SCs (ESCs) and induced pluripotent SCs (iPSCs) are promising ^[42].

Table 2: Stem Cell Therapies ^[42].

Company	Product or process	Indication	Development stage
Aastrom Biosciences	Ixmyelocel-T (patient-specific autologous multicellular therapy)	Critical limb ischemia	Phase III
Gamida Cell	StemEx (umbilical cord blood stem and progenitor cells expanded <i>ex vivo</i>)	HSCT in hematological malignancies	Phase II/III
Mesoblast	'Off-the-shelf' mesenchymal precursors	HSCT in hematological malignancies	Phase III
Osiris Therapeutics	Prochymal (adult human mesenchymal stem cells)	Crohn's disease	Phase III (three trials)
Osiris Therapeutics	Prochymal (adult human mesenchymal stem cells)	Graft versus host disease	Phase III (two trials)
Baxter Healthcare	Auto-CD34+ cells (adult autologous CD34+ cells)	Chronic myocardial ischemia	Phase III
TiGenix	Cx601 (adipose-derived allogeneic stem cell suspension)	Complex perianal fistula	Phase III
Bioheart	MyoCell (autologous myoblasts)	Congestive heart failure	Phase II/III
Cytori Therapeutics	Adipose-derived stem and regenerative cells (two dosages)	Acute myocardial infarction	Phase II/III
Stempeutics Research	Stempeucel (adult mesenchymal stem cells)	Critical leg ischemia	Phase II/III
Cardio3 Sciences (Belgium)	C-Cure (BM-derived stem cells treated with cardiopoietic cocktail)	Congestive heart failure	Phase III

Marketed products

Most of the SC therapies on the market and in development utilize MSCs. At least three osteobiologic products, Osteocel (NuVasive), Trinity (Orthofix) and LiquidGen (Skye Orthobiologics), use MSCs as a component of an allograft matrix and are believed to promote osteogenesis and reduce inflammation SC grafts are the fastest-growing area of the bone graft market ^[42].

CONCLUSION

Stem cells are undifferentiated or 'blank' cells found in the human body that have the potential to develop into many different cell types that carry out different functions. Most cells in the human body are differentiated. That means they are built to function in a particular organ system and carry out a specific function. A red blood cell, for example, is designed to carry oxygen, while a white blood cell is designed to fight off disease. These differentiated cells result from the process of cell division, a process that begins with undifferentiated stem cells. Pluripotent stem cells, found in embryos, can give rise to all the cells found in the human body – cells as diverse as those found in the brain, bone, heart and skin. Multipotent stem cells, found in adults or in babies' umbilical cords, have a more limited capacity. Their development is limited to the cells that make up the organ system that they originated from. For example, a multipotent stem cell in the bone marrow can develop into a red blood cell, a blood platelet or a white blood cell, but not into a skin cell or brain cell.

In recent years, clinical trials with stem cells have taken the emerging field in many new directions. While numerous teams continue to refine and expand the role of bone marrow and cord blood stem cells for their vanguard uses in blood and immune disorders, many others are looking to expand the uses of the various types of stem cells found in bone marrow and cord blood, in particular, mesenchymal stem cells, to uses beyond those that could be corrected by replacing cells in their own lineage. Early results from these trials have produced mixed results often showing minor or transitory improvements that may be attributed to extracellular factors. More research teams are accelerating the use of other types of adult stem cells, in particular, neural stem cells for diseases where beneficial outcome could result from either in-lineage cell replacement or extracellular factors. At the same time, the first three trials using cells derived from pluripotent cells have begun. Clinical trials on the use of stem cells are underway for a wide variety of conditions and there is an emphasis on the use of bone

marrow, hematopoietic (mobilized and recovered in blood and umbilical cord blood) and mesenchymal stem cells. While safety has been consistently demonstrated, particularly with autologous transplants, sustained curative benefit has not been consistently obtained. Allogenic transplants generally have major issues for continual immunosuppression to prevent rejection of grafted cells. In some cases, the benefit of cell therapy is through unidentified trophic effects of transient grafted cells. Nevertheless, progress for therapeutic benefit for patients is increasing and there is clear merit for using stem cells as delivery vehicles for correcting genetic mutations that cause severe disease phenotypes. Increasingly, new stem cell types are being

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