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STEM CELL BIOLOGY, CLASSIFICATION, APPLICATION-A REVIEW

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ABSTRACT

As precursor cells with the ability to self-renew the stem cells are used widely in treatment of diseases. Clinical research on stem cell-based treatments has improved significantly during the past few years. The process of stem cell specialization is influenced by both internal signals, which are governed by genes in DNA, and external cues, such as physical contact between cells or chemical secretion by surrounding tissue. Because of their pluripotency property the stem cell can develop into any cell type. In the bone marrow, these cells mostly transform into fat, bone, and cartilage cells. Pluripotent cells are referred to be totipotent if they have the ability to develop extraembryonic tissues in embryos. The stem cell can be classified into according to their differentiation and origin. According to their differentiation they can be classified into totipotent, pluripotent, multipotent, unipotent, oligo potent. According to their origin stem cell can be classified into embryonic stem cell, embryonic germ stem cell, Umbilical cord cell etc. They stem cell has wide range of application in the diseases like Heart failure, Diabetes mellitus, Parkinson disease liver disease etc.

Keywords: Clinical research, Totipotent, Pluripotent, Umbilical cord cells

INTRODUCTION

Cell-based therapy as a type of regenerative medicine is one of the most promising areas in modern science and medicine. Such progress opens the door for a wide range of

novel, perhaps curative medicines for some of the deadliest diseases afflicting humanity. Regenerative medicine is quickly emerging as the next major advancement in healthcare, with the goal of healing diseased cells, tissues, or organs and maybe replacing them with healthy ones to restore everything to normal. Fortunately, thanks to the research communities tireless efforts to investigate the potential uses in treating a variety of disorders, including Diabetes and neurological conditions, as well as many other diseases, regenerative medicine is becoming more and more feasible as a potential replacement for outdated drug-based treatments **[1]**.

Hopes that stem cell therapies would one day become a treatment for a wide range of illnesses have been boosted by recent research showing successful patient translation **[2]**. Clinical research on stem cell-based treatments has improved significantly during the past few years. A number of these research significantly affect how some diseases are treated **[3]**. Following therapy with keratinocyte cultures of epidermal stem cells, a case of Epidermolysis Bullosa showed evidence of skin healing **[4]**. Patients with macular degeneration saw a considerable improvement in their eyesight following transfer of induced pluripotent stem cells generated from patients (iPSCs) that were stimulated to grow into retinal pigment epithelial cells **[5]**.

Despite the growing number of papers describing successful stem cell-based treatments, several clinical trials have been unsuccessful in obtaining full regulatory approval for authentication as stem cell therapy. The most well-established stem cell treatment for blood and immune system illnesses today uses bone marrow transplants **[1, 6, 7]**.

In this review special emphasis is given on stem cell application in various abnormalities and diseases, classification and stem cell biology that will give deep insights about stem cells

Stem cell Biology

Following the sperm and ovum fertilization, a blastocyst is produced. Embryonic stem cells, which are transient stem cells, line the interior of it. The two cell types that make up a blastocyst are the trophectoderm and the inner cell mass (ICM), which transforms into epiblasts and triggers the development of a foetus (TE). It is up to blastocysts to manage the ICM microenvironment. The TE keeps expanding and develops the extraembryonic support structures, including as the placenta that are essential for the embryo's healthy development. The TE initiates the formation

of a specific support structure while the ICM cells continue to be undifferentiated, fully pluripotent, and proliferative **[8]**.

Because of their pluripotency, stem cells may develop into any type of cell in the body. Prenatal stem cells are created by the ICM. Endoderm, mesoderm, and ectoderm are three types of cell clusters that form throughout the embryo's genesis and development. These germ layers eventually give rise to the developed cells and tissues of the foetus and, later, the adult organism **[9]**. When hESCs develop into one of the germ layers, they become multipotent stem cells with potency restricted to the germ layer's cells. In human development, this is a quick process. After then, pluripotent stem cells appear as undifferentiated cells all over the organism. Two of its most crucial functions are differentiation into specialised cells under specific physiological conditions and proliferation by producing the following generation of stem cells.

The process of stem cell specialisation is influenced by both internal signals, which are governed by genes in DNA, and external cues, such as physical contact between cells or chemical secretion by surrounding tissue.

Additionally, stem cells act as the body's natural healing system. An organism can renew and produce new cells endlessly as long as it is still alive. Stem cell activity varies from organ to organ; for instance, division happens continuously in bone marrow, but only under certain physiological conditions in organs like the pancreas.

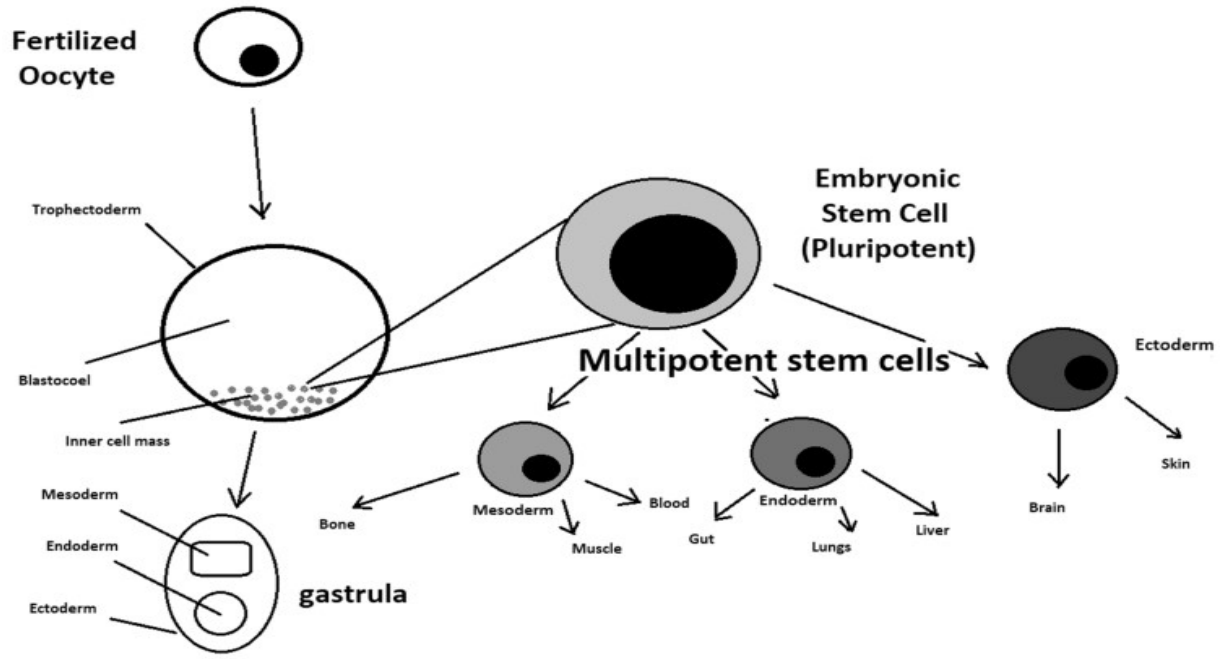

Fig. 1 Oocyte development and formation of stem cells: the blastocoel, which is formed from oocytes, consists of embryonic stem cells that later differentiate into mesodermal, ectodermal, or endodermal cells. Blastocoel develops into the gastrula

Stem cell functional division

Whole-body development

The development of the organism determines whether separate stem cells exist during cell division. Somatic stem cell ESCs and embryonic stem cell ESCs may be distinguished from one another. Without isolating them from the TE, it is possible to make ESCs, but this combination has limitations. Co-culture is often avoided because there aren't many multiplying activities. ESCs are created in the inner cell mass of the blastocyst, a stage of the pre-implantation embryo. 4 days following fertilization. The following step involves placing these cells on a culture plate with culture medium. The ineffective but common technique of passage is employed to move cells from one plate to another.

After development, adult stem cells are undifferentiated somatic stem cells and present throughout the body's differentiated cells. These cells' job is to speed up the development, repair, and replace of the cells that are killed every day. The potential spectrum of differentiation for these cells is constrained. Here are a few instances of different kinds.- Mesenchymal are stem cells that found in many different organs.

- In the bone marrow, these cells mostly transform into fat, bone, and cartilage cells. They are an anomaly as stem cells since they are pluripotent and can specialize in any germ layer cell.

- Oligodendrocytes and astrocytes, two of the supporting cells for nerve cells, are also produced by neural cells.

- Hematopoietic stem cells generate all types of blood cells, including erythrocyte, leukocytes, and megakaryocytes.

-Keratinocytes, which create an outer protecting layer of skin, are formed by dermal stem cells.

Somatic stem cells proliferate for a longer period of time than ESCs. Reprogramming adult stem cells to become pluripotent is possible. It can be done quickly by fusing with pluripotent cells or by putting an adult nucleus within a germ cell's protoplasm. The well-known Dolly sheep was cloned using the same procedure. Since they have the ability to divide into totipotent, multipotent, unipotent, and pluripotent cells, hESCs are crucial to the process of the complete body's development **[9]**.

Pluripotent cells are referred to be totipotent if they have the ability to develop extraembryonic tissues in embryos. The range of cell types that multipotent cells can grow into in a given tissue is constrained. Unipotent or oligopotent stem cells are those that produce tissues from a single cell lineage **[10]**.

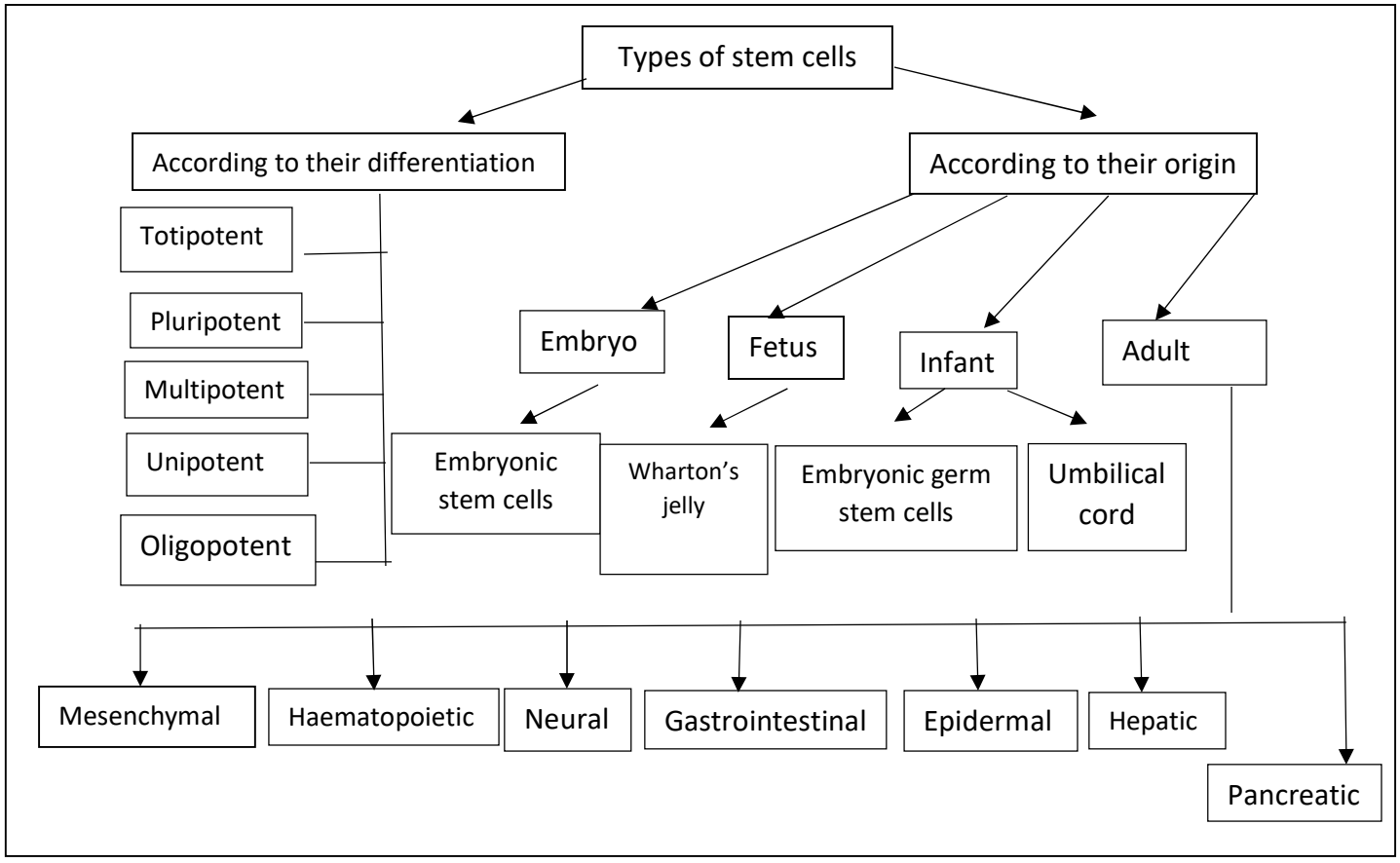

Figure 2: Classification of Stem Cells

Embryonic Stem Cells (ESCs): Blastocysts from mice or humans develop into pluripotent, self-

healing cells known as embryonic stem cells 4-5 days after conception **[11, 12]**. As primordial cell lines, they may be kept in culture and then coaxed to develop into any cell line **[13]**. They may differentiate into any type of somatic cell, including endodermal, mesodermal, and ectodermal embryonic germ layers. They therefore offer a lot of potential for treating tissue regeneration **[14]**.

Embryonic Germ Stem Cells: Embryonic germ (EG) cells arise in the final stages of embryo development. They originate from the earliest germline cells and develop over the first stages of development. They mostly come from foetal tissue when there is a little window of opportunity **[15]**. Although PGC-obtained cells were pluripotent, the growth of a mouse adenoma was unable to demonstrate this potential **[16]**.

Fetal stem cells: The organs of foetuses include basic cell types known as foetal stem cells. They can develop into two distinct stem cell types, hematopoietic stem cells and pluripotent stem cells. Pancreatic islet cells, foetal hematopoietic stem cells, and neural

crest stem cells were recovered from the fetuses **[17]**. Children and adults alike have used human foetal stem cells to cure some of the worst diseases in the world **[18]**.

Infant stem cell:

Umbilical cord stem cells: Adult peripheral blood and bone marrow stem cells are different from those seen in umbilical cord blood **[19]**. Cord blood multipotent stem cells have the ability to develop into neurons and liver cells.

The matrix of the umbilical cord, also called Wharton's jelly, is thought to include mesenchymal stem cells. These cells can proliferate forever, exhibit typical stem cell traits, and can be encouraged to differentiate into neurons in a culture dish **[20]**.

Adult stem cell: Adult stem cells are any stem cells that have been removed from mature tissue; they are found in the tissues of a fully developed child (whole embryo) or adult, and they can only make a small number of cell types. These cells are less capable than embryonic and foetal stem cells due to their stage of development **[21]**. Since they are crucial for tissue regrowth and repair, they are referred to by their tissue origin **[22]**. In bone marrow, adult stem cells can be found in large quantities **[23]**.

Mesenchymal stem cells: A kind of cell known as mesenchymal stem cells (MSCs) has the capacity to differentiate into several somatic lineages. Initially, they were referred as as fibroblast-like affixed cells that might transform into myocytes, osteocytes, chondrocytes, adipocytes, and tenocytes **[24]**. Because of their plastic adhesion, MSCs may be easily extracted from bone marrow and distinguished from hematopoietic stem cells **[25]**. They are utilised in regenerative medicine and tissue engineering **[26]**. MSCs have distinct biological features and already been are frequently used as supplements and also being used other in the treatment of certain cancers, treatments or the delivery of therapeutic molecules are used **[27, 28]**.

Hematopoietic stem cells: All hematopoietic divisions' hematopoietic stem cells are the progenitors of differentiated cells and have the capacity for self-renewal. They underwent transfers as a result, both after high-dose chemotherapy for cancer and for full recovery from hematologic problems **[29]**.

Neural Stem Cells: In the adult human brain, neural stem cells are multipotent, self-replicating cells that develop in certain molecular microenvironments. They could contribute to the therapy of brain cells **[30]**. As they are found in the central nervous system, neural stem cells have the capacity to self-renew and produce new glial and

neuronal cells. They have undergone extensive testing in mouse models for the treatment of breast, lung, and prostate cancers, both primary and metastatic cancers **[31, 32]**.

Gastrointestinal stem cells The gastric glands and intestinal crypts are a "niche" where the gastrointestinal tract's stem cells may be found. The axis and diffusion strategy of this altered clone in the gastrointestinal mucosa are highly debatable. This case revolves around the location and nature of the gastrointestinal stem cells **[33]**.

Epidermal stem cells: Transiently Amplified Cells (TA cells), epidermal stem cells, and terminally differentiated cells are three separate types of keratinocytes that make up the rapidly renewing tissue that is mammalian skin. Epidermal stem cells are capable of endless self-renewal. Contrary to TA cells, which are epidermal stem cell progeny that undergo terminal differentiation after 3-5 divisions, basal layer cells play significant roles in cellular regeneration, normal skin homeostasis, wound healing, and the formation of neoplasms. TA cells divide in the suprabasal layers before moving from the basal layer to the tissue surface, where they are usually lost as squames **[34]**.

Hepatic stem cells: The liver has a robust regenerating potential that employs several forms of regeneration Depending on the lesion's kind and severity. Adult liver cells can multiply to repair damaged tissue, allowing parenchymal function to be restored (35). Chronic liver damage activates a possible stem cell storage area in the smallest possible space branching out from the intrahepatic biliary system, which is known as intermediate hepatobiliary cells response. These hepatobiliary cells are produced by Hering canal, that increases in the biliary system before these cells become hepatocytes. The biliary tree in the human liver is organised differently, with the oval cells being referred to as hepatic progenitor cells since the canal of hering extends to the proximal part of the lobule **[36]**.

Pancreatic islets cells: Insulin-producing cells are developed from pluripotent stem cells. With the discovery of these cells, a unique cell source for the treatment of diabetes through cell transplantation and drug research will be made available **[37]**. Insulin-producing beta-cells are replaced every 40 to 50 days by apoptosis, followed by the proliferation and differentiation of new islet cells from pancreatic duct progenitor epithelial cells **[38]**.

Stem cell types according to differentiation

According to their ability to differentiate, classification of stem cell can be done into

totipotent, pluripotent, multipotent, unipotent, and oligopotent types **(Figure 1)**.

Totipotent stem cells: The ability to produce every form of cell is referred to as totipotency. Totipotency refers to a cell's ability to divide, develop, and give birth to healthy offspring of any cell type inside an organism. Oocytes and sperm, the most advanced cells in the human body, may produce any kind of tissue **[39]**.

Pluripotent stem cells: Pluripotency is the ability of a cell inside an organism to differentiate into any form of cell. They began as embryos of a mouse. All have been demonstrated to be capable of differentiating into cells that are typical of a range of adult tissue types, including teratoma and the embryoid body. Some have even been demonstrated to be capable of assisting in mouse development in chimaeras. The appearance, gene expression patterns, and growth factor requirements of various pluripotent stem cell types vary (40). hESCs and iPSCs may be used to generate the majority of effector T and NK cells (41,42). Additionally for the creation of anti-cancer vaccinations **[43, 44]**.

Multipotent stem cells: Multipotency is the property of cells to only make new cells from the tissue from which they were removed **[45]**.

Unipotent stem cell: Adult stem cells are prevalent in adult tissues and can heal injured tissue by replenishing specialised cells. They may heal damaged tissue by replenishing special cells and create a restricted number of cell types. They were believed to be either unipotent, able to create only one kind of cell, or multipotent, able to develop into a variety of cells due to their constrained lineage **[46]**.

Oligopotent stem cells: cells such as such as lymphoid or myeloid stem cells which are specialised cells are developed by Oligopotent cells **[47]**.

STEM CELL CLINICAL APPLICATIONS

Heart failure:

There is currently just one approved clinical research using PSCs to mend the heart. The "ESCORT" experiment sought to ascertain the feasibility and effectiveness of administering hESC-derived precursors to people who were suffering from severe heart failure. Cardiomyocytes made from ESC have never been implanted, despite the fact that the same group has reported progenitors identical to those of non-human primates **[48]**. There is no independent proof that the SSEA-1pos progenitors transplanted can create healthy cardiomyocytes. Only one patient has received therapy thus far without

having any problems with arrhythmias, tumour growth, or unfavourable immunosuppression-related side effects after three months of follow-up **[49].**

Recent advancements in related technology, however, such as scalable and significantly increased cardiac differentiation efficiency in a specific medium **[50]**, a number of enrichment techniques, such as fluorescence-activated cell sorting **[51, 52]**, or improved metabolism **[53]**. The first clinical studies including the transplantation of PSC-derived cardiomyocytes are predicted to begin in the following years, along with the development of the cardiomyocyte subtypes inside these cells **[54, 55]**.

Diabetes mellitus:

Much attention has been drawn to the ability of stem cells to restore damaged tissues and organs **[53]**. Stem cell therapy has emerged as an alluring option for providing Type 1 diabetics with cells that make insulin in response to glucose as an alternative to islet transplantation **[57]**. The environment influences how mesenchymal stem cells develop and specialise. When injected into the organ in vivo, MSCs are anticipated to develop into pancreatic cells that have both exocrine and endocrine functions. Therefore, MSCs made from bone marrow stem cells can be implanted to restore the pancreas' ability to generate paracrine actions and other effects associated to cell differentiation **[58]**. Through differentiation into insulin-producing cells directly, immune modulator secretion, which stops endogenous T cells from causing pancreatic cell death, or other as-yet-unidentified factors impacting insulin secretion or activity, MSC transplantation has a beneficial influence on diabetes **[59]**.

Stem cell therapy and Parkinson's disease:

Parkinson's disease (PD), a common neurological illness, causes bradykinesia, stiffness, and tremor. Although the pathologic aetiology of Parkinson's disease (PD) is a loss in nigrostriatal dopamine (DA) neurons, neuronal degradation also happens in non-DA-ergic systems **[60]**. Motor performance in a rat model of Parkinson's disease can be enhanced by MSCs' capacity to differentiate into tyrosine hydroxylase-positive neurons **[61]**. Additionally, transplanting these cells improved motor function in an animal model of Parkinson's disease. It has been shown that both rat and human MSCs can create DA-ergic cells **[62]**.

Autoimmune diseases:

Autoimmune illnesses are caused by the body's immune reaction versus normal cells and tissues. Due to their capacity to modify immune responses, MSCs have also been suggested as a potential therapy for

autoimmune illnesses. Hematopoietic stem cell transplantation (HSCT) is commonly necessary for patients with severe autoimmune disorders who do not respond to normal treatment **[63]**.

Liver diseases:

MSCs have been employed in several clinical studies during the past few years to treat patients with liver problems. The outcomes showed that utilising MSCs enhanced liver health in a steady and well-tolerated way **[64, 65]**. Amer and colleagues showed that the short-term safety and effectiveness of autologous implantation of hepatocyte-like cells generated by bone marrow MSCs into patients with final stage liver issues **[66]**. Patients with liver failure brought on by hepatitis B virus infection showed short-term efficacy in various biological and clinical markers after receiving homologous BM-MSC transplants, but long-term outcomes were not greatly improved **[67]**. According to recent studies, giving umbilical cord-derived MSCs to patients with liver cirrhosis that has become worse well tolerated, considerably improving liver function, and increasing overall survival **[65, 68]**. Cirrhosis and liver failure can arise from a number of persistent hepatic lesions. MSCs have the capacity to treat liver problems due to their ability for rejuvenation and immunomodulation properties **[69]**.

Ophthalmic Diseases:

The majority of ongoing clinical trials that use transplants of PSC-derived cell products are meant to cure macular degeneration. Since the eye is regarded to be an immune-privileged area, the majority of research currently being planned or conducted uses pre-existing heterologous ESC lines. It's intriguing to note that over 20 ESC-based research on ocular illness have been submitted from countries including Brazil, China, Israel, Korea, the United Kingdom, and the United States. While some studies are still recruiting participants, others have already finished their single study. Two patients were added to a clinical study for homologous iPSC-derived retinal cell transplantation after receiving authorisation from Japanese regulators. In this operation, an iPSC-based transplant is being tested for the first time. The first macular degeneration patient was treated with a retinal cell sheet made from hiPSCs in September 2014 **[70]**. One year after the transplant, there were no significant problems, and neither was there any unexpected development or indication of a systemic or localised malignancy. Up until December 2016, there were no evidence of rejection on the transplanted iPSC-RPE

sheet. Additionally, there was no improvement or decline in the treated eye's best corrected visual acuity, showing that the patient was a good candidate for iPSC-based homologous transplant.

The second patient was not treated because of three copy number abnormalities that were present in one patient's iPSC line but undetectable in the patient's original fibroblasts; these abnormalities would likely affect the expression of the impacted and nearby genes **[71]**. Even if the safety testing conducted indicated no indication that iPSC-derived RPE cells may be tumorigenic, this decision shows that the iPSC field is cognizant of the relevance of safety problems. Allogenic iPSC-derived HLA-matched cells were used to treat a second patient **[72]**.

Renal disease:

For example, CXCL16, SDF-1, CCL-25, and IL-6 are produced by prostate cancer, osteosarcoma, multiple myeloma, and other cancers and induce MSC migration to the tumour microenvironment **[78, 79]**. MSC migration and differentiation within tumours depend on the secretion of pro-inflammatory cytokines including TNF- and IL-1 by immune cells associated with tumours [Wise and Ricardo, 2011].

Cancer:

By encouraging the directed migration of a number of cell types, including as endothelial cells, immune cells, and MSCs, the extracellular matrix (ECM) and secreted paracrine proteins present in the tumour microenvironment influence the development and invasion of the tumour. Tumors frequently experience chronic inflammatory, oxidative, and hypoxic stress events, yet they never recover **[73, 74]**. MSC migration to the microenvironment of a tumour is therefore thought to be comparable to MSC migration to damaged or ischemic regions **[75, 76]**. Indeed, tumour cells and tumor-associated immune cells can contribute to this process by secreting a wide range of chemoattractant substances. For example, CXCL16, SDF-1, CCL-25, and IL-6 are produced by prostate cancer, osteosarcoma, multiple myeloma, and other cancers and induce MSC migration to the tumour microenvironment **[77. 78]**. MSC migration and differentiation within tumours depend on the secretion of pro-inflammatory cytokines including TNF- and IL-1 by immune cells associated with tumours **[79, 80]**.

CONCLUSION:

The mature and specialised cells that make up an organism are formed from stem cells, a type of cell that has an infinite capacity for growth. It examines a revolutionary approach

of reviving diseased tissues and organs that may one day be used to cure a variety of ailments.

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