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Stem cell therapy: An emerging hope in regenerative medicine

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Abstract
In recent years, a new revolutionary giant has developed which gives high hopes, promises and proficient scientific study area is Stem cell therapy. Recent research showing the effective application of stem cell therapies to patients has enriched the hope that such regeneration methods may one day become a remedy for a variety of difficult ailments. In the past few years, clinical trials in which stem cell therapies are involved have raised pretty exponentially. Some of these trials had a notable influence on a number of ailments, such as neurological disorders, pulmonary dysfunctions, diseases related to metabolism and the endocrine system, disorders of reproduction, skin burns, and cardiovascular conditions. Although mesenchymal stem cells (MSCs) have been put to use clinically to treat autoimmune and chronic inflammatory illnesses, concerns about the field of regenerative medicine remain due to their ability to endorse cancer growth and metastasis as well as their overstated therapeutic potential. The most significant obstacle to the development of hESC-based therapeutic medicines is an ethical quandary involving the killing of a human embryo. Induced pluripotent stem cells (iPSCs), which were first developed to address this problem, have since been proven to be effective, although there are still lingering concerns regarding their efficacy for use in medicine. The unwanted differentiation and cancerous transformation are significant safety concerns, iPSCs can be employed for human reproductive cloning, however, their limitless differentiation efficiency raises concerns about the possibility of producing genetically altered human embryos and human-animal chimeras. The issue is contentious because some people claim it goes against nature, yet nature herself gives an opportunity that opens a new avenue for people who suffer from untreated ailments and disorders.

Keywords: Stem cells, stem cell therapies, regenerative medicines, pluripotency, induced pluripotent stem cell (iPSC), Tissue banks, neurodegenerative disorder

Introduction
Stem cell therapy is a type of regenerative medicine that is intended to repair damaged cells in the body by reducing inflammation and modulating the immune system. It holds out considerable hope for future medical therapies since it can increase our understanding of how diseases begin, produce healthy cells to replace unhealthy ones, and test new drugs for both safety and effectiveness. Fortunately, the prospect of regenerative medicine as a contender to traditional drug-based therapies is swiftly becoming a reality due to the active interest of researchers in exploring its envisaged applications across a wide range of diseases like neurodegenerative diseases and diabetes, among many others (Gaipov & Myngbay, 2018) [9]. However, subsequent advancements, such as scientists' capacity to separate and culture embryonic stem cells, their use of somatic cell nuclear transfer for generating stem cells, and their use of methods to produce iPSC, have made it controversial. Human cloning and political views on abortion are frequently brought up in this debate. The public endorsement of therapies based on the provision of safeguarded umbilical cord blood has also generated criticism. Researchers anticipate being able to restore bodily tissues that have been harmed by illness or trauma with stem cells in the future (Ashan *et al*., 2007) [3]. When tissue and organ transplantation need to be performed, stem cells serve as the best approach because of their ability to differentiate into the precise cell types needed to facilitate the repair of damaged tissues. However, due to the complexity of stem cell-based therapies, researchers usually seek stable, secure, and easily accessible sources of stem cells that can differentiate into an assortment of progenitors (Aly, 2020) [1].

Definition and types of stem cells

Stem cells have the capacity for self-renewal and can replace the organ and tissue cell types that have been damaged or destroyed. The developmental potential of these cells decreases with each stage of specialization, which occurs in both embryonic and adult cells. On the basis of differentiation, potential stem cells are of 5 types: Totipotent, with the ability to mould into both extraembryonic and embryonic cell types. Endodermal, mesodermal, and ectodermal sorts of cells can all be synthesized by pluripotent organisms. Multipotent differentiate into any cell type of a cell family that is primarily closely related. Both oligopotent and unipotent cells have a knack to differentiate, but only in the context of a few cell types, and only one cell type respectively.

It can be divided into Embryonic and adult stem cells on the basis of their origin, the sources are-

- **Embryonic stem cells:** These are formed from embryos before they embed themselves in the uterus and are detected in the inner cell mass of the blastocyst after five days of development. They may be eternal. Blastocysts, hollow microscopic balls of cells, are the name for these cells, which are normally 4-5 days old.
- **Adult stem cells:** Adult stem cells are totipotent or pluripotent, undifferentiated cells. These cells are widespread throughout our body and help to replenish damaged or dying cells while preserving a healthy cell count.
- **Induced pluripotent cells:** They are derived from somatic cells, but scientists have the ability to reprogramme them to return to their pluripotent state. Modifying the expression of a number of genes was carried out.
- **Mesenchymal Stem Cells:** The stroma, or connective tissues that surround other tissues and organs, are mostly used to create these cells. The first mesenchymal stem cells, which can turn into bones, fat cells, and cartilage, were discovered in the bone marrow. Depending on the organ from which they come, mesenchymal stem cells have different properties.

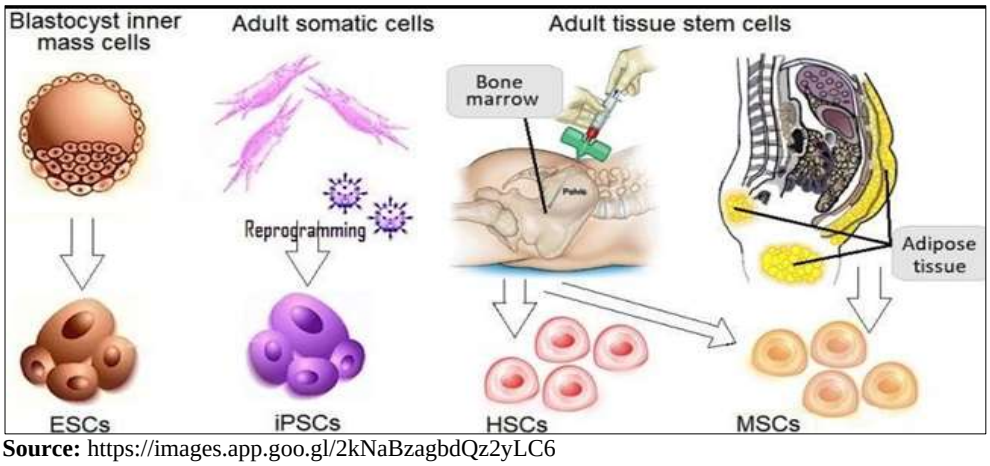

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Fig 1: Different types of stem cells and their sources

History and turning point in stem cell therapy

A significant turning point in the field of stem cell therapy emerged when researchers Shinya Yamanaka and Kazutoshi Takahashi discovered that it was conceivable to alter multipotent adult stem cells into a pluripotent state. By using this method, the life of the foetus was not in danger. The four transcription factors Oct-3/4, Sox2, KLF4, and c-Myc, which are mostly expressed in embryonic stem cells, could cause mouse fibroblasts to become pluripotent through retrovirus-mediated transduction (Takahashi *et al*., 2007; Takahashi & Yamanaka, 2006) [19-20]. Induced pluripotent stem cells are the name given to this novel type of stem cell. The experiment with human cells was successful a year later as well (Williams, B, 2019) [23]. With this accomplishment under its belt, the method went on to produce iPSC lines that can be tailored to the patient's requirements and are biocompatible with them, opening up a new avenue of stem cell research. Recently, research has emphasized reducing carcinogenesis and boosting the conduction system. But before iPSC-derived cells may be used in cell treatments, a number of issues still need to be resolved. These problems include locating and eliminating incompletely differentiated cells, addressing genomic and epigenetic alterations in the generated cells, and preventing the possibility that these cells would become tumorigenic when transplanted (Attwood & Edel, 2019) [4].

Applications of stem cell therapy

In the year 1963, McCulloch and Till's experiment demonstrated that bone marrow-derived cells can restore damaged tissue. This culminated in several hematopoietic stem cell transplantations and medicinal studies. Hematopoietic stem cell transplantation evolved and became the go-to therapy for patients with hematologic diseases and bone marrow failures during the course of the following 20 years. As more types of stem cells were discovered in various tissues over time, new clinical applications for them began to spring up (Shihadeh, 2015) [17]. Stem cell therapy, an area of regenerative medicine that is quickly developing, has demonstrated promising outcomes in the treatment of a number of illnesses and ailments. Over 40,000 transplants have been carried out globally to save thousands of lives. About 50% of stem cell-based clinical trials take 2 to 5 years to complete. To minimize potential detrimental consequences, every novel stem cell product should only be certified for clinical commercialization after effectively finishing Phase I-IV clinical trials. The number of stem cell-based businesses developing therapeutic applications has quickly expanded in recent years (Mousaei Ghasroldasht *et al*., 2022) [15]. Due to their high proliferative and regenerative capacity, immunomodulation ability, anti-apoptosis, angiogenesis, anti-scarring, and chemo-attraction activities, MSCs have recently been shown to be a

promising cellular therapy for COVID-19 patients. Their functions' immunomodulatory action serves as the main repair and regeneration process for the lungs (Begüm Nisa *et al*., 2022) [5].

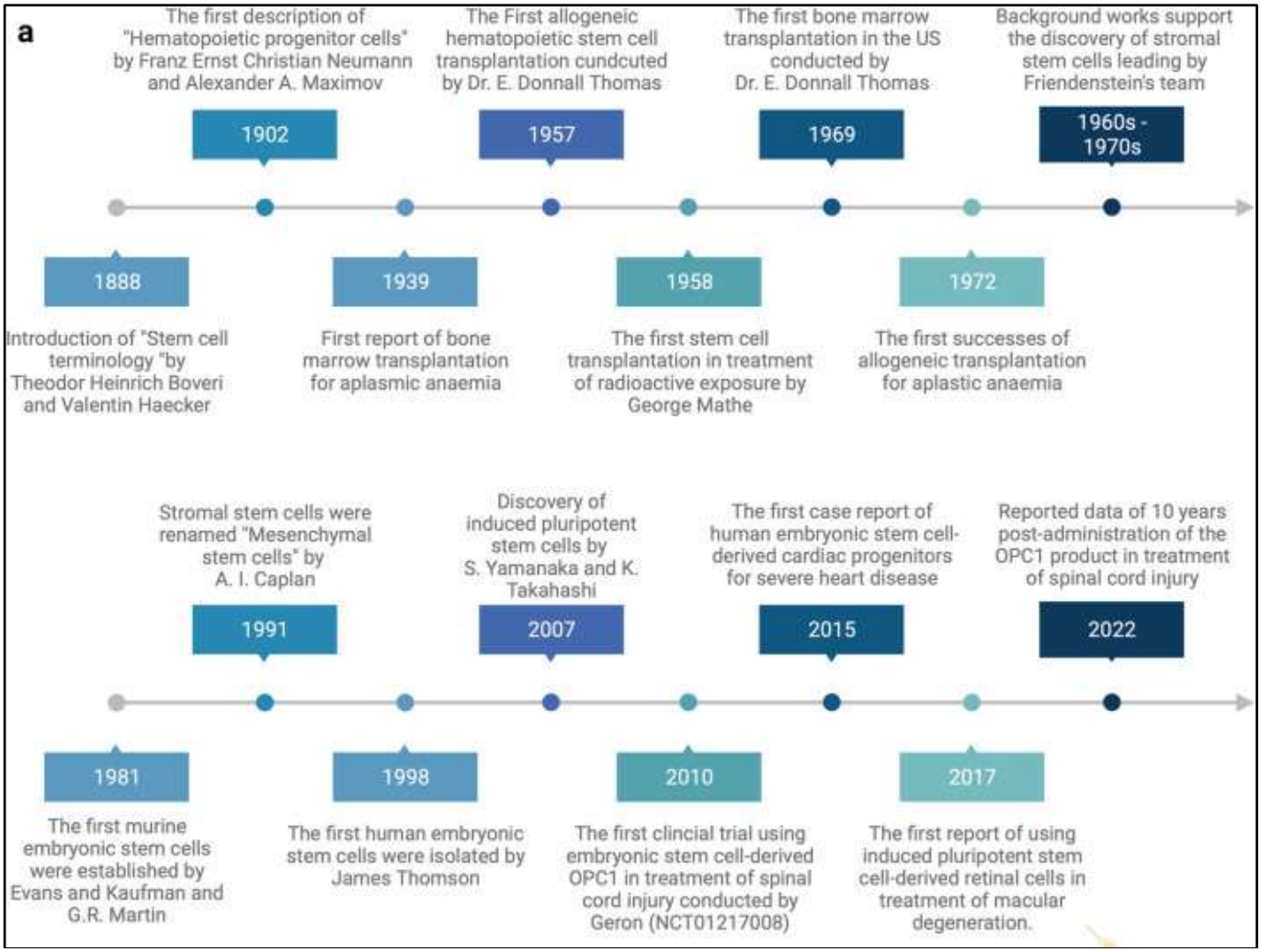
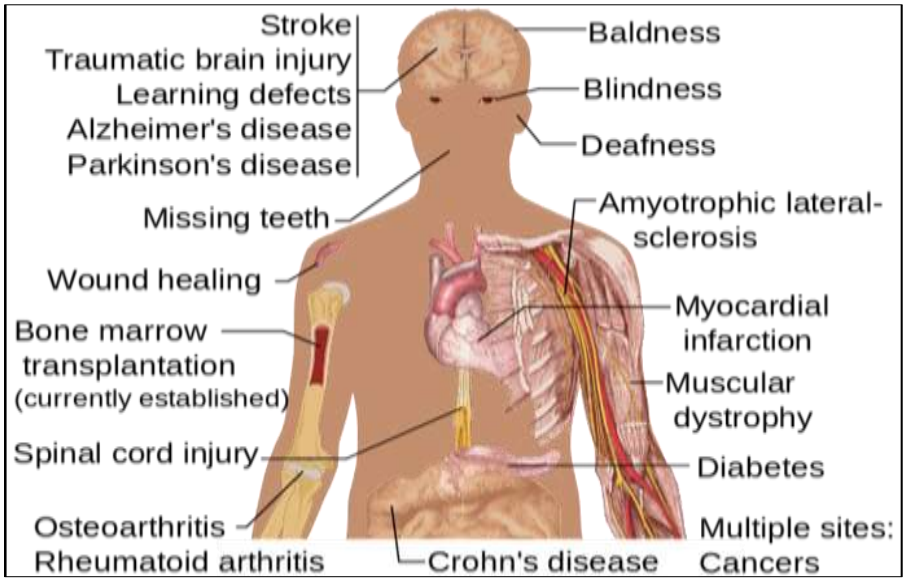


Fig 2: Stem cell therapy- the history and cell source (Hoang *et al*., 2022) [11]



Source:https://upload.wikimedia.org/wikipedia/commons/thumb/b/bd/Stem_cell_treatments.svg/731px-Stem_cell_treatments.svg.png?20120304050608

Fig 3: Diseases and conditions where stem cell treatment is promising

Table 1: List of diseases treated by stem cells in Human Medicine

Category of disorders	Name of diseases
Neurological disorders	Parkinson's diseases Multiple sclerosis (MS) Amyotrophic lateral sclerosis (ALS) Alzheimer's disease Spinal muscular atrophy (SMA) Stroke Traumatic brain injury (TBI) Spinal cord injury
Diabetes	Type 1 Diabetes mellitus
Ocular diseases	Age-related macular degeneration Retinitis pigmentosa Corneal diseases
Skin disorders	Severe burns Epidermolysis bullosa Frailty syndrome
Gastrointestinal disorders	Crohn's disease Ulcerative colitis Graft-versus-host disease (GVHD)
Musculoskeletal and connective tissue disorders	Osteoarthritis Cartilage defects Osteogenesis imperfecta Bone fractures and nonunions
Lung diseases	Chronic obstructive pulmonary disease Idiopathic pulmonary fibrosis Cystic fibrosis
Kidney diseases	Chronic kidney disease Acute kidney injury
Liver diseases	Liver cirrhosis Acute liver failure
Cardiovascular diseases	Ischemic heart disease Dilated cardiomyopathy Congestive heart failure Peripheral arterial disease
Autoimmune disorders	Systemic lupus erythematosus Multiple sclerosis Rheumatoid arthritis Sjogren's syndrome Systemic sclerosis
Inherited immune system disorders	Severe combined immunodeficiency Wiskott-Aldrich syndrome Chronic granulomatous diseases
Inherited metabolic disorders	Hurler syndrome Adrenoleukodystrophy Metachromatic leukodystrophy Gaucher disease
Bone marrow failure syndromes	Aplastic anemia Paroxysmal nocturnal hemoglobinuria Fanconi anemia Pure red cell aplasia
Hematologic malignancies	Acute myeloid leukemia (AML) Acute lymphoblastic leukemia (ALL) Chronic myeloid leukemia (CML) Multiple myeloma Myelodysplastic syndromes (MDS)

Source: The above data tabulated from (Shihadeh, 2015) [17], (Amira Ragab EL Barky*, 2017) [2], (Gaipov & Myngbay, 2018) [9], (Aly, 2020) [1], (Bhattarai, 2020) [6], (Hoang *et al*., 2022) [11], (Mousaei Ghasroldasht *et al*., 2022) [15]

Veterinary Medicine

The enhancement of stem cell therapies in veterinary helps to treat a variety of ailments and illnesses like myocardial infarction, stroke, tendon and ligament injury, osteoarthritis, osteochondrosis, and muscular dystrophy. This has been aided by research on horses, dogs, and cats.

Tissue banks

In order to furnish researchers with adaptable iPSCs cell lines to speed up stem cell treatments through genetic variation research and disease modelling, the California Institute for Regenerative Medicine (CIRM) recently developed an iPSCs repository (Attwood & Edel, 2019) [4]. The umbilical cord, which can be successfully cryopreserved after birth and enables stem cells to be kept and processed for use in cell-based therapies for an individual's incurable diseases, is another key asset for stem cell banking. Human exfoliated deciduous teeth (SHEDs) are a more appealing source for stem cell banking. These

cells can differentiate into more types of cells than the other adult stem cells (Ma *et al*., 2012) [13].

Haematopoietic stem cell transplantation

The most extensively studied tissue-specific stem cell by far is the hematopoietic stem cell, which is why hematopoietic stem cells are significant. Multipotent HSC transplantation is now the most popular stem cell therapy. Target cells are often derived from bone marrow, peripheral blood, or umbilical cord blood (Rocha & Gluckman, 2006) [16]. Allogenic, autologous, or syngeneic procedures are all possible. HSCs are responsible for producing all of the blood's functional haematopoietic lineages, including erythrocytes, leukocytes, and platelets. HSC transplantation treats illnesses including leukaemia and anaemia that are caused by the haematopoietic system's malfunction (Ashan *et al*., 2007) [3].

Stem cells as an arthroplasty replacement

An increased risk of developing osteoarthritis (OA), a degenerative condition of the joints, is associated with tendon issues. Because articular cartilage has a limited ability to regenerate and is avascular, OA is a prevalent condition (Chen *et al*., 2017) [7]. Even though arthroplasty is already a prevalent treatment for OA, it is not recommended for younger patients because they may outlive the implant and need additional surgeries down later in life (Widuchowski *et al*., 2007) [22]. However, these techniques need more development, and long-term hyaline cartilage maintenance research is needed.

Rejuvenation by cell programming

In 2011, the first version of the cell rejuvenation study was released. This was contingent on an epigenetic concept, which explains that all signs of parenteral ageing are removed from the zygote's DNA and its ageing clock is reset to 0 at the time of fertilisation. Their research focused on pancreatic and skeletal muscle cells, having a limited capacity for regeneration, and used the OSKM genes Oct4, Sox2, Klf4, and C-myc (Goya *et al*., 2018) [10]. They discovered through their technique that these genes can also be utilized for successful regenerative medicine (Lázaro *et al*., 2017) [12]. Their approach's key obstacle was the requirement to use a strategy excluding transgenic animals and doesn't necessitate an endlessly prolonged application. The first clinical strategy would be preventive and aimed at reducing or halting the pace of ageing. Later, attempts at gradual rejuvenation of the elderly are possible. Future applications of this technology could bring up moral concerns like overpopulation's detrimental effect on food and energy availability.

Stem cells in dentistry

The stem cells to rebuild dental structures and periodontal tissues have been successfully isolated from human teeth. Due to their accessibility, capacity to differentiate into osteoblasts and odontoblasts, and lack of ethical problems, these cells have been referred to as ideal cell sources. Additionally, dental stem cells showed improved immunomodulatory abilities, either through cell-to-cell communication or a paracrine effect. Regeneration of periodontal tissue, restoration of the mandibular bone defect, regeneration of dental pulp, and Sjögren's syndrome is currently being tested (Aly, 2020) [1].

Table 2: FDA approved Stem cell products and Companies in 2022

Stem cell Products	Origin Company
ABECMA (idecabtagene vicleucel)	Celgene Corporation, a Bristol-Myers Squibb Company
ADSTILADRIN	Ferring Pharmaceuticals A/S
ALLOCORD (HPC, Cord Blood)	SSM Cardinal Glennon Children's Medical Center
BREYANZI	Juno Therapeutics, Inc., a Bristol-Myers Squibb Company
CARVYKTI (ciltacabtagene autoleucel)	Janssen Biotech, Inc.
CLEVECORD (HPC Cord Blood)	Cleveland Cord Blood Center
Ducord, HPC Cord Blood	Duke University School of Medicine
GINTUIT (Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen)	Organogenesis Incorporated
HEMACORD (HPC, cord blood)	New York Blood Center
HEMGENIX	CSL Behring LLC
HPC, Cord Blood	Clinimmune Labs, University of Colorado Cord Blood Bank
HPC, Cord Blood - MD Anderson	MD Anderson Cord Blood Bank
HPC, Cord Blood - LifeSouth	LifeSouth Community Blood Centers, Inc.
HPC, Cord Blood - Bloodworks	Bloodworks
IMLYGIC (talimogene laherparepvec)	BioVex, Inc., a subsidiary of Amgen Inc.
KYMRIAH (tisagenlecleucel)	Novartis Pharmaceuticals Corporation
LAVIV (Azficel-T)	Fibrocell Technologies
LUXTURNA	Spark Therapeutics, Inc.
MACI (Autologous Cultured Chondrocytes on a Porcine Collagen Membrane)	Vericel Corp.
PROVENGE (sipuleucel-T)	Dendreon Corp.
RETHYMIC	Enzyvant Therapeutics GmbH
SKYSONA (elivaldogene autotemcel)	bluebird bio, Inc.
STRATAGRAFT	Stratatech Corporation
TECARTUS (brexucabtagene autoleucel)	Kite Pharma, Inc.
YESCARTA (axicabtagene ciloleucel)	Kite Pharma, Incorporated
ZYNTEGLO (betibeglogene autotemcel)	bluebird bio, Inc.
ZOLGENSMA (onasemnogene abeparvovec-xioi)	Novartis Gene Therapies, Inc.

Source: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products

The other side of the coin: controversies and limitations of stem cell therapy

Although stem cell therapy offers hope for future regenerative treatments and life, there are numerous moral and potentially fatal problems with it. One of the most challenging ethical issues currently facing is the rising number of clinics offering unproven stem cell-based therapies. Therefore, it is the moral obligation of researchers to ensure that the achievement of clinical translation success does not compromise moral considerations.

- The use of embryonic stem cells is debatable because doing so necessitates the destruction of an embryo. Its use is governed by laws and regulations in many nations due to ethical considerations (Volarevic *et al*., 2018) [21].
- Since iPSCs have an infinite capacity for differentiation, they are still viewed as a high-risk therapy option because transplanting these cells could result in the development of tumours (Clinic, n.d.)
- MSCs have been widely accepted as being safe, but ongoing observation and extended follow-up should be the focus of future studies to prevent the likelihood of tumour development after therapies (Volarevic *et al*., 2018) [21]. In contrast to their low frequency, HSCs require significant upkeep. Furthermore, its signalling mechanism is still unknown. The natural regeneration capacity of Adult stem cells is too limited, further acquisition and isolation are difficult and need research to implement (Sun *et al*., 2014) [18]
- When cells are reprogrammed, the chance of expression of oncogenes may increase. In spite of the fact that it is still inefficient and takes more time, a method for removing oncogenes after a cell gained pluripotency was uncovered in 2008. Deletion of the tumour suppressor gene p53 may speed up the reprogramming process, but as this gene is also a major cancer regulator, it cannot be removed to prevent additional mutations in the reprogrammed cell (Mascetti & Pedersen, 2016) [14].
- To transplant new, fully functioning organs created by stem cell treatment, millions of working, biologically accurate cooperating cells would be required. To incorporate such difficult treatments into general, broad regenerative medicine, cooperation across disciplinary boundaries and countries will be crucial.

Future scope of stem cell therapy

Despite the numerous difficulties encountered, the range of new stem cell applications grows with every new scientific investigation. It is currently making remarkable gains, with promises of clinical success in treating a number of ailments, including macular degeneration and neurological conditions. iPSCs are reshaping the field of stem cell research, with myriad potential uses for employing patient-derived stem cells to treat disease. It has now reached the clinic and will soon be accepted as a therapy option to use MSCs to rejuvenate periodontal and dental tissues. In order to achieve good immunological tolerance between stem cells and the patient's body, researchers use the patient's own cells and descend them into their pluripotent stage of growth (Aly, 2020) [1].

Conclusion

After decades of research, stem cell therapy is now a big game changer for medicine. Every experiment shows that stem cells have more potential, yet there are still many problems to be resolved. The field of transplantology and regenerative medicine is greatly impacted by stem cells. Neurological illnesses that are today incurable may one day be healed using stem cell therapy. Tissue banks are becoming more and more popular as they gather the cells that form the basis of regenerative medicine in the battle against diseases of the present and the future. We are now more capable than ever of extending human life thanks to stem cell therapy.

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