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Stem Cell Therapy, Solution to Unsolved Problems an Inclusive Review

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ABSTRACT

At present there are few diseases existing which do not have a perfect cure through medicines or surgeries, so stem cell therapy fills this space with its vast potential to palliate the sufferings of those kinds of diseases or ailments. With its application research is happening in this field at a remarkable rate. Stem cells keep the tendency to self-renew and differentiate into various several cell types. Its commonly done on all those multicellular organisms who multiplies themselves by cell division. Especially in the field of organ transplantation and tissue culture stem cell therapy has shown a greater impact. In these recent times we are not modifying its chemistry rather we are finding biological solutions for the biological trouble. It's a regenerative therapy which makes use of undifferentiated cells to mend certain issues. Stem cell established therapies includes investigative approach for several disorders, such as liver disease, autoimmune diseases ,neurodegenerative conditions Parkinson's disease diabetes, cardiovascular disease and for nerve regeneration, orofacial problems, temporomandibular joint reconstruction, alveolar bone regeneration) and many more. So here is the small review on the stem cells uses and benefits compared to the normal conventional medication treatments followed normally. Believed that stem cell therapy will make a huge impact on the face of human disease treatment and reduce the suffering caused.

Keywords: Embryonic stem cells; Scaffolds; Potency; Alzheimer's disease; Stroke treatment; Transcription activator-like effector nuclease; Bone marrow stem cells

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INTRODUCTION

Stem cells are majorly known as the harbingers of organic structured tissues. They are competent enough to generate daughter cells which are immature or undifferentiated and identical or of differentiating into varied cellular compositions [1]. There are procured from mainly two sources that are autologous and allogenic. Autologous embryonic stem cells are engendered by genetic copying and adult plastic stem cells coming from umbilical cord or bone marrow. On the other hand allogenes stem cells are descended from marrow, peripheral blood, cord blood and family donors or human leukocyte antigen may be typed or untyped orthogonal donors [2].

Stem Cells and its Types

Stem cells are widely classified as, embryonic stem cells (ESC) and adult stem cells (ASC).

Embryo stem cells:

They are the beginning of stem cells, embryos at a growing state prior during notation and generally appear in the womb. Blastocysts -32 cell stage is the development stage from where these pluripotent cells are cut off [3]. Pleuripotency is responsible for the cells to germ cells endoderm, mesoderm and ectoderm. They are developed more than 200 cell types in the body of an adult on giving reasonable amount of stimulation for a particular cell type [4]. It distinct ES cells from that of multipotent cells. Scientists have discovered a gene that recognized a gene which codes for transcription Sall4 protein capable to turn on gene and turn off it. These cistrons become critical for the identification cells of certain types. Expansion from the primitive cell is assisted by the

transcription factors developing the tissue and whole progress from the fecundated egg to grow into individuals. Proteins responsible for the pleuripotency of ES cells are, Oct 4 protein, an efficient marker for pleuripotent cells and embryonic Stem cells. Its face must be asserted at a decisive level to remain in undifferentiated state. Nanong protein, Required for sustainment of the uniformity in the state of the animal cells. Studies suggest that the Wnt-βcatenin signaling regulates pleuripotency [1,5].

Adult cells:
Cells that is undifferentiated and multiplied to revive the cells which are dying. They are called as somatic stem cells. Some of the properties that it possess:

Self-Renewal
Multipotency:
Bmi-1, among the transcriptional repressor polycambing group proteins, invented from onco gene in lymphoma [6] and afterwards seen to determine the number of hemato-poietic stem cells [6,7]. NNotch, it controls proliferation of stem cell and recently has evidenced for its functioning in various cell types involving neural, hematopoietic and mammary cells [8]. Wn and Sonic hedgehog, one of the pathways in stem cell regulation [9]. Plasticity, Differentiation of cells to another is termed as transdifferentiation, reproducibility of differentiation of stem cells are called as development plasticity [10,11]. Adult stem cells are present deep down the tissues of the organs spreads with limited capability to multiply. It's a bit constrain to convey components essentially require to explain the properties of embryonic cells by Induced pluripotent stem cells they are the markers of stem cells that are able to produce cell characteristic of three types of germ layers. iPSCs shown its vital role in development of drugs and disease modeling and mainly in transplantation of medicine [12,13]. The divisions in stem cells, those are totipotent cells, which produce and develop all the remaining cells and types of tissues in an organism, Pluripotent cells also generates most of the cells, multipotent stem cells generates a given amount of cells and tissues types, and rely mostly on the germ layers from the origin [13]. Bone marrow is the bank of almost all the adult stem cells. They are also classified into two types, [1] Hematopoietic stem cells, It gives birth to the blood cells like myeloid (macrophages, monocytes, neutrophils, megakaryocytes, basophils, erythrocytes, eosinophil's and few cells of dendrites) and lymphoid ancestries [14,15]. Stromal stem cells of bone marrow, stem cells of mammary responsible for growth of mammary glands at the time of puberty and gestation with a key role in breast cancer [16]. A cell gives rise to luminal and myoepithelial cells, these glands have exposed to reproduce needed organ in tested mouse [17]. MSCs are multipotent cells which differentiates into various types of cells be it *in vitro* or *in vivo* osteoblasts, chondrocytes, myositis, adipocytes, neuronal cells etc. and included beta islet in cells of pancreas. Produced from the bone marrow it may refer to stromal cells too. Mesenchymal stem cells are able to embrace cells obtained from other than marrow sources, like cells from umbilical cord and stromal cells which are multiple cell types with distinct potential for multiplication and distinctions. As a whole, mesenchymal stem cells constitute more of homogenous subpopulation owning to features particular to surface of cell markers [2]. Neural stem cells (NSCs), with the discovery of neurogenesis presence of stem cells in the adult brain have been contended. Adult neurogenesis is limited till subventriculare zone that covers lateral region of ventricles in brain, also organizations of the hippocampal in the dentate gyrus region. Newer neuron production in the hippocampus is nicely established and some more clarity about the presence of true self renewing stem cells is required [18]. NSC developed *in vitro* is called neuronal spheres those are the hovering heterogenous conglomerations of cells having large ratio of stem cells [2]. Olfactory adult stem cells, Human olfactory mucosa cells act as the source for olfactory adult stem cells especially the inner lining of nostrils [19]. Adipose derived cells, the cells obtained from human fat, using liposuction. This is same to that of MSCs gained from marrow cells in the bone. Human adipose derived stem cells (ASC's) are capable of differentiating into bone tissue, cartilage, fat, muscle and also into neuron tissues, with a huge scope in neurological application in future [20,21]. Multipotent progenitor cells, the marrow cells havens certain type of heterogeneous population which has got vast development capacity tagged as progenitor cells. It is said that they are crowd of stem cells deduced from closely bonded stem cells of embryos [22].

History behind:
The history started with Ernest A McCulloch and James E Till in 1960s in Canada [23,24]. Use of bone marrow transplant with respect to stem cell transplant (SCT) by Schretzenmyr in 1930's [25] as cells found from the bone marrow of adults [26]. By *in vitro* fertilization (IVF) in 1959 first animal made taking a step closer towards SCT (stem cell transplant). By the end of 1960s, teratocarcinomas identified from germ cells of embryo in mice and Embryonic Carcinomal (EC) cells found to be similar to that of stem cell. In 1968 fertilization of first human egg by *in vitro* means and increased tendency of exploitation of totipotency of stem cells in 1984-1988 pluripotent clonal cells were developed. In 1989 clonal lines of carcinoma embryonic human cells were obtained that ceded tissues from particular germ layers [25].

In 1998 Embryonic Stem cells (ES) cells acquired from blastocysts were cultured, and many passages were done. Human Embryonic Stem cells were derived from mass of inner cell in blastocysts during 2000s. Stem cell research was taken to next level as many lines of cell were passed and new lines were made, but more focus went more on cell differentiation in laboratories [2].

Stem Cells and its Properties

The characteristic features of these cells that differentiate it from modified cells are, Self-renewing capacity that is by asseverating their differentiation and undergoing number of cell division cycles, and to develop outside the host, under a specified condition in the given environment. Which makes it either totipotent or pleuripotent [13].

Stem Cells Extraction

Even they come from allogeneic contributions. ESCs and adult stem cell samples are generally placed under specified conditions in labs or cell banks [13,27]. The main supplier is the bone marrow, harvesting peripheral blood stem cell; rituxan and purging etc. are involved. Their particular receptors like TRA-1-60 and Oct4 which are known as markers of the stem cells that are on the surface and also extraction is made possible out of it [28]. Those developed on a suitable scaffold constructed of natural materials such as polytetrafluoroethylene, polyglycolic acid, fibrin sealant and different growth factors, during regeneration of tissue those which act as a temporary matrix [29,30].

Present Scenario in Stem Cell Therapy

Genetic therapy:

The genetic manipulation of human embryonic stem cells which provides a scope to introduce a therapeutic gene into them. It may be active or waiting to get activated, when modified embryonic stem cells differentiate to its desired cell type [31]. Like e.g. skin cells obtained from an immuno deficient mouse utilized to produce cellular therapy that restores important functions in it. Thus can be applicable in treatment of human immuno deficient patients too. They can provide continuous invariable *in vitro* source for cellular material and optimize certain protocols related to extension and genetic alteration techniques [32].

Drug testing:

Embryonic stem cells limitless proliferation helps to contribute for different cell types, as it offers a strange typical access to various tissues in human body its differentiation function human tissues provide substances which help in testing and improvise on its efficacy and safety parameters [33,34]. Human embryonic stem cells are extremely vital in identifying and detecting such drugs before they come for clinical trials, hence facilitating the drug discovery by safer and more efficacious treatment [35-37].

Brain damage:

In such cases reparative process helps in backing up but significant recovery is seen very few in elders making it less robust. Recently research done on rats induced with stroke on application with medicament to elevate the multiplication of cells with increasing the endurance and distinction of lately developed cells that were found to be victorious [5,38,39].

Cancer

Intracranial tumor induced into rodents which were then injected with neural cells of humans. These cells travels to carcinogenic tissues release cytosine deaminize, which converts prodrug that is nontoxic into a chemical therapeutic agent. As an observation the invasion of substance it was observed to abbreviate tumor proliferation by more than 70% [9,16].

Spinal cord injury:

Isolation of adult stem cells from blood of umbilical cord and then interjected into required back bone region [40].

Hurt to muscle:

Apparently ASCs corrects damage to muscles especially after heart diseases. Cardiac arrests are caused because of coronary artery blockage, preventing the reach of oxygen and nutrients to the heart tissues. After the attacks cells customize and remodel it to pump properly. Due to the decreased blood flow this try may be ineffectual and result in more cell death. Research revealed that administering marrow stem cells (BMSCs) to mice undergoing induced cardiac arrests showing 33% more efficient pumping of heart ,also the damaged tissue were regrown and matured by 68% [11,41].

Heart damage:
This started with a hypothesis that has ended up in clinical trials aiming for heart disease treatment and has proven to be therapeutically safe. None of it till now has proven efficacious. Recent trend is using patients own marrow cells from big bones such as femur etc., deducing it stem cells and side line derived blood stem cells [36,37].

Controversies Involved in Stem Cell Research
As it has to be harvested from human embryos for several vital applications, unfortunately still there are lot many ethical concerns revolving around it which has to be fulfilled every now and then. Adult stem cells offer a unique alternative by isolating, studying and manipulating without any harm to the donor. Currently there are several obstacles regarding the adult stem cells employment. As of scarcity of stem cell markers identification of most adult stem cells are hindered. Manipulations of adult stem cells in various different populations are generally not well explained. Adult cells regulation of their forte is in its babyhood [2].

Views of Stem Cell Research in Future
Less supply of blood:
Precursor RBCs, known as hematopoietic stem cells are developed with stromal cells, mimicking the similar atmospheric conditions of bone marrow, the site where RBCs are grown. Growth factors such as erythropoietin, added to coax stem cells to finish terminal differentiation. Many more researches been carried out for this technique to check the potential benefits into blood transfusion and gene therapy [2].

Baldness:
Hair follicles are another source of stem cells, and many researches are going, on these follicles. Hair cloning technique being adapted to treat baldness and can be predictable for the job by acquiring cells from follicles of already accessible tissues, reproducing and proliferating using repetitive culturing, embedding newer follicle which shrinks with the process of getting old or ageing. This process may give a positive response by regenerating healthy hair [42].

Missing teeth:
Theoretically, stem cells extracted from the patients are coaxed then turned into a tooth bud that on placing in the gum will generate newer teeth at a probable time span of few months for its growth. Fusion to jaw lines and secretion of substances which supports tube lines in the body connection is predicted [2].

Deafness:
Regeneration of cochlear cells using of stem cells is predicted for its future treatment as it never grows back once if it is gone or destroyed, so it gives a huge scope for stem cells to grow those limited follicles present in the ear.

Blindness and vision improvement:
Restoring vision by successful transplantation of retinal stem cells, using embryonic stem cells, top potent stem cells sheets are developed and grown in the laboratory. On transplantation over the damaged retina, it induces neural repair and ultimately restoring vision. All of its trials are going on [43].

Regeneration of bone:
Mesenchymal stem cells amassed from various animals and humans have shown regeneration power of functional tissue on delivering at the region of skeletal defects in certain animals for experimentation. Stem cells Mesenchyma are able to regenerate bone in a clinically significant osseous defect and thus provides a substitute to autogenous bone grafting [2].

Diabetes type I:
When patients own immune system demolishes the cells of the pancreas responsible for production of insulin diabetes type I is caused. studies indicate that it can show the separation of embryonic stem cells to form and develop cells which produce insulin that are required in transplantation therapy for diabetes [2].

Clinical Applications and Research
Ulcerative lesions:
Oral ulcers and wound healing: For a cutaneous wound to heal properly it requires a good accumulation and integration after its multiplication of the cells together which then should have a good supply of extra cellular matrix and rich supply of blood through blood vessels. Sometimes large wounds leaves behind unacceptable scars that which happen due to the memory of the cells on its impact created making it to follow the same

manner in the coming cell division. Bone marrow cells can differentiate and divide into osteoblasts, chondrocytes and adipocytes and can renew by its own. They disseminate at the place of damage and augment tissue rebirth and wound healing by down regulation process of proinflammatory cytokines and production of soluble factors with antioxidant, antiapoptotic, and proangiogenic properties. All the outcomes were to be seen in the mouse hence, it is a promising therapypeutic method for oral lesions [44].

Role of mesenchymal stem cells in wound healing:

The study was done in a dog which was first administered with mocresol to bring on oral mucosal wounds in it. Afterwards a suspension of autologous bone marrow-mesenchymal stem cells in phosphate buffer was given to check its wound healing property. The lesion was curing at a faster rate by the vascular endothelial growth factor and accumulation of collagen fibers on the affected part and therefore induced ulcers were cured in comparison with the standard. Adipose derivative cells were used for treating ulcers with formocresol. Hence healing was effective [45,46].

Oral mucositis:

Most enfeebling side effects which happen by doing chemo or radiotherapy is oral mucositis. Management of this problem is quiet symptomatic. So the treatment is done by using mesenchymal cells which has got immune idolatry, anti-swelling part. To increase their therapeutic efficacy factors like pro inflammatory cytokines should be used [44]. Mice having oral mucositis were treated with spheroid gingival derivative of mesenchymal stem cells (GMSCs) and it decreased the asperity and severity of ulcer by reforming the papillae layer, the muscle layer and breadth was closely observed to those of untreated disease group. Spheroid derivatives of GMSCs is also potent for injury sites, its formation into epithelial cells by trans differentiation, and supplying oxygen to deprived cells and challenges regarding oxidation has been improved. Hence it was an effective therapy in oral mucositis caused due to the side effects of carcinoma treatment.

Pemphigus vulgaris:

A kind of disease which is affected only to the old aged patients crossing above 60, its quiet dangerous as it gives out auto antibodies blocking the functions of desmosomal glycoproteins in the keratinocytes and when left untreated causes intraepithelial bullae and severe mucosal ulcer formation. Drug of choice are corticosteroids [47]. Allogeneic hematopoietic stem cell transplant (HSCT) used in patients of pemphigus vulgaris. Surprisingly effect starts showing within a day [48] but needs to undergo clinical trials for its official usage [49].

Premalignant Disorders

Oral sub mucous fibrosis:

Oral sub mucous fibrosis is a pernicious disorder mainly associated with both substantially unwholesomeness with more risk of oral carcinomas. Causative agents are somewhat related to all the habits acquired by a particular person like using pan, guthka and areca nuts. The mechanism by which it is caused is the increase in the level of cytokinine which releases more amounts of reactive oxygen species that may even cause the oxidative stress. For the treatment of this disease no conventional therapy was able to give a solution, where stem cells technology came into picture and was also anticipated for quite a while. These cells primary function is to do the free radical scavenging and its destruction with the paracrine effect of the growth factors present in them. Ultimately forcing the host stem cells to transform into new fibroblasts which takes away all structurally altered dis united collagens. BMC invasively administered to buccal mucosal layer and below the tongue with coadministeration of local anaesthetics. With a continuous treatment it helped to decrease the blanching suppleness, reduced sensation of irritation of burns and a fair opening of mouth which was a hindrance earlier. [50,51].

Oral lichen planus:

Epipathogenisis remains unclear till now. Acts by some nonspecific mechanisms like actuation of cytotoxic t cells and mast cell degranulation triggering of basal epithelial cells. T cells with MSCs intended to treat this kind of disorders and their immunomodulatory functions suppress the T cells and beta cells [52,53,27].

Malignant Lesions

Oral carcinomas:

Even after lot of big researches in this field still it's not giving 100% assurance about the cure, as all carcinomas have the tendency to relapse. So on that will be the discussion about stem cells contribution in treatment of oral cancer by suppressing tissue regeneration, immunomodulation, neo angiogenisis etc. Reconstructing many tissues orally in cases of osteosarcoma and ewingsarcoma. Stem cells even have their contribution in cell markers due to presence of various chemo attractants VEGF released by tumor cells and sometimes act as carrier cells [28-30,54-56].

Potential Applications in Dentistry

Regeneration of damaged coronal dentin and pulp:

Using the entire artificial techniques only teeth placement used to be done which is actually dead but here it's not the case pulp generation and then dentin deposition has to be done. Which is actually the intrinsic property of that particular body part? So that's why no medication has a substitution for this problem. Apexification is the technique where regeneration of pulp for the development of both perpendicular and horizontal roots (vertical and lateral) [57]. Pulp can be created using allogenic stem cells into the base root cells [58]. DPSCs can be prepared *in vitro* that has the capability to produce dentin and that can be made useful in osteogenesis and dentinogenesis [59,60].

Craniofacial defects repair and regeneration:

It completely dependent upon natural/synthetic osteoconductive biomaterials, autologous bone grafting, allogeneic bone grafting. If they can be gleaned in a scaffold and transplanted into affected part for regeneration of lost tissues which causes lot of complications associated to the normal conventional techniques. A new fabrication procedure to generate an engineered autologous tissue which repairs segmental mandibular defect. Thus it enhanced ontogenesis and penetration of blood vessels to bone and accelerates tissue regeneration. In an animal model, mixture of MSCs and platelet-rich plasma developed bone implant contact and appropriate bone density in defected mandibular region. To future to promote the regenerative potential, genetic engineering technologies can be utilized to broaden stem cells life and osteogenesis. Even these application needs to undergo a lot of trials before being into official practice. [61-66].

Regeneration of tooth:

With advancements over dentures and bridges, their drawback is the deficiency of natural structural relationship with respect to alveolar bone. The main mechanism involved would be accumulation of bone particles on tooth surface. The rebuilding of murine teeth with the help of cultured stem cells on shifting to renal capsules ended up in growth of tooth like structures. Recent transplantation done in an anthrotopic site of mouse jaw. SCAP and PDLSCs placed in a scaffold and were put into the sockets of the lower jaw. Creation of post channels so as to leave some place after the insertion and then later the bio roots were exposed with an insertion of porcelain crown [67-69].

Few Troubles to Overcome

Sources:

Only 1-4% of the stem cells can be extracted from adult tissues as it is a very technique sensitive protocol. Banking upon till what time it can be stored safely, and retaining the original cells is still a question mark. MSCs who are immunomodulatory lacks MHC type II (major histocompatibility complex) antigen and thus immune reactions will not get provoked. Because of no risk of immune rejection autologous stem cells ideally suits patients and the processes are least expensive, and do not require legal and ethical concerns. Cells should be gratified from an autologous source, isolated and reproduced before it is used and that makes it a time consuming process. The problem of harvesting cells from patients and time consumption can be overcome by using pre-existing allogenic cell lines. Usage of allogenic stem cells is still an issue regarding the safety and *in vivo* studies have been done which supports their immunological safety [70-78].

Signaling molecules [79]:

Growth factors have a greater impact on tissue cell regeneration. They are generally proteins that bind to certain receptors and encourage cellular multiplication and differentiation. Dentin contains many proteins that are capable of stimulating tissue responses. Dentin tissue can itself lead to the release of growth factors on demineralization. Calcium hydroxide therapeutic effect may come from the growth factors in dentin matrix. These growth factors help in signaling for events like tertiary dentinogenesis. Two important groups growth factor-beta (TGF-β) and bone morphogenic proteins (BMPs) plays an important rolein the transformation. Even though we are well known with the functions of signaling molecules, some more clarity is required regarding their spatial arrangement and other compatibility issues [77-88].

Scaffolds:

The scaffolds have to be biodegradable and their degradation rate should co-occur with the tissue formation rate. So as to promote cell seeding and diffusion of nutrients it needs to be highly porous. During fabrication of their own natural matrix, the scaffolds provide structural integrity and then ultimately breaks down leaving out the new tissues. During this time, they should undergo appropriate differentiation of their offspring [89,90].

Scaffold materials:
Many natural and synthetic materials were included for several scaffolds. Materials like collagen, agarose, glycoseaminoglycans (GAGs), alginate, and chitosan have been used from natural source. From synthetic side more extensively used materials which includes hydroxyapetite phosphate, tricalcium phosphate, and various other polymers like polyglycolic acid, polylactic acid, and polycaprolactone. Synthetic polymers showed better conductive effect and less contraction on comparison with collagen [91-95].

Designs and delivery of scaffolds:
It requires soft three dimensional scaffold matrixes for root canal system, such as polymer hydrogel which is noninvasive and can be easily administered by injecting into the root canals. Researchers are making it photo polymerizable to get rigid structures when on implanting to any tissue site. One major issue is the vascularization of the transplanted part. Increased vascularization required in order to support the verve of the transplanted cells in the scaffold. Works on developing a scaffold system which helps in promoting angiogenesis by infusing growth factors such as vascular endothelial growth factor (VEGF) and platelet derived growth factor to endothelial cells. For pulp generation this kind of techniques is very much important because blood comes only from the apical end of the region [96-105].

Stem Cell Treatment of Degenerative Eye Disease
When the retinal cells are not able to regenerate by themselves or gets damaged by any means then permanent blindness occurs as it cannot be repaired as the oxygenic mechanism is inhibited and cannot be reproduced by treatment or surgery. Therefore retinal ganglions have to be made *in vitro* through artificial methods ND cell development. Their major source involves, embryonic induced pluripotent stem cells, neural stem cells and endogenous retinal stem cells and retinal pigment epithelial stem cells [106-109]. Neutrophils activates the threonine kinase in mammalian target of rapamycin (mTOR), inhibits kinase-3β glycogen synthase activity [108,110]. (GSK3β) other roles, regulation of growth cone dynamics [111]. Stimulation of mTOR helped to regenerate these neuronal tissues of studies conducted in mice [112].

NTF Treatment Strategies
Treatments are limited for RGC axonregeneration and delivering individual NTF only cannot help in neuron protection as it is not showing complete action hence intravitreal injection of recombinant BDNF and CNTF rescues axotomised RGC from death for up to 7 days [113,114].

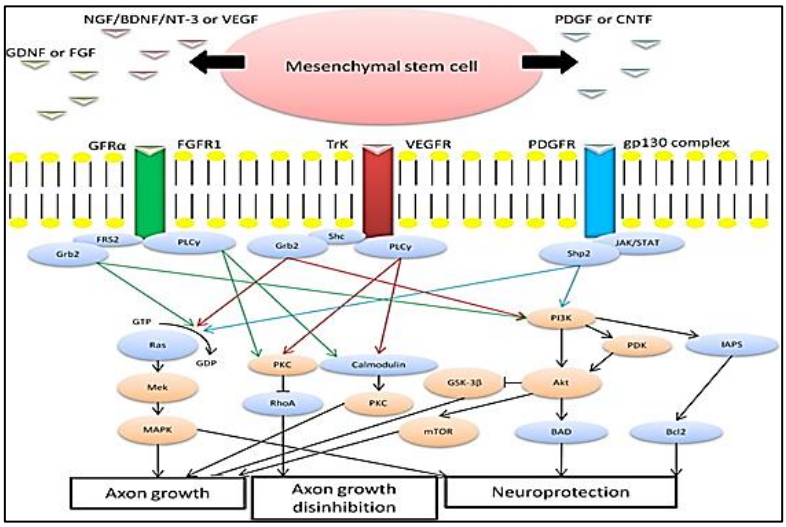

Figure 1: Mechanism of MSCs [115]

The diagram shows the mechanism through which MSCs exert their neurotropic effects on the injured CNS (Figure 1).

Current Clinical Trials Done on Degenerative Eye Disease
Genome editing in human pluripotent stem cells:
To study about variation of genes hPSC established disorder model are well-suited [116]. Bewildering effects of deviations in genetic background of unrelated hPSC lines [117]. To overcome these problems custom-engineered endonucleases which enables accurate and programmable alteration of endogenous hPSC genomic sequences can be used [118]. This strategy will prove priceless for research of human disorders [117]. Like custom engineered nucleases with double-strand breaks (DSBs) repairing either through non-homologous end

joining (NHEJ) or homology-directed repair (HDR) [119]. DSB repair through NHEJ causing frame shift mutations and ultimately results in knockout of protein-coding genes [120]. One of the suitable advantages is the deletion of the unwanted sequences. Zinc-finger nucleases (ZFNs) were greatly used in hPSCs [121]. In an array form the construction allows perfect targeting of genetic loci, as it binds to a particular nucleotide triplet. A substitute for custom-engineered endonuclease is effector nuclease from the plant pathogen Xanthomonas (TALEN) [122]. They are TALE DNA-binding domain fused to a non-specific FokI nuclease domain. TALEN-mediated genome editing for transduction of single cell hPSCs is shown in Table 1 and Figure 2.

Table 1: Survey on degenerative eye disease [115]

Type of treatment	Disorders	Number of Subjects	Observation
BMSC Intra vitreal	Glaucoma, Amd	300	visual field, visual acuity,
BMSC Intra vitreal	Diabetic , retinitis pigmentosa, retinopathy, Amd	15	adverse effect of Incidence severity
BMSC Intra vitreal	retinitis pigmentosa	10	ERG, Visual acuity, contrst sensivity, VEP, colour vision , visual field
BMSC Intra vitreal	Ischemic retinopathy	10	Visual acuity, VEP, ERG Incidence and severity of adverse events, visual field
BMSC Intra vitreal	Amd	50	Visual action
BMSC Intra vitreal	macular dystrophy, amd, stargardts	30	fovea avascular region
BMSC Intra vitreal	Optic atrophy	1	Incidence and severity of adverse events
Intra venous bone marrow mononuclear cells	Dry amd	10	Reduction in optic nerve regeneration visual function and Visual acuity
Intra vitreal AMSC	Dry amd	24	Incidence severity of adverse effect, Visual acuity
retinal ESC resultant RPE	Amd	100	VEP, OCT,Visual acuity, quality of life, visual field
retinal ESC derivative RPE	stargardts muscular dystrophy	12	Incidence severity in adverse effect, Visual acuity
Sub retinal ESC resultant RPE	Dry amd	10	Incidence severity in adverse effect

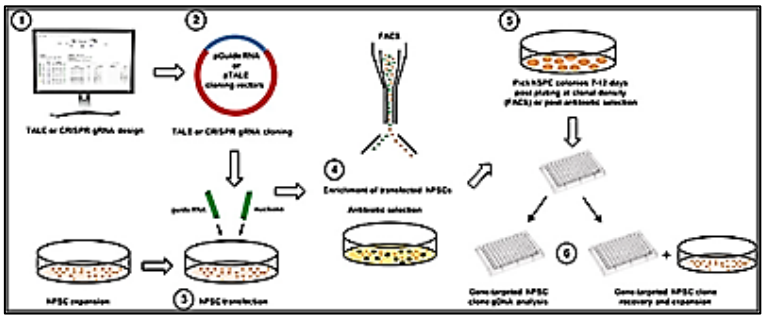

Figure 2: Human pluripotent stem cell gene-editing workflow [123]

DNA Binding Domain, Nuclease, and Template Design

Most suitable engineered endonuclease utilizes Methylation mechanism for target binding [124]. Less binding means less working of TALEN and strong affinity reduces its specificity but its activity is partly related to DNAase1 hypersensitivity [125,126]. But CRISPR/Cas9 limits to loci harboring a protospacer-adjacent motif (PAM), it designs to target any sequence and offers higher targeting densities [127]. Both genome-editing methods have been used to target various genomic loci for the production of NHEJ mediated gene knockout hPSC lines [120,128,129-131] (Figure 3).

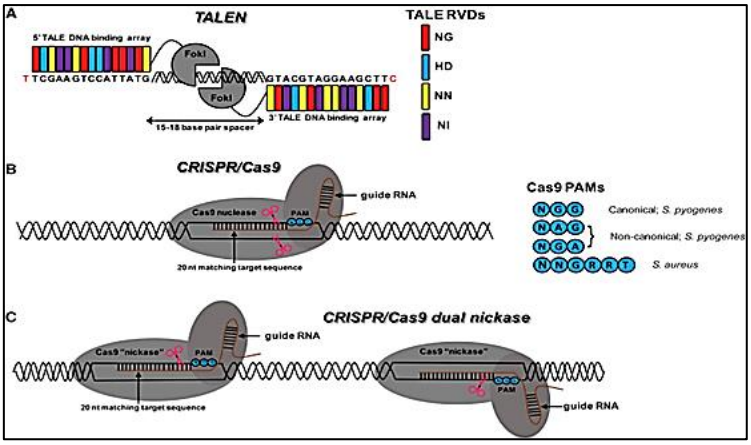

Figure 3: TALEN and CRISPR/Cas9 custom-engineered nucleases (A) Depicting TALE DNA binding array; (B) The CRISPR/Cas9 system that contains a 20-nucleotide-long target DNA-matching sequence (C) Cas9 nickase (Cas9D10A) creating a DNA nick instead of a DSB.

Stem Cell Therapy for Stroke

Neural stem cell:

Wayward to old presumptions, neurogenesis evidence in adult human brain has been demonstrated [132]. Neural stem cells (NSC) are a multipotent variant cells present in the brain which are located in the subventricular zone (SVZ) of the third ventricle [133] and sub granular zone (SGZ) of dentate gyrus [134], responding to brain insults that causes neuronal death such as stroke [135], few of them like Huntington's disease [136], and Alzheimer's [137] disease. They multiply but also move to areas of injury [138]. For stem cell therapypies *in vitro* culture can be done and even if intravenously administered, they have the capability to move into ischemic portions [139]. Generally after a stroke NSC expand, mature into well differentiated neurons and transform into neuronal circuits [140]. Later, the rise in many growth factors that cause changes in NSC's mitotic cell cycle like reduction of G1 phase [141] boosting mitotic rate up to a 12-fold increase in number [134] as well as initiates phosphatidylinositol 3-kinases-Akt signaling pathway enhancing cell survival, proliferation, differentiation and migration [142,143]. Stroke also activates many genes involved in neurogenesis during embryonic development, especially those of transforming growth factor-beta [TGF] superfamily (bone morphogenic protein 8 [BMP2], bone morphogenetic protein type 1 receptors [BMPR1] and growth differentiation factor 2 [GDF2]) [144]. These newly formed neurons differentiate into the phenotype of most of the neurons that were lost during ischemia, in an attempt to regenerate lost circuits and recover lost functions. Discouragingly, one of the setbacks is their slim capacity to migrate into areas of the cortex where higher mental functions lie. What is more, after a couple of weeks 80% of these newly formed neurons die and actually just 0.2% of dead tissue is replaced. We hypothesize that if the percentage of incorporated renewed cells could be increased somehow, (e.g. neurotrophic or angiogenic factors) restoration of neurological functions would be much greater as well [138].

Bone marrow stem cells:

Bone marrow stem cells (BMSC) are an array of different type of multipotent and pluripotent cells homed in the spongy tissue of almost all bones. Two basic lineages prevail, hematopoietic stem cells (HSC, PBSC if obtained peripherally) and mesenchymal stem cells (MSC). HCS give rise to all the type of blood cells and are typically CD34+, CD133+ and negative for all markers of differentiation or further lineagecommitment (CD13-, CD71-, CD19-, CD61-) [145]. MSC lie on the stroma of the bone marrow, and contrary to HSC, they can differentiate into a broader variety of cell types, such as osteoblasts, chondrocytes, myocytes and adipocytes and even neurons [146]. MSC are usually CD34 [147]. BMSC actually have limited cellular differentiation ability in comparison to other type of stem cells, evidence suggests instead that the beneficial properties are due to immunomodulatory mechanisms, as they migrate to sites of inflammation (by the mechanisms explained before) [148] and secrete many bioactive molecules [149]. This is supported by the fact that PBSC are also used with efficacy in the autologous therapy of non-hematopoietic tissues like neurons, [150] skeletal muscle [151] and heart [152]. In multiple sclerosis and amniotrophic lateral sclerosis for instance, immunodulatory effects and improvements were observed just 24 hr after intra thecal delivery of MSC, which would be an irrational time frame for differentiation and rather backs up the hypothesis of a bystander effect instead [153]. Furthermore, six months later, evidence of integration or even survival of these cells was very poor [154]. In an animal model, CD34+ cells (HSC) were tracked by magnetic resonance, where they prove they migrate to lesion sites but just persisted for about 3 to 4 weeks [155]. Even though there is a very low rate of trans differentiation into neurons, there is still clinical recovery, motor evoked potential improvements, as well as reconstruction of the ischemic tissue [156]. As stated before, the benefits of BMSC would be by enhancing endogenous neurogenesis rather than cellular lineage reprogramming. The mechanisms involved appear to be paracrine secretion of bioactive molecules and upgrade regulation of receptors that reinforce and augment the natural recovery processes implemented by the brain, subsequently increasing the number of new functional neurons derived from endogenous neuroblasts. It has been proved that exogenous administration of brain-derived neurotropic factor (BDNF) stimulates neurogenesis, [157] therefore, endogenous secretion of BDNF and similar trophic factors by stem cells would aid in such purposes. BMSC increases concentration of SDF1a as well as expression of the SDF-1 receptor, CXCR4 in the perischemic area [158]. There is also promotion of basic fibroblast growth factor (bFGF) [159] and other trophic factor like nerve growth factor (-NGF) which would not only promote proliferation, but will reduce apoptosis as well [160]. BMSC increase the number of oligodendrocyte progenitors and increase axonal density around the ischemic lesion, extending and orienting axons parallel to the boundary of the penumbra [161]. They do this by reducing expression of axonal growth inhibitory proteins, such as reticulon and neurocan, enabling axonal and neurite outgrowth [162]. MSC also share the properties of secreting many trophic factors (BDNF, SDF-1, NGF,

bFGF, and VEGF) and promoting neurogenesis [163] with the added benefit of a greater potential than regular HSC to trans differentiate into neurons themselves [164,165]. MSCs carry the benefit of being readily obtained from bone marrow and easily expanded by culture *in vitro*, though this involves a time frame of 4 to 5 weeks before being delivered back to patients. MSC are pretty safe. Because of their low major histocompatibility complex proteins they are considered immune privileged and cause no immunogenicity, neither acute nor chronic [166]. In a recent meta-analysis, there was no association between MSC and neoplastic potential, infection, embolism or zoonosis; in fact the only side effect was transient low-grade fever. Angiogenesis also plays a critical role in functional recovery. As in neurogenesis, angiogenesis is induced by several growth factors present in the penumbra 3 to 4 days after a stroke [167]. It is so relevant, that patients who have a high density of blood vessels after stroke survive longer than those who do not [168]. Animal models with denser vascularisation have a better functional outcome as well [169]. This density is determined by the presence of vascular growth factors, for there is a correlation between greater concentration gradients of them and increased blood vessel neoformation [170]. Interestingly, neurogenesis actually enhances symbiotically angiogenesis by secreting the same factors [171,172]. Given that BMSC up-regulate expression and paracrine secretion of angiogenic growth factors such as vascular endothelial growth factor (VEGF) and its receptor (VEGFR2) as well as angiopoeitins 1 and 2 and their receptor (TIE-1 and TIE-2), [173] it is hypothesized that they would magnify the beneficial properties of neurogenesis and angiogenesis along with improving clinical outcomes and survival rate [174]. Deciding which is better among HSC, PBSC or MSC is still unachieved. The only human clinical trial comparing HSC and expanded MSC found out that patients had better clinical outcomes (Barthel Index [BI]) with HSC [175].

Other type of stem cells:

Besides BMSC and NSC, other type of stem cells may be used for stroke and other diseases. Pluripotent stem cells (e.g. ESC), with a wider trans differentiation spectrum, have the theoretical advantage over multipotent cells in its use for regenerative medicine, however, the downside is the accompanying increased risk of developing malignancies as well [175]. In addition to this ESC bear ethical, technical and legal issues regarding the use of human embryos [176]. As promising as they might be, iPCS have not been approved yet to be used in any clinical trial involving humans as concerns involving tumorigenicity abound [177]. The iPCS display more genetic and epigenetic abnormalities than other type of stem cells [178]. Actually their capability of developing pluripotent malignancies, such as trachoma surpasses that ESC [179].

Design of Clinical Trial

Hitherto there is still no optimum model for a clinical trial. With stroke being so diverse and many aspects of stem cell therapy still unexplored, many variables have to be thrown into the equation [180].

Selection of Patient

Selecting patients with little to no predicted natural recovery may highlight the benefits of cell therapy, though this represents an obstacle given that most patients do not exhibit explicit recovery until 3-6 months after stroke, a time frame which limit most of the clinical trials that advocate for administration of stem cells much earlier [181]. The expected recovery can be anticipated early (within days after stroke) by the use of specialized techniques of neuroimaging (e.g. fiber numbers asymmetry) [182] and neuro physiological assessments (e.g. motor-evoked potentials), [183] which would help us select patients with the worst prognoses to treat them in acute phases, though these are not yet used routinely[184]. Double blinding enhances statistical power to the clinical trial, but this may not be fitting for the more invasive interventions, such as intrathecal or intracerebral approaches.

Dosage

A consensus regarding dosage has not been met. Nonetheless, there is clear relation between more cells administered and better outcomes [159,185]. Therefore, given the safety profile of autologous stem cells, efforts to recollect the highest number cells possible must be done. This of course would not apply for allogeneic stem cells, where the risk of graft versus host disease and rejection are much greater with higher doses [186]. Another matter regarding dosage concerns the use of granulocyte colony stimulating factor (GCS-F) either as an attempt to increase number of available stem cells for collection, or even as a mean of treatment itself. GCSF, as an up-regulator of hematopoiesis has demonstrated to increase exponentially the number of PBSC and could theoretically work as if these have been exogenously administered (i.e. migrate to penumbra and enhance recovery). Safety of GCS-F has been established in hyper acute stages of stroke (24-48 h after onset), which would carry an enormous advantage over stem cells, given that these would be difficult to have at hand that much early, especially in unstable patients. Although the trend is toward better outcomes, [187] efficacy of GCS-F has not been thoroughly proven and is yet to be determined if they could be used as an alternative therapy alone or even as a co-adjuvant of stem cell therapy.

Route of Administration

The American Stroke Association in its recommendation for future stem cell research states that the safest and most effective route of cell delivery should be defined using preclinical trials [181]. There are four major possible routes, intravenous (IV), intra-arterial (IA), intrathecal (IT) and intracerebral (IC) [188,189]. It is clear due to the many clinical trials, that the IV route is the safest and most feasible for administrating stem cells. Unfortunately, the most effective route is yet to be determined (Figure 4).

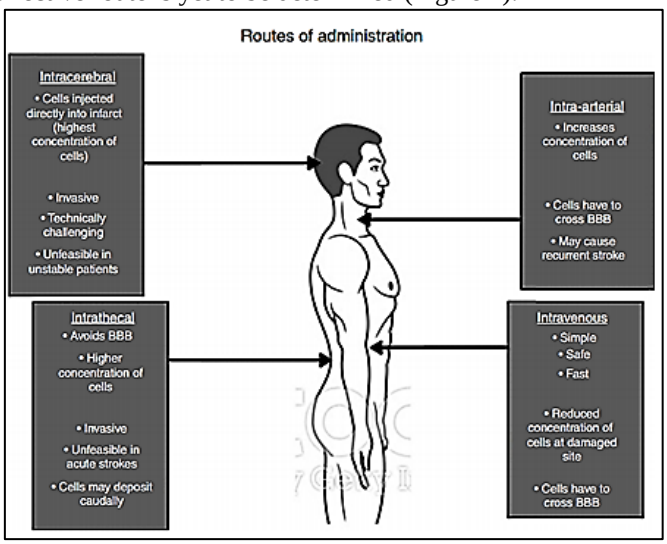

Figure 4: Route of administration

Treatment of Alzheimer's Disease using Stem Cell Therapy

Around 47.5 million patients are being diagnosed or reported with dementia worldwide out of which 7.7 million are with a new case incidence. Usually it's seen that AD (ALZHEIMER'S DISEASE) is one of the major reasons, that ranges from almost 60%-70% in all dementia cases. According to the prognosis, the number may shoot up to 114 million patients by 2050. AD is said to be a conglomeration of various disease. Prognosis involves deposition of protein called as amyloid on the bulwarks of cerebral vessels and parenchymal tissues of the brain [190-193]. The deposition being named as "senile plaques". It causes oxidation at the intercellular space and lessened performance of enzyme called lysosomal hydrolase which resulted in poor restoration of amyloid. Amyloid deposition leads to downfall of neurons by virtue of their toxicity and articulation of genetic apoptosis inductors (c-jun). It majorly accounterments on amyloid precursor protein (APP) and N-Methyl-DAspartate (NMDA) receptors. This leads to immune response boost as well. Major cause in the course of pathogenesis related to similar form of Apo lipoprotein E (APOE) influencing transition of APP to amyloid and showing negative impact on regeneration of synaptic structures [194]. Secondary pathogenesis development characterized by oxidative stress, decreased vasoreactivity, inflammatory changes, excitotoxicity, contravention of energy substances manufacturing by the cell etc. [195]. Abnormalities of cholinergic, glutamatergic and catecholaminergic systems are closely associated to cognitive and amnestic processes in pathogenesis of AD. Usually AD treatment consists of 2 main associations of medicines, Glutamate NMDA receptors and Cholinesterase Inhibitors (ChEI). Deteriorative processes taking place in the nuclei of basalis results in hypocholinergic malady leading to impairment in excitation and focus or concentration, with psychotic malfunctions and poor cognition. Cascading glutamates in accumulation of β-amyloid in the brain. Commencement of NMDA receptors consequences in tau phosphorylation. Modern medicines offered for treatment of AD is use of memantinum, galantaminum, rivastigmin and donepezilum which are commonly approved. Even though with distinct action of mechanisms and varying characteristics of each drug, analysis shows that their effect is same for all the patients with AD. [196] Addition of memantinum acted as an agonist [197]. Memantinum shows selective noncompetition of antagonists on NMDA receptors which prevents excitotoxic activation of receptors. Meta-analysis studies showed that on combining ChEI and memantinum lead to fewer disturbances in the behavior and enhanced cognition [198]. With DOMINO-AD protocol it was kept on a check. Many side effects were seen with the current existing treatment methods for AD patients. An idea that came up was the use of neurotrophic arrangements. Less molecular mass complex of neuromodulator cerebrolysin, the most effective in treatment of AD, which clears the check points of blood brain barrier [199]. Cerebrolysins supports in mitigation of adverse effects and devote in better tolerance of ChEI by AD patients. Due to the psychotic abnormalities there was a fear in prescribing this combination. None of the above mentioned therapy techniques showed 100% effectual results and this opened a different angle for researchers to include the usage of stem cell therapy. Treatment using extracted Fetal Stem Cells (FSCs) suspensions is the

newer method for the treatment of the AD patients. A mouse was taken and administered with adult donor cells into its brain successfully it then migrates to the pretentious sites of the brain where it multiplies into functionally active neurons and supports restorative functions. IV infusion could be used as the main route of administration of MSCs [200-203]. When given systemically, entrapment of various cells on different tissues of the capillary bed, in the lungs especially [200,204-206]. Administering MSCs via internal carotid artery incomparably ameliorates stem cells migration and conciliating at the damaged part of brain in comparison with the administration via femoral vein [207]. Same way, MSCs administration is done via the artery vertebral is for the patients with sub-acute Spinal Cord Injury (SCI) improves better than intravenous route [208]. Micro vascular occlusions are one of the major concerns for administration of cells directly into the artery. Whereas in Myocardial Infraction (MI), delivering bone marrow cells to the heart or nearby parts of damage helps in multiplication of cells in the peri infarct region [209]. On studying about the factors facilitating MSCs migration and its compatibility towards a receptor explained the homing effect which majorly depends on chemokine receptor, CXCL12, CXCR4 and hematopoietic stem cells (HSCs) [210-214]. Recently it was seen that CXCR4 also aids in migration and homing of CXCL12 [215]. It requires traveling between endothelial cells to reach the target tissue or organs. Transplanted stem cells those which are viable travel and differentiates into cholinergic astrocytes, neurons, and oligodendrocytes which in turn recovers cognitive shortfall. Stem cells stimulate precursors of neurons, deepen neuroplasticity and helps to decrease pro inflammatory cytokines that ceases neuronal apoptosis. MSCs Cerebral transplantation reduces load of amyloid and phosphorylation of tau in the brain, but also enhances the cognition and memory of AD like pathologies in mice having PS1/APP mutation [216]. Many Clinical studies prove invulnerability and effectiveness in use of stem cells for translation of potential complex [217].

CONCLUSION

Stem cells will have a phenomenal success in future and assures substantial solution for the diseases which are believed to be non-curable. However, with its pre and post-transplant troubles which relates to the provoking of immune system and rejection of many tests are required to perfect and optimize the treatment patterns with course of diet and authentic procedures for healthy aid. We can look forward to see a new horizon in stem cell therapy by witnessing its application in the coming time particularly in organ growth and development, substitution of lacking tissue such as tooth dentin, hair follicles, cochlear cells and retina. But in spite of remarkable improvement observed in animal models, translation to clinical scenarios has not been achieved so far. Many unsolved issues still remain regarding timing, dosage, type of cell, and route of administration. And until these are not addressed, conclusion concerning efficacy should not be given at all. Therefore, larger double-blind randomized clinical trials with homogeneous selection criteria and domain specific end points are strongly encouraged to clarify this matter. Certainly, a predictive marker of which patients would benefit the most from stem cell therapy would be of immense aid. Given the magnitude of physical, emotional and economic burden that have its colossal impact on society as whole, efforts to find the appropriate stem cells therapy should not surcease but encouraged.

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