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General Idea About the Reach of Stem Cell Regenerative Medicine: Evidence Based Review

Atul Dwivedi[1], Shweta Shukla Dwivedi[2]*, Muhammad Raheel Tariq[3], Xiaoming Qiu[4], Suzhen Hong[1], Yu Xin[1]

[1]Department of Clinical and Basic Sciences, Medical college of Hubei Polytechnic university [HBPU] Huangshi, Hubei, China

[2]Department of Dental Surgery, Jabalpur, Madhya Pradesh, India

[3]Department of Internal Medicine, North Sichuan Medical College, Affiliated Hospital of North Sichuan Medical College, Sichuan, China

[4]Department of Radiology, Huangshi Central Hospital, Affiliated Hospital of Hubei Polytechnic University [HBPU], Edong Health Care Group, Huangshi, Hubei, China

ABSTRACT

The use of Stem cells regenerative Medicine in the treatment of variety of disease is an innovation in the field of medicine. Therapeutic effect of MSCs can be clearly seen from wide range of studies. And this therapy can improve outcomes in case of damaged tissue or diseased tissue. The need of stem cell regenerative medicine increased because there is huge gap between demand of donated organs and needy patients who suffered from severe illness. This review outlines the, types of stem cells and their source, several innovative applications of SCRM for the treatment of disease, role of SCRM in orthopedics, role of micro - RNA, Glycans in the regulation of stem cells, Route of Administration &potential application of SCRM.

Key words: Stem cell regenerative medicine, Application of stem cells, Mesenchymal stem cells

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Corresponding author: Shweta Shukla Dwivedi

e-mail✉: shweta0761@gmail.com

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INTRODUCTION

Stem cells are simply defined as cells following 2 basic criteria. First, stem cells have self-renewal property throughout their life i.e. the cells divide to produce identical daughter cells and so maintain stem cell population. Second, stem cells have potential to undergo differentiation to become specialised progeny cells [1]. Stem Cell Regenerative Medicine (SCRM) is the fastest growing, the most recent & emerging branch of medicine, which deals with restoration of organ function of the patient suffering from severe injuries or chronic disease, where body's own regenerative capability is not sufficient for proper healing [2]. SCRM is regeneration of human cells, tissues, or organs to restore the normal health of patient by using growth factors to intensify the healing potential [2,3]. Additionally, in bones and joints disorders, even after arthroplasty, hardware implants can't work as like our original joints. Simultaneously there is no method or approach ideal for fixation for all kind of pilon fractures or we can say that every method has its own complications like nerve injury, wound complications, hardware irritation, non-Union, malunion etc. In this case SCRM can provide a definitive treatment in wide variety of bone disorders [4-6].

In cervical disc degeneration disease (CDDD), spine surgeons commonly perform Anterior Cervical Discectomy and Fusion (ACDF), on the other hand, Artificial cervical disc Replacement (ACDR) Techniques is increasingly used by spine surgeons in order to decrease onset of Adjacent Segment Degeneration (ASD*). ACDR is a '

Double Edged Sword 'with potential drawbacks and motion sparing benefits [7].

In regenerative medicine, Mesenchymal stem cells have immunomodulatory functions and ability to differentiate into cartilage, hence are considered as potential and ideal source for Intervertebral Disc Regeneration [8].

In recent scenario, donated tissues and organs are on high demands for chronically ill and aged population and unfortunately this huge demand cannot meet the need, hence this demand is real driving for searching other options. Stem cells have for indefinite potential for cell division, can differentiate into other sort of cells, and have emerged as leading entity for treatment of age associated diseases, healing in non-Union case and reparation of congenital defects [1]. Onset of disease such as Paget's disease, osteoarthritis, rheumatoid arthritis, osteogenesis imperfecti and osteoporosis happens only when there is an imbalance between bone and cartilage resorption and formation [9,10]. Osteoporosis is the most common type of musculoskeletal disorder which is also known as primary osteoporosis. Primary osteoporosis occurs mainly because of differentiation of a osteoblast or macrophage in to a osteoclast, it leads to deterioration of bone mass with advancing old age [11,12]. It is believed that osteoclastic bone resorption is regulated by RANK L/ osteoprotegerin (OPG)/RANK pathway, while osteoclastic activity controlled by canonical or Wnt/Beta-catenin signalling pathway (13-15). Vitamin D, calcium supplements, Teriparatide (recombinant human 1-34 amino acid sequence of parathyroid harmone), Harmone Replacement Therapy (HRT) Selective Estrogen Receptor Modulator(SERM), RANK legand inhibitors & strontium ranelate are the main therapeutic strategies used but at the same time the issue of side effects and safety need to be kept in mind [16]. Additionally, Gender, obesity, genetic predisposition, inflammation, stress, Tobacco smoking, nutritional status, lifestyle, and physical activity are multiple risk factors for osteoporosis [17].

Stem cell regenerative medicine for osteoporosis could potentially reduce the incidence of fracture and restore the lost mineral density by either increasing numbers or restoring the function of resident stem cell that can proliferate and differentiate into bone forming cells. This osteoporosis therapies can be administered by exogenous introduction of stem cells derived from adipose tissues, bind marrow, umbilical cord blood tissues. The main problem in the way of stem cell base osteoporosis therapy is the uncertainty of stem cell fate [18].

Stem cells can be manipulated in vitro for correction of genetic aberrations by using viral vector transduction. When such stem cells transplanted into the patients, might restore the normal function. A fundamental risk of neoplastic transformation of individual transduced clones is there because the sites of viral vector insertion varies in distribution [19]. However, these risks may be minimised/avoided by adopting safe design of viral vectors and second option is to pursue preclinical evaluation of these clones in animals [20].

Micro RNAs and regulation of stem cells

Hristo, et al. identified micro RNAs (mi RNAs) in differentiated and undifferentiated mouse embryonic stem (ES) cells, their results suggest that mi RNA may play a role in maintaining pluripotent cell state and in the regulation of early development [21]. The characteristic features of a stem cell are its self - renewal and to give origin to numerous differentiated cells. This unique virtue is controlled by a powerful and reciprocal interaction between extrinsic signalling, epigenetic, transcriptional & post-transcriptional regulations. Micro RNA (mi RNA) plays a key role in regulating stem cell renewal & differentiation [22].

Embryonic stem cells [ES] and Tissue stem cells (or. Adult stem cells) mediates tissue development and homeostasis [23]. Inner cell mass blastocyst - stage embryo give rise to ES and fetus; in this process they generate progenitor cells &tissue stem cells, progenitor cells and ultimately each and every cell type of an organism. Both tissue stem cell and embryonic stem cells are capable of producing differentiated cells and replicating themselves. Self replication is hallmark feature of stem cells, this feature in tissue stem cell is achieved by a special pattern of asymmetric divisions. During this asymmetric division,two daughter cells are generated, out of which, one daughter cell retains self-renewal property while another daughter cell is committed to specialised function [24]. Self - renewal division of stem cell is controlled by both intercellular and intracellular mechanisms [25]. Intercellular mechanisms

consist of signalling from neighbouring niche cells, whereas intracellular mechanisms consist of differential gene expressions that is controlled at epigenetic, transcription, translational & post - translational levels. Micro- RNAs have emerged as Key controller in translation regulation, stem cell fate and behaviour [26].

Glycans in stem cell regulation

There are various kinds of glycans regulate stem cell status, structure of many of them evolutionarily conserved from Drosophila to mammals. Cell surface glycans are tissue specific and regulated developmentally, play essential role as a modulators in ligand - receptor interactions, binding to many signal ligands including Wnt, Hedgehog, epidermal growth factor, fibroblast growth factor, bone morphogenetic proteins and in cell - cell interactions and cell-extra cellular interactions. These signals play essential role for stemness and differentiation of different kinds of stem cells. Additionally, the intercellular O-linked N-acetylglucosamine found only on cytoplasmic or nuclear proteins, regulates core transcription factors of stemness and phosphorylation of downstream signal components [27].

Types of stem cells

Based on trans differentiation potential, stem cells can be divided in to 4 types 1. Unipotent 2. Multipotent 3. Pluripotent 4. Totipotent [28].

Sources of stem cell

There are several methods for obtaining human embryonic stem cells [hES] and other Multipotent or pluripotent cells. These method are reprogramming somatic cells, arrested embryos, somatic cell nuclear transfer, single cell embryo biopsy, altered nuclear transfer [29].

Amniotic fluid derived stem cells [AFS]

Isolated amniotic fluid- derived [AFS] stem cell presents a tremendous possibility in the field of SCRM. AFS cells are Multipotent, showing ability to differentiate in to all three embryonic germinal layer cells. They express both embryonic and adult stem cell markers, expand massively without feeder cells, double in 36 hours and are without any tumorigenic potential. They differentiate easily into specific cell lineage and can be easily isolated without human embryo tissue, that is why avoiding the controversy concerned with use of human embryonic stem [ES]cells [30].

Placenta- derived stem cells [p-SC]

Placenta is a potential source if stem cells. Placenta- derived stem cells [p- SC] are having the characteristic of both embryonic and mesenchymal stem cells ie. they are non - carcinogenic, and characteristic of differentiating into all embryonic germ layers. Basically feral membranes are source of placenta derived stem cells, many preclinical have been done to assess the potential of p-SC worth in different streams of medicine, such as cardiology, neurology, orthopedics, gastroenterology, etc. showing promising outcomes, but with some drawbacks [31].

Retinal stem cells [RSC]

Retinal stem cells are rare variety of pigmented cells stem cells have been identified in adult mouse eye. Tropept, et al. reported the identification of stem cell in the adult mouse eye, which shows the possibility of retinal regeneration, though mature mammalian retina is regarded lacking regeneration potential. Single pigmented ciliary margin cells can proliferate in vitro to produce sphere colonies of cells that can differentiate into retina specialised cells such as Müller glia, bipolar neutrons, photoreceptors rods [32].

Human Embryonic Stem Cells [HESC]

Embryonic stem cells are pluripotent cells that are capable of differentiating in to about all type of cells, including glial and neuronal fate cells [33]. Hence these cells are differentiated oligodendrocytes and motor-neutrons [34,35] and possibly used for the treatment of neurodisorders, trauma and spinal cord injury, lumbar disc degeneration disorder, cervical disc degeneration disorder, spinal cord injury [SCI] because of tumors, violence (war wounds, stab wound and gunshot wound), multiple sclerosis, SCI in fall from height. Human embryonic stem cells treatment showed significant improvement in sitting balance, control and sensation of bowel and bladder, coordination & power of lower and upper limb movements in five paraplegic or quadriplegic patients but without any adverse effect [36].

Sources of stem cells are bone marrow, periosteum, placenta, adipose tissue, umbilical cord, human amniotic fluid, synovial tissue, dental pulp, skin, adipose tissue and skeletal muscles. Among above sources mentioned, bone marrow, adipose tissue and muscle derived mesenchymal stem cells are most commonly used, because they can be obtained easily and available in ample quantity too [37].

Route of administration

Stem cells can be directly applicable to the lesion sites either via local injections or through surgical procedures with appropriate carriers. Mesenchymal cells [MSCs]may be taken via initial phase of differentiation under in vitro condition and then implanted into lesion sites. Additionally, MSCs can be administered intravenously. These mesenchymal cells have capability to migrate to the desired tissue or organ, the same quality has been used to treat the disease like Osteogenesis Imperfecti [38] and several other diseases ,details are mentioned in table 1. (Table 1).

Risks

There are several factors play role in long term outcomes of stem cell regenerative medicine. The epigenetic and genomic of cell lines that have been manipulated in vitro prior

Table 1: Application of stem cells in different diseases.

Disease / condition	Mode of application	Prognosis & future use
Cardiac dysfunction [39]	Systemic infusion of CA - AdSCs myocardium	Regeneration of ischemic myocardium/ MI can be treated
Eye disease [40]	Intravitreal transplantation of AdSCs	Restoration of vascularisation/, diabetic retinopathy can be treated
Muscular deformities [41]	Transplantation of PEG fibrinogen coaxed MABs	Muscle fibril regeneration; skeletal muscle disease treatment
Corneal anomalies [42]	LPSCs transplantation to corneal tissue	Corneal tissue regeneration; multiple eye disease treatment
Intestinal degeneration [43]	IPCs derived crypt - villi organoid transplantation	Goblet mucosa regeneration; intestinal diseases treatment
Acoustic dyscrasias [44]	IESCs derived hair cells transplantation	Cochlear regeneration; acoustic problems treatment
Neurodental problems [45]	Transplantation of DSPSCs as neurones	Treatment of neurodental problem might be possible.
Diabetes [46]	Transplantation of SCs derived PPCs organoid	PPCs occupancy as beta - cell can be used in the treatment of type I DM & typeII DM
Spinal cord injuries [47]	ESCs transplantation to site of injury	Regeneration of spinal tissue & balance and sensation improved: treatment of spinal injury in trauma cases
ARMD (Age-related macular degeneration) and glaucoma [48,49]	ESCs (Embryonic stem cells) - derived cones and RGCs (Retinal ganglion cells)transplantation in eye	Patient Recovered from ARMD & macular degeneration & vision restored
Bladder deformities [50]	BD - MSCs transplantation to bladder	Regeneration in bladder tissue from different origin MSCs
Dental problems [51]	Transplantation of EMSCs +DSCs biopolymer tissue	Regeneration of oral tissue ; treatment in periodontics
Alopecia [52]	Transplantation of GAG - coated DPCs	Regeneration of hair follicle ; treatment of alopecia
Muscle degeneration [53]	Adipose - derived stem cells (ADSC) injected intralesional, paralesional and intravenously	Enhanced muscle healing ; muscular disorders can be treated
Congenital heart disease [54]	Transplantation of fibrin and coaxed AFSCs	Regeneration of tissue; treatment of heart defects
SLE [55]	Infusion of WJ- SCs	Improvement of renal function, tissue degeneration stopped.
Peritoneal fibrosis [56]	WJ-SCs, IP Infusion of WJ-SCs	Effective in treating encapsulating peritoneal fibrosis
Hodgkins lymphoma [57]	Transplantation of UCSCs	Treatment of Hodgkin's lymphoma & Other cancers
Cartilage and tendon injuries [58]	Transplantation of UCB- SCs,UCB-SCs-HA gel	Recovery in cartilage and tendon injuries.
Neurodegenerative disorders and LSD [59]	Allogenic UCSCs and biomaterial coaxed UCSCs organoids	Treatment of stroke, Parkinson's disease, ALS, AD, Krabbe's disease, hurler syndrome, ALD, ALS etc.
Blood cancer and Anaemia [60]	Two- step infusion of myeloid and lymphoid	Treatment of haematological malignancies and aplastic anaemia
AIDS [61]	Transplantation of HIV1 resistant CD4+ cells transplantation	As an alternative treatment of antiretroviral therapy
Diaphragm abnormalities [62]	Implantation of decellularised diaphragm	Replacement therapy through Donor derived niched therapy
Orodental deformities [63]	Bone marrow derived stem & progenitor cell	Regeneration of defects in skin, gum and oral bone.
Eye defects [64]	IPSCs derived NPCs transplantation	Treatment of Age-related eye defects and ARMD
Neurodegenerative disorders [65]	iGABA-INs & cortical spheroid transplantation	ASD, ALZHEIMER'S, seizure, treatment of epilepsy
Liver & lung disease [66]	Transplantation of A1AD mutation corrected iPSCs	Treatment of COPD
Degeneration of lung [67]	Biomaterial coaxed iPSCs transplantation	Lung tissue regeneration
Bone defects because of Tumour or trauma [68]	Uncultured mononuclear cells obtained from bone marrow aspiration with collagen sponge scaffold	Healing of all sorts of bone defects / treatment of non-Union cases.
Burn wound [69]	Not applicable	Stem cells accelerate healing in burn wounds by inducing granulation tissue formation, neo angiogenesis and collagen deposition.
Osteogenesis Imperfecti [70]	Intraperitoneal injection of early chorionic stem cells (e-CSC) isolated from placenta during ongoing pregnancy	Reduced fractures, increased bone volume and ductility, increased number of hypertrophic chondrocytes, and unregulated endogenous genes responsible for intramembranous and endochondral ossification.
Ageing [71]	Administration of Adipose - derived stem cell (ADSC) and mesenchymal stem cell (MSC), bone marrow derived mesenchymal stem cells (BMMSC)	These all ADSCs, MSCs, & BMMSCs have shown similar ability to rejuvenate aged skin.
Traumatic Brain Injury [72]	Not Applicable	SCRM may play an important role in the treatment of TBI, we need achieve more knowledge regarding factors, which can improve the outcome in TBI patients and further large sized clinical trials needed to prove the efficacy of SCRM.

Table 2: Shows risk factors and risk associated with Stem Cell Regenerative Medicine (SCRM) [74].

Risk factors	Identified risks
Tumorogenic potential	Rejection of cells
Proliferation capacity	susceptibility to diseases
Differentiation status	neoplasm formation (benign or malignant growth)
Long term viability	in vivo Differentiation of cells in unwanted cell types
Excretion patterns (eg. Growth factors, cytokines, chemokines)	disease transmission
donor history is absent	Reactivation of latent species of bacteria and viruses
Contamination by infectious agents (virus, fungus, bacteria, mycoplasma, prions, parasites)	unwanted immune response (eg.GVHD)
Cell and culture products handling procedure.	lack of efficiency of the treatment
Storage, conservation and transportation conditions	unwanted physiological and anatomical effects (eg. Arrhythmias)
SCRM is irreversible kind of treatment	Immunosuppressive agents used in post therapeutic treatment may cause other complications.
use of immunosuppressive agents	
initiation of immune response	

to transplantation play an important role in the clinical application of stem cell therapy. Additionally, the use of Embryonic stem cells [ESCs]raises ethical and social issues, because of which, many federal funding were stopped and that hampered the progress of stem cell therapy research [73]. Rest all the risk factors associated with stem cell regenerative medicine [SCRM] mentioned in [74].

Future perspectives

Implementation of Artificial Intelligence in several branches of medicine is well known, as it can change several important decisions in clinical settings. Innovative gene therapy and stem cell therapy in pediatric patient could also be optimized with integration of AI techniques. Hopefully, AI techniques may minimize the risk associated with Stem Cell Regenerative Medicine [75,76]. Several studies tried to contribute to the definitive treatment of Polycystic Ovarian Syndrome [PCOS], but there is no effective treatment as of now. PCOS is a multi-headed monster with increased risk of obesity, type II Diabetes mellitus, cancer, infertility, Obstructive Sleep Apnea [OSA], Hirsutism, Metabolic syndrome, and psychological disorders [77]. Qi Xie, et al. Concluded that Human umbilical cord - derived MSCs [HUC-MSCs] treatment significantly improved ovarian and uterine pathological changes of PCOS mice [78].

CONCLUSION

Stem cell regenerative medicine [SCRM]is a unique branch of medicine with huge therapeutic potential. Therapeutic potential of stem cells to regenerate the damaged tissue and enhance the body's natural healing power. But at the same time, SCRM has its own risks and drawbacks as mentioned above. More clinical studies over a longer time are needed to evaluate the benefits and drawbacks of SCRM.

ABBREVIATIONS

RANKL: Receptor Activator of Nuclear Factor Kappa-B-Ligand.

OPG: Osteoprotegerin.

SCRM: Stem Cell Regenerative Medicine.

SERM: Selective Estrogen Receptor Modulator.

ES: Embryonic Stem Cell.

mi RNA: micro RNA

GVHD: Graft Versus Host Disease.

BMMSC: Bone Marrow Derived Mesenchymal Stem Cells.

ADSC: Adipose Derived Stem Cell.

e-CSC: Early Chorionic Stem Cell.

A1AD: Alpha-1 antitrypsin deficiency

COPD: Chronic Obstructive Pulmonary Disease.

IPSC: Induced Pluripotent Stem Cells.

CDDD: Cervical Disc Degenerative Disease.

ACDF: Anterior Cervical Discectomy and Fusion.

ASD*: Adjacent Segment Degeneration.

OPG: Osteoprotegerin.

SERM: Selective Oestrogen Receptor Modulator.

ES: Embryonic Stem Cell.

P-SC: Placenta Derived Stem Cells.

RSC: Retinal Stem Cells.

HESC: Human Embryonic Stem Cells.

SCI: Spinal Cord Injury.

MSC: Mesenchymal Cells.

ADSC: Adipose Derived Stem Cells.

MI: Myocardial Infarction.

PEG: Polyethylene Glycol.

MABs: Monoclonal Antibodies.

IVDD: Intervertebral Disc Degeneration Disease

hES: Human Embryonic Stem Cells.

AFS: Amniotic Fluid Derived Stem Cells.

IPCs: Induced Pluripotent Cells.

IESCs: Induced Epithelial Stem Cells.

UCSCs: Umbilical Cord Stem Cells.

DPSCs: Dental Pulp Stem Cells.

PPCs : Pancreatic Progenitor Cells.

ESCs: Embryonic Stem Cells.

ARMD: Age Related Macular Degeneration.

BD- MSCs: Bone Marrow Derived Mesenchymal Stem Cells.

EMSCs: Early Mesenchymal Stem Cells.

AFSCs: Amniotic Fluid Stem Cells.

WJ- SCs: Wharton's Jelly Mesenchymal Stem Cells.

SCRM: Stem Cell Regenerative Medicine.

T1DM: Type 1 Diabetes Mellitus.

T2DM: Type 2 Diabetes Mellitus.

AD: Alzheimer's Disease.

ALD: Adrenoleukodystrophy.

MLD: Metachromatic Leukodystrophy.

ALS: Amyotrophic Lateral Sclerosis.

TBI: Traumatic Brain Injury.

ASD: Autism Spectrum Disorder.

MI: Myocardial Infarction.

AI: Artificial Intelligence.

PCOS: Polycystic Ovarian Syndrome.

HUC- MSCs: Human Umbilical Cord-Mesenchymal Stem Cells.

REFERENCES

1. Burns CE, Zon LI. Portrait of a stem cell. Dev Cell 2002; 3:612-613.
2. Mason C, Dunnill P. A brief definition of regenerative medicine. Regener Med 2008; 3:1-5.
3. Tabata Y. Biomaterial technology for tissue engineering applications. J Royal Society Interface 2009; 6:S311-S324.
4. Dwivedi A, Dwivedi SS, Tariq MR, et al. Stem cell regenerative medicine-A new hope in orthopedics-Review Article. J Stem Cell Biol Transplant 2019; 3:1-4.
5. Dwivedi A, Dwivedi SS, Su Zhenhong, et al. Open reduction and Internal Fixation (ORIF) of posterior pilon variant fractures with butteress plate through posterolateral approach. Int J Contemporary Med Res 2018; 5:1-5.
6. Dwivedi A, WX Jian, Dwivedi SS, et al. Pilon fracture: An unsolved riddle an updated review. Int J Contemporary Med Res 2017; 4:718-725.
7. Dwivedi A, WX Jian, Dwivedi SS, et al. Artificial cervical disc replacement, "a double-edged sword"-A clinical review. Int J Contemporary Med Res 2017; 4:1163-1168.
8. Sakai D, Mochida J, Iwashina T, et al. Differentiation of mesenchymal stem cells transplanted to a rabbit degenerative disc model; potential and limitation for stem cell therapy in disc regeneration. Spine 2005; 30:2379-2387.
9. Florencio Silva R, Sasso G, Sasso E, et al. Biology of bone tissue: Structure, function, and factors that influence bone cells. Bio Med Res Int 2015; 2015:421746
10. Rodan GA, Martin TJ. Therapeutic approaches to bone disease. Science 2000; 289:1508-1514.
11. Teitelbaum SL. Bone resorption by osteoclasts. Science 2000; 289:1504-1508.
12. Bone health and osteoporosis: A report of the surgeon general. Office of the surgeon general (US), Rockville, MD, 2004.
13. Gogakos AI, Cheung MS, Bassett JD, et al. Bone signaling pathways and treatment of osteoporosis. Expert Rev Endocrinol Metab 2009; 4:639-650.
14. Manolagas SC. Wnt signaling and osteoporosis. Maturitas 2014; 78:233-237.
15. Kim JH, Kim N. Signaling pathways in osteoclast differentiation. Chonnam Med J 2016; 52:12-17.
16. Mc Greevy C, Williams D. Safety of drugs used in the treatment of osteoporosis. Ther Adv Drug Saf 2011; 2:159-172.
17. Higgs J, Derbyshire E, Styles K. Nutrition, and osteoporosis prevention for the orthopaedic surgeon. EFORT Open Rev. 2017; 2:300-308.
18. Antebi B, Pelled G, Gazit D. Stem cell therapy for osteoporosis. Curr Osteoporosis Rep 2014; 12:41-47.
19. Nienhuis AW, Dunbar CE, Sorrentino BP. Genotoxicity of retrieval integration in hematopoietic cells. Mol Ther 2006; 13:1031-1049.
20. Chai C, Leone KW. Biomaterials approach to expand and direct differentiation of stem cells. Mol Ther 2007;15:467-480.

21. Houbaviy HB, Murray MF, Sharp PA. Embryonic stem cell specific micro RNAs. Developmental Cell 2003; 5:351-358.
22. Vamsi KG, Haifan Lin. Micro RNAs: Key regulators of stem cells. Nat Rev Mol Cell Biol 2009; 10:116-125.
23. Sell S. Stem cells. Handbook Humana Totowa, New Jersey 2003.
24. Lin H. Cell biology of stem cells: An enigma of self renewal. J CellBiol 2008; 180:257-260.
25. Lin H. The stem cell niche theory: Lessons from flies. Nature Rev Genet 2002; 3:931-940.
26. Blakaj A, Lin H. Piecing together the mosaic of early mammalian development through microRNAs. J Biol Chem 2008; 283:9505-9508.
27. Nishihara S. Glycans in stem cell regulation: From drosophila tissue stem cells to mammalian pluripotent stem cells. FEBS Lett 2018; 592:373-379.
28. Fortier LA. Stem cells: Classifications, controversies and clinical applications. Veterinary Surg 2005; 34:415-423.
29. Hipp J, Atala A. Sources of stem cells for regenerative medicine. Stem Cell Rev 2008; 4:3-11.
30. Joo S, Ko lK, Atala A, et al. Amniotic fluid-derived stem cells in regenerative medicine research. Arch Pharm Res 2012; 35:271-280.
31. Oliveira MS, Barreto Filho JB. Placental derived stem cells: Culture, differentiation and challenges. World J Stem Cells 2015; 7:769-775.
32. Tropepe V, Coles BLK, Chiasson BJ, et al. Retinal stem cells in the adult mammalian eye. Science 2000; 287:2032-2036.
33. Erceg S, Ronaghi M, Stojkovic M. Human embryonic stem cell differentiation toward regional specific neuronal precursors. Stem Cells 2009; 27:78-87.
34. Lee H, Shamy GA, Elkabetz Y, et al. Directed differentiation and transplantation of human embryonic stem cell derived motor neutrons. Stem Cells 2007; 25:1931-1939.
35. Nistor GI, Totoiu MO, Haque N, et al. Human embryonic stem cells differentiate into oligodendrocytes in high purity and myelinated after spinal cord transplantation. Glia 2005; 49:385-396.
36. Shroff G, Gupta R. Human embryonic stem cells in the treatment of patients with spinal cord injury. Annals Neurosci 2015; 22:208-216.
37. Mafi R, Hindocha S, Mafi P, et al. Sources of adult mesenchymal stem cells applicable for musculoskeletal applications-A systematic review of the literature. Open Orthop J 2011; 5:242-248.
38. Horwitz EM, Prockup DJ, Gordon PL, et al. Clinical response to bone marrow transplantation in children with severe osteogenesis imperfection. Blood 2001; 97:1227-1231.
39. Nagata H, Li M, Kohbayashi E, et al. Cardiac adipose derived stem cells exhibit high differentiation potential to cardiovascular cells in C57BL/6 mice. Stem Cells Translational Med 2016; 5:141-151.
40. Cronk SM, Kelly Gross MR, Ray HC, et al. Adipose derived stem cells from diabetic mice show impaired vascular stabilisation in murine model of diabetic retinopathy. Stem Cells Translational Med 2015; 4:459-467.
41. Fuoco C, Rizzzi R, Biondo A, et al. **In vivo** generation of a mature and functional artificial skeletal muscle. Molecular Med 2015; 7:411-422.
42. Ksander BR, Kolovou PE, Wilson BJ, et al. ABCB5 is a limbal stem cell gene required for corneal development and repair. Nature 2014; 511:353- 357.
43. Shaffiey SA, Jia H, Keane T, et al. Intestinal stem cell growth and differentiation on a tubular scaffold with evaluation in small and large animals. Regenerative Med 2016; 2:45-61.
44. Mizutari K, Fujioka M, Hosoya M, et al. Notch inhibition induces cochlear hair cell regeneration and recovery of hearing after acoustic trauma. Neuron 2013; 77:58-69.
45. Potdar PD, Jethmalani YD. Human dental pulp stem cells: Applications in future regenerative medicine. World J Stem Cells. 2015; 7:839-851.
46. Greggio C, De Franceschi F, Figueiredo M, et al. Artificial three-dimensional niches deconstruct pancreas development **in vitro**. Development 2013; 140:4452-4462.
47. Shroff G, Gupta R. Human embryonic stem cells in the treatment of patients with spinal cord injury. Annals Neurosci 2005; 22:208-216.
48. Zhuo S, Flamier A, Abdouh M, et al. Differentiation of human embryonic stem cells into cone photoreceptors through simultaneous inhibition of BMP, TGF beta and Wnt signalling. Development 2015; 142:3294-3306.
49. Sluch VM, Davis CHO, Ranganathan V, et al. Differentiation of human ESCs to retinal ganglion cells using a CRISPR engineered receptor cell line. Scientific Reports 2015; 5:2015.
50. Dominici M, Le Blanc K, Müller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The international society for cellular therapy position statement. Cytotherapy 2006; 8:315-317.
51. Oshima M, Tsuji T. Whole tooth regeneration as a future dental treatment. Advances in experimental medicine and biology. 2015; 881:255-269.
52. Lin BJ, Wang J, Miao Y, et al. Cytokines loaded layer-by- layer ultrathin matrices to deliver single dermal papilla cells for spot-by- spot hair follicle regeneration. J Materials Chemistry 2016; 4:489-504.
53. Brown SG, Harman RJ, Black LL. Adipose derived stem cell therapy for severe muscle tears in working German shepherd: Two case reports. Stem Cell Discovery 2012; 2:41-44.
54. Benavides OM, Brooks AR, Cho SK, et al. **In situ** vascularisation of injectable fibrin/poly (ethylene glycol) hydrogels by human amniotic fluid derived stem cells. J Biomed Material Res 2015; 103:2645- 2653.
55. Wang D, Li J, Zhang Y, et al. Umbilical cord mesenchymal stem cell transplantation in active and refractory systemic lupus erythematosus: A multicenter clinical study. Arthritis Res Therapy 2014; 16:79.

56. Fan YP, Hsia C, Tseng K, et al. The therapeutic potential of human umbilical mesenchymal stem cells from wharton's jelly in the treatment of rat peritoneal dialysis-induced fibrosis. Stem Cells Translational Med 2016; 5:235-247.

57. Thompson PA, Perera T, Martin D, et al. Double umbilical cord blood transplant is effective therapy for relapsed or refractory Hodgkin lymphoma. Leukemia Lymphoma 2016; 57:1607-1615.

58. Park GY, Kwon DR, Lee SC. Regeneration of full thickness rotator cuff tendon tear after ultrasound guided injection with umbilical cord blood derived mesenchymal stem cells in a Rabbit model. Stem Cells Translational Med 2015; 4:1344-1351.

59. Escolar ML, Poe MD, Provenzale JM, et al. Transplantation of umbilical-cord blood in babies with infantile Krabbe's disease. New England J Med 2005; 352:2069-2081.

60. Gaballa S, Palmisiano N, Alpdogan O, et al. A two step haploidentical versus a two step matched related allogenic myeloablative peripheral blood stem cell transplantation. Biology Blood Marrow Transplantation 2016; 22:141-148.

61. Di Gusto DL, Stan R, Krishnan A, et al. Development of haematopoetic stem cell based gene therapy for HIV-1 infection: Consideration for proof of concept studies and translation to standard medical practice. Viruses 2013; 5:2898-2919.

62. Gubareva EA, Sjöqvist S, Gilevich IV, et al. Orthotopic transplantation of a tissue engineered diaphragm in rats. Biomaterials 2016; 77:320-335.

63. Kaigler D, Pagni G, Park CH, et al. Stem cell therapy for craniofacial bone regeneration: A randomised, controlled feasibility trial. Cell Translantation 2013; 22:767-777.

64. Tsai Y, Lu B, Bakondi B, et al. Human iPSC-derived neural progenitors preserve vision in an AMD like model. Stem Cells 2015; 33:2537-2549.

65. Colasante G, Lignani G, Rubio A, et al. Rapid conversion of fibroblasts in to functional forebrain GABA ergic interneurons by direct genetic reprogramming. Cell Stem Cell 2015; 17:719-734.

66. Wilson AA, Ying L, Liesa M, et al. Emergency of a stage dependent human liver disease signature with directed differentiation of alpha -1 anti trypsin deficient iPS cells. Stem Cell Reports 2015; 4:873-885.

67. Dye BR, Hill DR, Ferguson MA, et al. **In vitro** generation of human pluripotent stem cell derived lung organoids. Elife 2015; 4:e05098.

68. Jäger M, Jelinek EM, Wess KM, et al. Bone marrow concentrate: A novel strategy for bone defect treatment. Curr Stem Cell Res Ther 2009; 4:34-43.

69. Francis E, Kearney L, Clover J. The effect of stem cells on burn wounds: A review. Int J Burn Trauma 2019; 9:1-12.

70. Jones GN, Moschidou D, Abdulrazzak H, et al. Potential of human fetal chorionic stem cells for the treatment of osteogenesis Imperfecta. Stem Cells Development 2013; 23:3.

71. Zarei F, Abbaszadeh A. Application of cell therapy for anti- aging facial skin. Current Stem Cell Res Therapy 2019; 14:244-248.

72. Dwivedi A, Dwivedi SS, Tariq MR, et al. Traumatic brain injury and stem cell therapy. J Res Med Dent Sci 2020; 8:92-94.

73. Leventhal A, Chen G, Negro A, et al. The benefit and risks of stem cell technology. Oral Disease 2012; 18:217-222.

74. Herberts CA, Kwa MSG, Hermsen HPH. Risk factors in the development of stem cell therapy. J Translational Med 2011; 9:29.

75. Dwivedi A, Dwivedi SS, Tariq MR, et al. Scope of Artificial Intelligence in Medicine. J Res Med Dent Sci 2020; 8:137-140.

76. Sniecinski I, Seghatchian J. Artificial intelligence: A joint narrative on potential use in Pediatric stem and immune cell therapies and regenerative medicine. Transfusion Apheresis Sci 2018; 57:422-424.

77. Dwivedi A, Dwivedi SS, Tariq MR, et al. Mini Review: Update on polycystic ovarian syndrome. J Clin Trials 2020;10:393.

78. Qi Xie, Xiong XL, Xiao N, et al. Mesenchymal stem cells alleviate DHEA-Induced polycystic ovary syndrome [PCOS] by inhibiting inflammation in Mice. 2019; 2019:1-12.