

ADVANCES IN STEM CELL BIOTECHNOLOGY AND REGENERATIVE MEDICINE: APPLICATIONS, CHALLENGES, AND FUTURE PERSPECTIVES

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ABSTRACT

Stem cell biotechnology and regenerative medicine are rapidly advancing fields with substantial therapeutic potential. Stem cells, capable of differentiating into various cell types, play a crucial role in tissue engineering and developmental biology. They are increasingly applied in drug testing, disease modelling, and cell-based therapies for conditions like arthritis, Parkinson's disease, type 1 diabetes, and coronary diseases. Mesenchymal stem cells (MSCs) show promise in regenerative therapies for heart failure, wound healing, and tooth regeneration, although clinical outcomes remain variable. Advances such as lab-grown blood stem cells offer revolutionary possibilities for bone marrow transplants, particularly for children with blood disorders. Furthermore, regenerative medicines are being developed to grow new tissues and organs, offering potential cures for chronic conditions like heart disease and fibrosis. These innovations highlight the transformative potential of stem cell biotechnology, offering hope for long-term, effective treatments for a variety of debilitating diseases and improving overall human health and longevity.

Ethical considerations in stem cell biotechnology include debates over the use of embryonic stem cells, the regulation of gene-edited stem cells, and ensuring equitable access to advanced therapies. Addressing these challenges involves developing universal donor cells and immune-evasive stem

cell lines to minimize ethical and immunological concerns. Additionally, there is a growing focus on strategies to enhance the long-term safety, viability, and functional integration of transplanted stem cells into host tissues. Robust regulatory oversight and public engagement are essential to build trust, ensure safety, and establish ethical guidelines for clinical or medical applications.

Keywords: *Cell-derived Therapy, Pluripotent, Regenerative Medicine, Stem cell Biology, Transplantation.*

INTRODUCTION

Stem cells are cells with the ability to differentiate into a large number of different body cell types. They have the power to replenish their tone and can be incorporated into any type of creature's cell. Both adult cells and embryos can develop stem cells. There are numerous exciting options for specialization. Because the experimental energy decreases with each stage, a pluripotent cell can differentiate into a smaller range of cell types than a unipotent stem cell. Certain types of stem cells exist and are essential to regenerative medicine. Human embryos are the source of embryonic stem (ES) cells, whereas mature organs and tissues are the source of adult stem cells. The body uses adult stem cells primarily to repair and restore damaged tissue. Additionally, stem cells obtained from the placenta are known as placental stem cells, stem cells discovered in amniotic fluid are known as amniotic fluid stem cells, and stem cells extracted from the umbilical cord following childbirth are known as cord blood stem cells (O'Brien et al., 2009). Children with blood malignancies are treated with cord blood stem cells (Ancans, J. et al. 2012). One excellent source of fetal mesenchymal stem cells (MSCs) is placental stem cells. Each stem cell in the body has a niche, which is a unique home. When external stressors like injury or transplanting change their niche, stem cells have the capacity to adapt to new settings. As a result, they can grow into a wider variety of cells that their new environment needs. For instance, skin sweat gland stem cells can grow into glandular structures that make milk when they are put into breast fat pads. Along with nearby stem cells filling a void, committed progeny can also dedifferentiate and assume the same role

within the body. The fifth Making induced PSCs (iPSCs), or PSCs derived from adult stem cells, is an additional choice. According to Kuriyan et al. (2017) and Biehl et al. (2009), they can be used in place of ES cells. Individual cells that comprise the entire organism can be produced by the division and differentiation of totipotent stem cells. totipotency is the capacity to differentiate into both embryonic and extra-embryonic tissues. A zygote, which is produced when a sperm fertilizes an egg, is an example of a totipotent cell. These cells may eventually become a placenta or any of the three origin layers. The blastocyst's inner cell mass becomes pluripotent about four days later.

Pluripotent cells develop from this framework. Pluripotent stem cells, or PSCs, are able to differentiate into cells of any origin layer, but they are unable to create extraembryonic structures such as the placenta. One example is embryonic stem cells, or ESCs. ESCs originate from the inner cell mass of preimplantation embryos. Another example is the use of induced pluripotent stem cells (iPSCs) derived from the epiblast estate of implanted embryos. Their pluripotency varies from lower-energy representations, which are multi-, oligo-, or unipotent cells, to fully pluripotent cells, which are similar to ESCs and iPSCs. One technique to assess their range and effort is the teratoma conformation test. iPSCs, which are artificially generated from actual cells, can also be advantageous for PSCs. Their operations and culture have enormous potential for regenerative medicine, both today and in the future.

Compared to PSCs, multipotent stem cells have a smaller range of insulation, but they can differentiate into particular cell lineages. Hematopoietic stem cells, which can differentiate into several kinds of blood cells, are one example. A hematopoietic stem cell develops into an oligopotent cell following insulation. Moreover, its insulating qualities are unique to cells from its predecessors. Because some multipotent cells can differentiate into unrelated cell types, pluripotent cells have been postulated. Numerous cell types can be differentiated from oligopotent stem cells. The ability to differentiate into white blood cells but not red blood cells is

known as myeloid stem cell.

Two characteristics that set unipotent stem cells apart are their limited capacity for insulation and their unusual ability to divide continuously. They are a good choice for the restorative application of regenerative medicine because of their last point. Dermatocytes are an example of a unipotent cell; these cells can develop into them. The potential of using mesenchymal stem cells (MSCs) to regenerate different tissues, including bone, cartilage, and other human tissues, has been investigated by several researchers in recent years. In order to improve the use of the biomimetic method in biomedical devices and human prosthetics, new materials have also been investigated and mixed with MSCs (O'Brien et al., 2009). The challenges of using MSCs in bone and dental applications have been addressed by using stem cell types such as dental pulp, human-periapical odontogenic cysts, and periodontal ligament (Mousaei et al., 2022). The coupling of MSCs with advanced biomaterials has made it possible to apply regenerative medicine to organs and tissues that have either been damaged or have experienced degenerative processes (Kuriyan et al., 2017 & Biehl, et al., 2009). But stem cell transplantation has also been researched for cancer and other severe diseases. (2014; Srijaya et al.).

As a result, the field of regenerative medicine has recently placed a strong emphasis on novel biomaterials and stem cell functions. The enormous quantity of research that has been done on these subjects has allowed for significant advancements to be made thus far.

Application Of Stem Cell in Human Disease

Heart disease

Since the remedial uses of stem cell- grounded treatments for cardiac conditions have lately been completely covered in reviews (Bolli et al., 2021) and (Liu et al., 2021) this study will make on them in the corridor that follow, with an emphasis on hPSCs and MSCs. A substantial quantum of preclinical and clinical exploration generally supports the safety biographies of stem cell- grounded curatives, particularly adult stem cell remedy (e.g., MSC- grounded products).

Clinical trials, still, haven't yet produced substantiation of the treatment's effectiveness because, indeed in phase III trials, several studies have produced antithetical findings and no statistically significant variations in infarct size, cardiac function, or clinical issues (Zhang, J. et al., 2021). A meta-analysis's findings demonstrated that stem cells from colorful sources demanded any remedial function. The given cells may have a remedial effect through immunological regulation rather than regenerative function, which could regard for the dismal issues of the clinical trials to far. thus, to ascertain the effectiveness of the treatments, precisely planned, randomized, and placebo-controlled phase III studies with proper cell medication ways, patient selection, follow-up schedules, and applicable clinical assessments must be carried out. The stylish cell source and lozenge, the delivery system and timing of administration, the distribution of cells after administration, and the medium of action are more issues that must be addressed.

Liver Disease

The largest critical organ in the mortal body, the liver carries out vital natural tasks similar as metabolism, abetting in digestion, detoxifying the body, storing vitamins, and further (Si-Tayeb et al., 2010). Liver failure, cirrhosis, cancer, alcoholic liver complaint, non-alcoholic adipose liver complaint (NAFLD), and autoimmune liver complaint (ALD) are among the pathological conditions that may arise from a disturbance of liver homeostasis and function. Although there are veritably many applicable and available patron organs, orthotropic liver transplantation is the only effective treatment for serious liver diseases. At the moment, liver ancestor cells, hPSCs, MSCs, and HSCs are linked to stem cell-grounded treatments for liver illness.

Liver Cirrhosis

In liver cirrhosis, the hepatic vascular structure defeats due to parenchymal extermination after expansive nodular regrowth with thick fibrotic septa, which is one of the primary causes of morbidity and mortality encyclopedically (Arroyo et al., 2016). Actually, unless a liver transplant is done, liver cirrhosis is

allowed to be the final stage of liver illness that eventually results in death. currently, stem cell- grounded remedy further specifically, MSCs is showingpledge as a treatment for liver cirrhosis. The MSC group(n = 30) and the control group(n = 15) were resolve up among 45 habitual hepatitis B cases with decompensated liver cirrhosis in a clinical trial employing umbilical cord deduced MSCs(UC-MSCs)(Zhang et al., 2012). The MSC group's ascites volume was much lower than the control groups, according to the data. The MSC groups also showed a significant enhancement in liver function, as seen by a drop in the sodium model for end- stage liver complaint score, a drop in total blood bilirubin situations, and an increase in serum albumin attention(Zhang et al., 2012). Results from a phase II trial that used BM- MSCs in 25 cases with liver cirrhosis caused by HCV also showed analogous issues(El- Ansary et al., 2012). In line with theseexaminations, three further clinical trials that concentrated on alcoholic and hepatitis B- convinced liver cirrhosis were carried out and vindicated that the administration of MSC bettered and restored liver functioning(Xu et al., 2014) and(Fang et al., 2018). The safety and possible remedial benefits of MSC- grounded curatives might be further corroborated and the viability of treating contagion- related liver cirrhosis established by the big cohort study as the clinical trial carried out by Fang(Fanget al., 2018) 49 According to a randomized controlled phase 2 trial, cases with liver cirrhosis do n't parade remedial benefits from systemic preface of BM- MSCs(Mohamadnejad et al., 2019) 50. Liver cirrhosis is n't solely caused by MSCs. An open- marker clinical trial that was lately carried out in 19 children who had liver cirrhosis as a result of biliary atresia following the Kasai operation demonstrated the approach's safety and viability by demonstrating the enhancement in liver function following the administration of bone gist mononuclear cells(BMNC), as determined by biochemical tests and pediatric end- stage liver complaint(PELD) Scores(Nguyen et al., 2022). Another trial that used BMNCs in 32 cases with decompensated liver cirrhosis demonstrated the safety and efficacy of administering BMNCs in discrepancy to the control group(Bai et al., 2014). A recent long- term disquisition of cases who entered supplemental blood- deduced stem cells showed that

the chance of developing hepatocellular melanoma did n't rise, and the long- term survival rate was significantly better than in the control group(Guo et al., 2019). Cases with liver cirrhosis shared in a multicentre, open, randomized controlled phase 2 trial that involved CD133 HSC infusion; nevertheless, the issues didn't show enhancement of liver conditions, and cirrhosis continued(Newsome et al., 2018). specially, these issues are harmonious with previous randomized controlled exploration that set up no remedial pledge in bone gist- deduced stem cells and G- CSF administered through the hepatic roadway(Spahr et al., 2013).

Cancer

Stem cell remedy is a delicate conception that should be used and handled precisely while treating cancer. In addition to shielding cancer cases from expensive, potentially dangerous, or hamstrung stem cell- grounded curatives, clinicians and experimenters should also shield those without a cancer opinion from the possibility of developing cancer. For the treatment of cancer, untested stem cell conventions generally used three cell- grounded curatives autologous HSCTs, stromal vascular bit(SVF), and multipotent stem cells, like MSCs. A miracle known as" graft- versus- excrescence goods" occurs when allogeneic HSCTs produce patron lymphocytes that aid in the repression and retrogression of hematological malice and certain solid excrescences(Barisic et al., 2022). Still, stem cell conventions give allogeneic cell- rested remedy for the treatment of solid malice despite limited scientific confirmation supporting the safety and effectiveness of the treatment. High- quality confirmation from the Cochrane library shows that gist transplantation via autologous HSCTs in combination with high- cure chemotherapy does n't ameliorate the overall survival of women with metastatic bone cancer. In addition, a study including further than 41,000 bone cancer cases demonstrated no significant difference in survival benefits between cases who entered HSCTs following high- cure chemotherapy and cases who passed conventional treatment(Mello et al., 2001). therefore, the use of autologous T- cell transplants as monotherapy and advertising stem cell- rested curatives as

if they're medically approved or preferred treatment of solid excrescences is considered untrue statements and needs to be advised to cancer cases(Sissung et al., 2020). Because of their special rates, multitudinous preclinical studies conducted over the once many decades have shown the pledge of MSC-grounded remedy in the treatment of cancer. Through ingrain tropism regulated by growth factors, chemokines, and cytokines, they give the capacity to resettle toward damaged regions. In order to reply to external cues, MSCs must express certain C - X - C chemokine receptor type-4(CXCR4) as well as fresh chemokine receptors(similar as CCR1, CCR2, CCR4, CCR7, etc.)(Fu et al., 2019). likewise, the MSC face expresses particular adherence proteins, including as CD49d, CD44, CD54, CD102, and CD106, which enable the cells to cleave, rotate, resettle, and enter the blood vessel lumen in order to insinuate the injured towel(Zachar et al., 2016). Like injured apkins, excrescences release a variety of chemo attractants that, through the CXCL12/ CXCR4 axis, also draw MSC migration. Diffusible cytokines like interleukin 8(IL- 8) and growth factors like transubstantiating growth factor- beta 1(TGF- β 1), platelet- deduced growth factor(PDGF), fibroblast growth factor 2(FGF- 2), vascular endothelial growth factor(VEGF), and extracellular matrix motes like matrix metalloproteinase 2(MMP- 2) have also been shown in earlier exploration to tightly regulate MSC migration toward the cancer point(Cronwright et al., 2005). The main issues with MSC- grounded remedy are the protumor and antitumor goods that arise from the commerce between MSCs and cancer cells after they've effectively migrated to nasty towel. The regenerative parcels of MSCs, which control towel form and recovery, are extensively honored. The protumor conduct of these cells are also responsible for this special capability. According to a previous study, MSCs cache chemokine(C - C motif) ligand 5 (CCL- 5) in response to bone cancer cells, which controls the excrescence irruption process(Aldinuucci et al., 2020) and(Karnoub et al., 2007). According to other exploration, MSCs release a variety of growth factors that help cancer cells from dying, including VEGF, introductory FGF, HGF, PDGF, and others.85 likewise, MSCs can change into cancer- associated fibroblasts, a particular type of

cell that lives in the excrescence medium and can promote carcinogenesis, in response to signals given by cancer cells, similar as TGF- β , (Schmohl et al., 2020) and (Mishra et al., 2008). The development of cancer rectifiers has made use of MSCs' strong excrescence repression capabilities, despite their demonstrated involvement in protumor conditioning.

About 25 clinical trials that use MSCs as a remedial treatment for cancer have been registered on ClinicalTrials.gov therefore far (Liang et al., 2020). The maturity of these trials are phase 1 and 2 examinations that assess the treatment's efficacy and safety. MSCs and an oncolytic contagion strategy have been coupled in studies that take advantage of MSC- grounded remedy. Oncolytic contagions are particular kinds of contagions that can be set up naturally or through inheritable engineering. They've the capacity to specifically infect cancer cells and destroy them without harming the healthy cells around them (Cao et al., 2020). A finished phase I/ II exploration that used BM- MSCs infected with the oncolytic adenovirus ICOVIR5 to treat resistant and metastatic solid excrescences in both adult and pediatric cases showed that the treatment was safe and offered early substantiation of its eventuality as a treatment (Melen et al., 2016). In one pediatric illustration, the same experimenters reported that three times after administering MSC- grounded remedy, all suggestions of malice had fully faded (Garcia- Castro et al., 2016). According to a 2019 study, adipose-deduced MSCs fitted with the vaccinia contagion have the capacity to exclude resistant excrescence cells by combining strong contagion modification with excrescence cell sensitization to contagion infection (Draganov et al., 2019). Advances in stem cell- grounded remedy and further conventional treatments like chemotherapy, radiation, and surgery have steered in a new and instigative period in cancer exploration and treatment. Although stem cell- grounded remedy has been viewed as a new and charming remedial system for the treatment of cancer, preclinical exploration has shown disagreeing results regarding the protumor and antitumor goods. The use of stem cell- grounded remedy, particularly MSCs, gives cancer cases new stopgap despite this disagreeing reality by offering a new and more effective tool in acclimatized drug.

Arthritis

Arthritis: The broad term for cartilage diseases that affect in common discomfort and inflammation is arthritis. The most current type of arthritis brought on by cases is osteoarthritis(OA). Declination and shy articular cartilage rejuvenescence(Martel- Pelletier et al., 2016). analogous to bitsy joints at the hand and large joints at the knee and hips, OA affects one or further diarthrodial joints, performing in excruciating pain and a posterior loss in mobility. Primary OA, also known as idiopathic OA, and secondary OA are the two types of OA that are brought on by analogous unproductive factors similar as trauma, surgery, and aberrant common development at birth(Olsson et al., 2021). Due to the fact that traditional OA treatments are ineffective and may affect in excruciating pain and lengthy recuperation. thus, stem cell remedy has gained a lot of attention in the regenerative sector and has recently surfaced as a pivotal system for OA(Mahmoudian et al., 2021). It has been demonstrated that administering HSCs can lessen bone lesions, promote bone rejuvenescence, and accelerate the vascularization process in degenerative cartilage. Three intraarticular injections of redundant blood stem cells were used in ten OA cases inatrouble to gauge their efficacy. Analysis conducted after injection showed a significant drop in all parameters and a drop in the WOMAC score. Every case finished the 6-nanosecond walk tests, adding by further than 54 measures. An enhancement in cartilage density was shown by MRI examination, indicating thatpost-administration cartilage declination was lessened. CD34 stem cells were suggested as a way to ameliorate the restorative eventuality of HSCT indeed further(Kubsik-Gidlewska et al., 2016). Due to their immunoregulatory parcels, MSCs are presently the subject of a significant number of studies aimed at treating OA. anti-inflammatory parcels. MSCs have been the primary cell source in a number of small- and large- scale studies, demonstrating their safety profile and wordless efficacy in lowering cartilage declination, easing pain, and, in certain situations, promoting the rejuvenescence of cartilage shape and structure. There's still important to learn about the ideal source of MSCs for the treatment of OA, whether it comes

from the umbilical cord, adipose tissue, or bone marrow. The salutary goods of MSC-grounded remedies on OA cases were verified by a routine evaluation that examined 61 out of 3172 papers with roughly 2390 OA cases; still, the study also regarding BM-MSCs, clinical trials proved clinical problems at the 1-time follow-up, with of those trials reporting clinical problems that were noticeably better than those in the control group. still, a strong examination of the data set revealed that while the issues of the remaining eight trials were extremely low, those from six trials were low. also, after one injection, the positive confirmation from the MRI analysis was low to truly poor strength of confirmation. The outgrowth examination of autologous adipose tissue-derived MSCs(AT-MSCs) likewise produced similar results. As a result, the review set up that the restorative eventuality of MSC treatment on clinical enterprises and MRI analysis wasn't well validated. (redundant blood tube, and so forth), as well as clinical outgrowth assessments and control curatives in between randomized clinical studies. likewise, the information of the superior source of MSCs for the treatment of OA couldn't be demonstrated by routine analysis (Molnar et al., 2022). The authors support the idea that stem cell-based remedies could be regarded as a necessary treatment for OA when first-line treatments, similar as education, exercise, and body weight operation, have failed, indeed though they've been demonstrated to be safe and doable in the operation of OA.

Diabetes

Diabetes treatment Clinical experiments have employed a variety of stem cell types to treat diabetes (Path et al., 2019). Diabetes mellitus may result from autoimmune reasons (type 1 diabetes), lifestyle decisions and genetic inheritance (type 2 diabetes), or even pregnancy-related hormonal changes (gestational diabetes). Insulin injections are a common treatment for diabetes, but they provide challenges because of their high cost and transient nature²⁴. By directly repairing the pancreatic cells, stem cells can address this issue. Additionally, stem cells are being used to treat diabetes-related ailments such as wounds that don't heal (Lopes et al., 2018).

Wound healing

Healing wounds Stem cells have antibacterial qualities because they secrete antimicrobial substances, aid in immune response regulation, and encourage cell proliferation and differentiation at the wound site. Autologous stem cell usage eliminates the risk of immunological rejection (Ayavoo et al., 2021).

Tooth regeneration

Regeneration of teeth Dental reconstruction with MSCs has been the subject of numerous investigations. Dental pulp-derived stem cells (DPSCs) may encourage periodontal regeneration in a canine model, according to a study by Khorsand et al., 2013. Additionally, it was demonstrated that canine DPSCs could be isolated successfully and that they were capable of multi-lineage differentiation and fast proliferation.

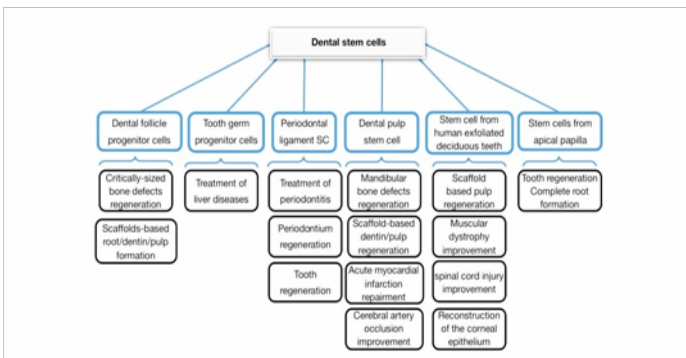


Fig.1 illustrates further uses for dental-derived stem cells.

Limitations, Ethical Concern and Future Perspective

The difference between categorizing embryonic stem (ES) cells as embryos or as specialized body tissues significantly affects their ethical considerations. This classification shapes individuals' perspectives, with some prioritizing the protection of embryos while others assign minimal moral value to early-stage embryos.

Currently, there are three potential sources for stem cells: adult stem cells from donors, ES cells derived from surplus preimplantation embryos, and embryonic stem cells (EG cells) sourced from aborted fetuses.

Harvesting stem cells from naturally abandoned fetuses raises smaller moral issues but faces practical challenges due to the difficulty of segregating functional EG cells from spontaneously abandoned tissue. Roughly 60% of robotic revocations affect from fatal anomalies, with chromosomal abnormalities linked in 20% (Boue et al., 1975).

The use of ES or EG cells attained from optional revocations raises specific moral questions for those opposing revocation or the destruction of early embryonic life. This dilemma leads to enterprises of conspiracy with perceived wrongdoing, particularly in religious surrounds.

When the potential for reproduction of a physical cell is contrasted with the implied growth of an embryo, it becomes clear that the former may have more experimental potential. The source of stem cells, embryonic fragment cells, naturally aid in the formation of new tissue. Nevertheless, these cells are pluripotent rather than totipotent as they are unable to generate necessary structures for additional development when isolated from the embryo.

Advanced technology might potentially render these cells totipotent, as demonstrated in a 1993 Canadian study using genetically altered embryos and mouse stem cells to grow and colonize an entire organism(Nagy et al., 1993).

An endless supply of specialized cells for medicinal applications is now possible because to the creation of iPSCs, which have made it possible to extract stem cells from a patient's cells. IPSCs can be genetically matched to the patient, which significantly reduces the risk of immunological rejection and allows for personalized treatment for a variety of diseases.

New treatment options for hereditary illnesses and genetic disorders are made possible by combining stem cell technology with gene editing methods like CRISPR-Cas9.

Gene-edited stem cells can be used to treat genetic diseases and lessen the chance that dangerous mutations would be passed on to future generations.

Conclusion

In conclusion, after decades of research, the treatment of stem cells has become an astounding medical revolution. The possibilities for stem cells increase with each experience, but there are still many challenges to solve. In any case, stem cells have a major impact on transplantation and regenerative medicine. Currently, stem cell treatment provides prospects for handling neurodegenerative disorders. The use of patient cells is possible via induced pluripotency. The organizational banks are gaining popularity as they collect cells, the source of regenerative therapy in the fight against current and future diseases. We are more capable than ever of extending human life thanks to stem cell therapy and all of its restorative advantages.

References

- Arroyo, V. et al. Acute-on-chronic liver failure in cirrhosis. *Nat. Rev. Dis. Prim.* 2, 16041 (2016).
- Bai, Y. Q. et al. Outcomes of autologous bone marrow mononuclear cell transplantation in decompensated liver cirrhosis. *World J. Gastroenterol.* 20, 8660–8666 (2014).
- Barisic, S. & Childs, R. W. Graft-versus-solid-tumor effect: from hematopoietic stem cell transplantation to adoptive cell therapies. *Stem Cells* 40, 556–563 (2022).
- Biehl, J. K. & Russell, B. Introduction to stem cell therapy. *J. Cardiovasc. Nurs.* 24, 98–103 (2009). quiz 104-105.
- Bolli, R., Tang, X. L., Guo, Y. & Li, Q. After the storm: an objective appraisal of the efficacy of c-kit⁺ cardiac progenitor cells in preclinical models of heart disease. *Can. J. Physiol. Pharm.* 99, 129–139 (2021).
- Boué J, Bou A, Lazar P. Retrospective and prospective epidemiological studies of 1500 karyotyped spontaneous human abortions. *Teratology.* 1975;12:11-26.
- Cronwright, G. et al. Cancer/testis antigen expression in human mesenchymal stem cells: down-regulation of

SSX impairs cell migration and matrix metalloproteinase 2 expression. *Cancer Res.* 65, 2207–2215 (2005)

Draganov, D. D. et al. Delivery of oncolytic vaccinia virus by matched allogeneic stem cells overcomes critical innate and adaptive immune barriers. *J. Transl. Med.* 17, 100 (2019).

Ejtehadifar M, Shamsasenjan K, Movassaghpour A, et al. The Effect of Hypoxia on Mesenchymal Stem Cell Biology. *Adv Pharm Bull* 2015;5:141-9.

Fang, X. et al. A study about immunomodulatory effect and efficacy and prognosis of human umbilical cord mesenchymal stem cells in patients with chronic hepatitis B-induced decompensated liver cirrhosis. *J. Gastroenterol. Hepatol.* 33, 774–780 (2018).

Farahzadi R, Fathi E, Mesbah-Namin SA, et al. Zinc sulfate contributes to promote telomere length extension via increasing telomerase gene expression, telomerase activity and change in the TERT gene promoter CpG island methylation status of human adipose-derived mesenchymal stem cells. *PLoS One* 2017;12:e0188052.

Fathi E, Farahzadi R. Isolation, culturing, characterization and aging of adipose tissue-derived mesenchymal stem cells: a brief overview. *Brazilian Archives of Biology and Technology* 2016;59

Friedenstein AJ, Chailakhyan RK, Latsinik NV, et al. Stromal cells responsible for transferring the microenvironment of the hemopoietic tissues: cloning in vitro and retransplantation in vivo. *Transplantation* 1974;17:331-40.

Fu, X. et al. Mesenchymal stem cell migration and tissue repair. *Cells* 8, 784 (2019).

Garcia-Castro, J. et al. Treatment of metastatic neuroblastoma with systemic oncolytic virotherapy delivered by autologous mesenchymal stem cells: an exploratory study. *Cancer Gene Ther.* 17, 476–483 (2010).

Gholizadeh-Ghalehaziz S, Farahzadi R, Fathi E, et al. A mini overview of isolation, characterization and application of amniotic fluid stem cells. *Int J Stem Cells* 2015;8:115.

Guo, C. et al. Long-term outcomes of autologous peripheral blood stem cell transplantation in patients with cirrhosis. *Clin. Gastroenterol. Hepatol.* 17, 1175–1182 e1172 (2019).

Han, S. B., Seo, I. W. & Shin, Y. S. Intra-articular injections

of hyaluronic acid or steroids associated with better outcomes than platelet-rich plasma, adipose mesenchymal stromal cells, or placebo in knee osteoarthritis: a network metaanalysis. *Arthroscopy* 37, 292–306 (2021).

Hosseini Mansoub N, Gurdal M, Karadadas E, et al. The role of PRP and adipose tissue-derived keratinocytes on burn wound healing in diabetic rats. *Bioimpacts* 2018;8:5-12.

<https://pmc.ncbi.nlm.nih.gov/articles/PMC6691074/>

Jevotovsky, D. S., Alfonso, A. R., Einhorn, T. A. & Chiu, E. S. Osteoarthritis and stem cell therapy in humans: a systematic review. *Osteoarthr. Cartil.* 26, 711–729 (2018).

Khorsand A, Eslaminejad MB, Arabsolghar M, et al. Autologous dental pulp stem cells in regeneration of defect created in canine periodontal tissue. *J Oral Implantol* 2013;39:433-43.

Kubsik-Gidlewska, A. et al. CD34+ stem cell treatment for knee osteoarthritis: a treatment and rehabilitation algorithm. *J. Rehabil. Med Clin. Commun.* 3, 1000012 (2018).

Kuriyan, A. E. et al. Vision loss after intravitreal injection of autologous “stem cells” for AMD. *N. Engl. J. Med.* 376, 1047–1053 (2017).

Liu, C., Han, D., Liang, P., Li, Y. & Cao, F. The current dilemma and breakthrough of stem cell therapy in ischemic heart disease. *Front. Cell Dev. Biol.* 9, 636136 (2021).

Lopes L, Setia O, Aurshina A, Liu S, Hu H, Isaji T, et al. Stem cell therapy for diabetic foot ulcers: A review of preclinical and clinical research. *Stem Cell Res Ther.* 2018;9:188.

Mahmoudian, A., Lohmander, L. S., Mobasheri, A., Englund, M. & Luyten, F. P. Early-stage symptomatic osteoarthritis of the knee – time for action. *Nat. Rev. Rheumatol.* 17, 621–632 (2021).

Markoski MM. Advances in the use of stem cells in veterinary medicine: from basic research to clinical practice. *Scientifica (Cairo)* 2016;2016:4516920.

Martel-Pelletier, J. et al. Osteoarthritis. *Nat. Rev. Dis. Prim.* 2, 16072 (2016).

Melen, G. J. et al. Influence of carrier cells on the clinical outcome of children with neuroblastoma treated with high dose of oncolytic adenovirus delivered in mesenchymal stem

cells. *Cancer Lett.* 371, 161–170 (2016).

Mello, M. M. & Brennan, T. A. The controversy over high-dose chemotherapy with autologous bone marrow transplant for breast cancer. *Health Aff. (Millwood)* 20, 101–117 (2001).

Mobarak H, Fathi E, Farahzadi R, et al. L-carnitine significantly decreased aging of rat adipose tissue-derived mesenchymal stem cells. *Vet Res Commun* 2017;41:41-7.

Mohamadnejad, M. et al. Randomized placebo-controlled trial of mesenchymal stem cell transplantation in decompensated cirrhosis. *Liver Int.* 33, 1490–1496 (2013).

Mohammadian M, Shamsasenjan K, Lotfi Nezhad P, et al. Mesenchymal stem cells: new aspect in cell-based regenerative therapy. *Adv Pharm Bull* 2013;3:433-7.

Molnar, V. et al. Mesenchymal stem cell mechanisms of action and clinical effects in osteoarthritis: a narrative review. *Genes* 13, 949 (2022).

Mousaei Ghasroldasht, M., Seok, J., Park, H. S., Liakath Ali, F. B. & Al-Hendy, A. Stem cell therapy: from idea to clinical practice. *Int. J. Mol. Sci.* 23, 2850 (2022).

Nagy A, Rossant J, Nagy R, Abramow-Newerly W, Roder JC. Derivation of completely cell culture-derived mice from early-passage embryonic stem cells. *Proc Natl Acad Sci U S A.* 1993;90:8424-8.

Newsome, P. N. et al. Granulocyte colony-stimulating factor and autologous CD133- positive stem-cell therapy in liver cirrhosis (REALISTIC): an open-label, randomised, controlled phase 2 trial. *Lancet Gastroenterol. Hepatol.* 3, 25–36 (2018).

NIDDK. Symptoms and causes of diabetes. 2016. United States: NIDDK; Available from: <https://www.nih.gov> [Last accessed on 2023 Sep 01]

O'Brien, T. & Barry, F. P. Stem cell therapy and regenerative medicine. *Mayo Clin. Proc.* 84, 859–861 (2009).

Olsson, S., Akbarian, E., Lind, A., Razavian, A. S. & Gordon, M. Automating classification of osteoarthritis according to Kellgren-Lawrence in the knee using deep learning in an unfiltered adult population. *BMC Musculoskelet. Disord.* 22, 844 (2021).

Päth G, Perakakis N, Mantzoros CS, Seufert J. Stem cells in the treatment of diabetes mellitus-Focus on mesenchymal stem cells. *Metabolism.* 2019;90:1-15.

Sissung, T. M. & Figg, W. D. Stem cell clinics: risk of proliferation. *Lancet Oncol.* 21, 205–206 (2020).

Si-Tayeb, K., Lemaigre, F. P. & Duncan, S. A. Organogenesis and development of the liver. *Dev. Cell* 18, 175–189 (2010).

Spahr, L. et al. Autologous bone marrow mononuclear cell transplantation in patients with decompensated alcoholic liver disease: a randomized controlled trial. *PLoS ONE* 8, e53719 (2013).

Srijaya, T. C., Ramasamy, T. S. & Kasim, N. H. Advancing stem cell therapy from bench to bedside: lessons from drug therapies. *J. Transl. Med.* 12, 243 (2014).

Srionrod N, Bootcha R, Petchdee S. Foal Deciduous Teeth Stem Cells Enhance Wound Healing in Rabbit Wound Model. *The Thai Journal of Veterinary Medicine* 2016;46:155-61.

Takahashi K, Tanabe K, Ohnuki M, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* 2007;131:861-72.

WebMD Editorial Contributors. Understanding diabetes-diagnosis and treatment 2021. Available from: <https://www.webmd.com> [Last accessed on 2023 Sep 01]

Wiggers, T. G., Winters, M., Van den Boom, N. A., Haisma, H. J. & Moen, M. H. Autologous stem cell therapy in knee osteoarthritis: a systematic review of randomised controlled trials. *Br. J. Sports Med* 55, 1161–1169 (2021).

Xu, L. et al. Randomized trial of autologous bone marrow mesenchymal stem cells transplantation for hepatitis B virus cirrhosis: regulation of Treg/Th17 cells. *J. Gastroenterol. Hepatol.* 29, 1620–1628 (2014).

Zachar, L., Bacenkova, D. & Rosocha, J. Activation, homing, and role of the mesenchymal stem cells in the inflammatory environment. *J. Inflamm. Res.* 9, 231–240 (2016)

Zhang, J. et al. Basic and translational research in cardiac repair and regeneration: JACC state-of-the-art review. *J. Am. Coll. Cardiol.* 78, 2092–2105 (2021).

Zhang, Z. et al. Human umbilical cord mesenchymal stem cells improve liver function and ascites in decompensated liver cirrhosis patients. *J. Gastroenterol. Hepatol.* 27(Suppl 2), 112–120 (2012).