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Stem Cells Biology: An Updated Review

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Abstract

Stem cells are partially differentiated cells in multicellular organisms that can change into various types of cells and increase indefinitely to produce more of the same stem cell which is considered as the earliest type of cell in a cell lineage. Treatment with those cells is regarded as an innovative approach in regenerative medicine, offering promising capabilities for healing and restoring damaged tissues and organs. Mesenchymal stem cells, derived from different sources like bone marrow, fat, and dental pulp, are highlighted for their self-renewal, immune-modulation, and regenerative abilities. Regenerative medicine is one of the more recent fields or methodologies that revolutionizes the path for upgrading human health and quality of life, relying on the use of stem cells. The process of using stem cells indicates marvelous capabilities for healing and restoring damaged tissues and organs. The current overview examines the science or biology of stem cells, showing their various sources, and their potential applications across a wide range of medical fields, carried by discussing multiple studies exploring the stem cells. The review further explores the potential of stem cell therapy for treating neurological disorders, autoimmune diseases, cardiovascular conditions, liver diseases, ophthalmic conditions, bone injuries, kidney disorders, and dental issues.

Keywords: Stem cells, Regenerative medicine, Mesenchymal stem cell, Cell therapy, Dental stem cell, Apical papilla cell.

1. INTRODUCTION

Regenerative medicine is a new multidisciplinary methodology that aims to revolutionize the way to improve human health and quality of life by preserving, sustaining, or improving tissue and organ functions (Akhtar, 2024; Atala, Lanza, Mikos, & Nerem, 2018). Since most human tissues and organs do not regenerate on their own, stem cell therapy has become a popular tissue and organ repair technique (Aziz, Yusop, & Ahmad, 2020; Balistreri *et al*., 2020).

Stem cell therapy is commonly viewed as a key twenty-first-century breakthrough technology capable of treating a vast range of biologically incurable diseases (Ahmed *et al*., 2024; Ranjit, Varma, Maddela, & Reddy, 2021). These cells have great potential in cell replacement therapy for diseases including Parkinson's, cardiovascular disease, and diabetes, as well as tissue engineering as a stable cell source for grafts to restore and rebuild diseased tissues (Abusalah, Abd Rahman, & Choudhary, 2024; Parmar, Grealish, & Henchcliffe, 2020).

Stem cells have received a lot of attention in recent decades due to their potential use in medicine because they can differentiate between osteogenic, adipogenic, and chondrogenic lineages allowing them to be used in therapeutic regimens of cartilage and bone regeneration (Hussain, Tebyaniyan, & Khayatan, 2022; Robert, Marcon, Dallagiovanna, & Shigunov, 2020).

Human stem cells are unspecialized cells that can be found in the body and have the capacity to differentiate into each cell in an organism in addition to the ability to self-renew which can be found in both embryonic and adult cells (Chowdhury & Ghosh, 2021; Shlush & Feldman, 2021). Stem cell therapy has been a very important and advanced biomedical research topic in recent years and the advancement of therapeutic techniques has sparked high hopes (Kandula & Wake, 2022; Skoracka, Bajewska, Kulawik, Suchorska, & Kulcenty, 2024).

While we have made considerable strides in our understanding of stem cell biology, our understanding of these cells is still constrained due to their complexity and dynamics, all of these necessitate more extensive researche to be done in this area to be a part of this new evolution in medical sciences, since advances in our understanding of these vital cells would have a major impact on our understanding of tissue regeneration and diseases curing (Ntege, Sunami, & Shimizu, 2020; Shang *et al*., 2021).

Therefore, the goal of this review is to present, review, and discuss the studies done on stem cells. Discussing the origins and the biology of stem cells as well as the applications of stem cells in medicine.

2. LITERATURE REVIEW

2.1 History

More than 30 years earlier, mesenchymal stem cells (MSCs) were formally identified to represent a population of cells derived from the bone marrow and periosteum of human and mammalians that could be separated and extended in culture while retaining their ability to be stimulated to form several mesodermal phenotypes and tissues in laboratory (J. Li *et al*., 2023; Zupan & Stražar, 2024).

In the 1990s, the ability to shape bone, cartilage, fat, and other tissues in vitro became an experiment for distinguishing this type of multipotent cells, and many companies sprung up to medically harness MSCs' regenerative abilities, the idea that a multipotent progenitor or "stem cell" persisted in adult's bone marrow was previously not just questioned, but aggressively dismissed, especially by the orthopedic industry (Caplan, 2017; Wakitani, Mera, Nakamura, & Gobbi, 2024).

Previously known as bone marrow mesenchymal stem cells or mesenchymal stromal cells, the name skeletal stem cells has newly been used to characterize cells in the bone marrow (Arora & Robey, 2022; Triffitt, 2021).

2.2 Stem Cell Biology

A blastocyst is formed after the sperm and ovum are fertilized, embryonic stem cells, which are short-lived stem cells, make up the inner lining, a blastocyst is made up of two cell types: the inner cell mass (ICM), which forms epiblasts and leads to the development of a fetus, and the trophectoderm (Sutharshan, Priyadharshini, & Sinduja, 2022; Toyooka, 2020). Blastocysts are in charge of managing the microenvironment inside the ICM, the blastocyst begins to develop and develops the extraembryonic support structures needed for the embryo's successful origin, such as the placenta. As the blastocyst begins to form a specialized support system, the ICM cells remain undifferentiated, pluripotent, and proliferative (Aguila, Osycka-Salut, Treulen, & Felmer, 2022; Thowfeequ & Srinivas, 2022; Zakrzewski, Dobrzyński, Szymonowicz, & Rybak, 2019).

Pluripotency is the tendency of stem cells to develop into different kinds of cells, the ICM is a research and development center for human embryonic stem cells (hESCs), cells form endoderm, mesoderm, and ectoderm groupings through embryogenesis, which give rise to specific cells and tissues in the fetus and, eventually, the adult body, when human embryonic stem cells (hESCs) divide into one of the germ layers, they are becoming multipotent stem cells with the potential restricted to that germ layer's cells, human growth is happening at a breakneck pace (Rebuzzini, Zuccotti, & Garagna, 2021; Zakrzewski *et al*., 2019).

Thereafter, pluripotent stem cells appear as undifferentiated cells in the body, and their primary functions are replication through the development of new stem cells and division into specialized cells under certain physiological conditions (Mohammadi *et al*., 2022; Siddiqui & Saba, 2020).

External signals, such as physical interaction between cells or chemical secretion by surrounding tissue, and internal signals, which are mediated by genes in DNA, affect the stem cell specialization mechanism (Kong *et al*., 2021).

Stem cells also serve as the body's internal healing mechanism, as long as an organism is living, it may replenish and shape new cells indefinitely, while the Stem cell function varies depending on the organ; for example, in bone marrow, division is permanent, while in organs like the pancreas, division happens only under special physiological conditions (Fazeli & Ahanjan, 2022; Mummery, Van de Stolpe, Roelen, & Clevers, 2021).

2.3 Categorization

The three groups of stem cells are induced pluripotent stem cells, embryonic stem cells, and adult stem cells (de Figueiredo Pessôa, Bressan, & Freude, 2019). Adult stem cells, also defined as mesenchymal stem cells, may come from both human and animal sources. Human MSCs (hMSCs) are nonhematopoietic multipotent stem cells that can differentiate into chondrocytes, mesodermal lineages such as adipocytes, and osteocytes, as well as ectodermal and endodermal lineages (Ebrahimi *et al*., 2023).

hMSCs were discovered for the first time in bone marrow, and since then they have been extracted from a variety of tissues, such as amniotic fluid, adipose tissue, dental tissues, endometrium, and umbilical cord, that contain possible MSCs. Kangari, Talaei-Khozani, Razeghian-Jahromi, and Razmkhah (2020) hMSCs have indeed been cultured in specific media for a long time with no significant anomalies (Zhao *et al*., 2024). MSCs also have immunomodulatory effects, have immune receptors that control the host tissue's microenvironment, and secret cytokines (Wong, Lenzini, Giovanni, Knowles, & Shin, 2021).

2.4 Isolation and Initial Culturing

Different procedures for MSC isolation, identification, and development have been published previously, but all mesenchymal stem cells regardless of protocol meet the minimum requirements proposed by the International Society for Cellular Therapy (Naji *et al*., 2019).

The tendency of mesenchymal stem cells to bind to a plastic surface was used to separate them, but this process resulted in the creation of heterogeneous cells (mesenchymal stem cells plus progenitor cells) (Wilson, Webster, & Genever, 2019). Stem cells that originate from bone marrow are considered the most appropriate cell origin and are used as a benchmark for comparing MSCs from other origins (Snowden *et al*., 2020).

Stem cells from other tissues, unlike bone marrow, can be collected conveniently using noninvasive methods and their proliferation can be preserved over several passages (Chu *et al*., 2020). MSCs are extracted from bone marrow, synovial fluid, and peripheral blood, and seeded onto culture plates using the Ficoll density gradient configuration with minor modifications (Han *et al*., 2020). Few hematopoietic cells bind to the plastic plate when isolating stem cells from bone marrow, and yet these cells are flushed away upon sub-culturing, keeping only adherent fibroblast-like cells (Bhat, Viswanathan, Chandanala, Prasanna, & Seetharam, 2021; Binsila *et al*., 2019).

Recently, a new marrow filter system was used to investigate an effective approach for isolating bone marrow mesenchymal stem cells that is less time-intensive and eliminates the possibility of external contamination (Banu *et al*., 2024).

Mesenchymal stem cell growth and proliferation are influenced by oxygen accumulation in addition to culture media and supplementation. Stem cells are cultured with low glucose and growth factors including epidermal growth factor, and fibroblast growth factor (Nikolits, Nebel, Egger, Kreß, & Kasper, 2021).

2.5 Stem Cells Applications in Medicine

Stem cells can be applied in different fields of medicine including new drug testing (Ryu, Lee, & Park, 2019). Each experiment on living tissue can be safely carried out on differentiated cells derived from pluripotent stem cells. If any unfavorable side effects occur, medication formulations may be tweaked until they are effective enough (Zakrzewski *et al*., 2019). The drug can be released into the market without causing any injury to live test subjects, when comparing the results of two medications, though, the circumstances must be comparable to measure the drugs properly. To do this, scientists must gain complete control over the differentiation process to produce pure colonies of differentiated cells (McQuade *et al*., 2018; Yoshida, Miwa, Kawachi, Kume, & Takahashi, 2020).

Mesenchymal stem cells are also a promising cell source for treating degenerative diseases, inflammatory, and autoimmune diseases because of their anti-inflammatory molecules secretion, homing capacity, multilineage capacity, and immunoregulatory impact (Marg *et al*., 2020; Sarsenova *et al*., 2022). Stem cells can help in treating the following diseases:

2.5.1 Neurodegenerative Diseases

Since the central nervous system regenerates slowly, neurologic impairments are frequently permanent. As a result of stem cells' regenerative potential, numerous stem cell transplantation treatments have been studied in basic science and preclinical studies, with some showing promising results (Alessandrini, Preynat-Seauve, De Bruin, & Pepper, 2019; Park, 2024). Both fundamental scientists and physicians have invested a great deal of time and money into the translation of stem cell treatments for the treatment of neurological disorders over the years (Johnson & Greene, 2021). A significant body of data supporting the effectiveness and efficacy of stem cell therapy has come from preclinical studies using disease models. Several neurological disorders, including Parkinson's disease, Alzheimer's disease, and macular degeneration, have undergone or are currently undergoing clinical trials (Namiot, Niemi, Chubarev, Tarasov, & Schiöth, 2022).

Despite these remarkable and motivating breakthroughs, big roadblocks remain in the way of translating scientific science into real-world clinical practice. Until stem cell therapy is used in the real world, these challenges must be overcome (Beetler *et al*., 2023).

2.5.1.1 Amylotrophic Lateral Sclerosis

Mesenchymal stem cells were genetically modified to produce a Glial cell line-derived neurotrophic factor (GDNF), which enhanced the pathological phenotype and raised the number of neuromuscular attachments in a rat model study (Wang, Hu, Jiang, & Feng, 2020).

2.5.1.2 Parkinson's Disease

A progressive depletion of nigrostriatal dopaminergic neurons is a pathological characteristic of Parkinson's disease, which also results in rigidity, sluggish physical movements, tremors, and postural dysfunction (Ramesh & Arachchige, 2023).

New techniques are now being used, such as genetic modifications of mesenchymal stem cells that cause the secretion of particular factors or enhance the differentiation of dopamine cells (Ying Chen, Shen, Ke, & Gu, 2020; Mendes Filho *et al*., 2018).

Mesenchymal Stem Cells were applied through the nose to treat neurodegenerative patients by a research team from the University Hospital of Tubingen in Germany (El-Ayoubi *et al*., 2024). The tests were carried out on Parkinson's disease rats who were given BM-MSCs through the nose. MSCs were present in the hippocampus, cerebral cortex, olfactory lobe, brain stem, and cortex after four and half months of therapy, indicating that mesenchymal stem cells could persist and proliferate in vivo successfully (Conese *et al*., 2019).

2.5.1.3 Alzheimer Disease

Alzheimer's disease is also a major health problem in today's world and there is no solution. Neural loss and Chronic neuroinflammation are the hallmarks of this disease (Passeri *et al*., 2022).

Alzheimer's disease is difficult to treat with commercially available pharmaceuticals due to the multifaceted nature of AD anatomy and our inadequate knowledge of its etiology (Srivastava, Ahmad, & Khare, 2021).

Alzheimer's disease is difficult to handle with today's pharmaceuticals, although stem cell treatment that can be targeted to repair neuronal dysfunction in Alzheimer's patients may be able to fill this gap (L. Kumar, 2021). Although Alzheimer's disease stem cell therapy is still in development, it has a wide variety of potential uses, ranging from substitution therapy to disease modeling and drug production. The current effectiveness of stem cells in animal model trials suggests that they could one day be used to treat Alzheimer's disease (Götz, Bodea, & Goedert, 2018; Liu, Yang, & Zhao, 2020).

2.5.2 Autoimmune Disease

Mesenchymal stem cells (MSC) have a variety of immunomodulatory characteristics that are mediated by soluble mediators and direct cell–cell interaction (Song, Scholtemeijer, & Shah, 2020). The safety and therapeutic effectiveness of MSC therapy have been studied in a variety of autoimmune disorders due to these immune regulatory properties (Leyendecker Jr, Pinheiro, Amano, & Bueno, 2018).

2.5.2.1 Crohn’s Disease

In genetically prone individuals, Crohn's disease (is a debilitating persistent enteropathy caused by a toxic T-cell reaction to antigens of the gut microbiota (Baer, 2023). Growing research supports the use of mesenchymal stem cells as a new therapeutic option for this disease, highlighting their protection and potential efficacy (Gabriel *et al*., 2023; Wainstein *et al*., 2018). Via a diverse paracrine and cell-cell contact-mediated action, mesenchymal stem cells have potent immunomodulatory effects on antigen-specific T cells in Crohn's disease, which could be used for widespread therapeutic application (Queckbörner, 2020).

2.5.2.2 Systemic Lupus Erythematosus

Systemic lupus erythematosus is a multisystemic, polymorphic, autoimmune disorder that involves multiorgan destruction and is characterized by the presence of autoantibodies directed toward autoantigen development in cellular communication (Accapezzato *et al*., 2023; Zhou, Li, Liao, Lin, & Lin, 2020).

While some patients respond well to presently offered medications, others are resistant to them.

Mesenchymal stem cells are a suitable choice for curing Systemic Lupus Erythematous because of their immunomodulatory and tissue regeneration properties (Karimi *et al*., 2024).

2.5.2.3 Rheumatoid Arthritis

Rheumatoid arthritis is an inflammatory disorder affecting the joints due to a lack of immune self-tolerance. Mesenchymal stem cells are shown to be effective in disease treatment and disease development reducing in preclinical trials on animal models (Pignatti, Maccaferri, Pisciotta, Carnevale, & Salvarani, 2024). The infusion of human mesenchymal stem cells into animal models resulted in an increase in the animal's inflammatory response (MacDonald & Barrett, 2020). They also showed that after injecting MSCs, antigen-specific cells expanded, lowering the levels of inflammatory cytokines and chemokines while increasing IL-10 secretion (Shephard, Merkhan, & Forsyth, 2022).

2.5.2.4 Type I Diabetes

Diabetes is a metabolic illness that affects hundreds of millions of people all over the world (R. Kumar *et al*., 2020). Type 1 diabetes is described by the absence of pancreatic cells that have been killed by an autoimmune reaction (Kamal & Kassem, 2020). As a result, in type I Diabetes patients, substitution therapy with functional cells originating from extrinsic sources could be a better choice than insulin treatment. Unfortunately, owing to a lack of donors, only a small percentage of diabetic patients will benefit from entire pancreas or pancreatic islet transplantation (Langlois, Pinget, Kessler, & Bouzakri, 2024).

Significant numbers of human β-like cells derived from human embryonic stem cells (hESCs) or human induced pluripotent stem cells have been produced to treat type I Diabetes thanks to the rapid progress of cell reprogramming technologies (hiPSCs) (Amirruddin, Low, Lee, Tai, & Teo, 2020; Cierpka-Kmiec, Wronska, & Kmiec, 2019).

2.5.3 Cardiovascular Disease

Cardiac cell transplantation is a novel technique for myocardial reconstruction that is currently being tested in animal models (Guo *et al*., 2020). MSCs are thought to be an excellent source of cardiomyocyte specialization(Sun, Lu, Yin, & Liu, 2020). Even so, cardiomyocyte differentiation in vivo is very unlikely, and in vitro, differentiation works best with young cell origins (Rowton, Guzzetta, Rydeen, & Moskowitz, 2021).

While MSCs represent one of the most important cell types for effective cell therapy, it has become increasingly clear that no single cell type will achieve complete myocardial regeneration (Tripathi *et al*., 2023). MSC therapy may have a bright future as the primary sustaining, trophic, and orchestrating cell type in a cell therapy that combines various cell types to take advantage of their distinct characteristics and benefits (Bagno, Hatzistergos, Balkan, & Hare, 2018; Hoang *et al*., 2022).

New blood vessels are created by the mechanisms of vasculogenesis and angiogenesis. Vasculogenesis is the process of endothelial precursor cells, or angioblasts, transforming into endothelial cells and forming a primitive vascular network from scratch (Amoupour *et al*., 2022). Angiogenesis corresponds to the sprouting or intussusception of new capillaries from previously existing blood vessels (Nitzsche *et al*., 2022).

Neovascularization is a critical stage in active adipose tissue engineering, co-implantation of adipose-derived stem cells (ASCs) with endothelial cells to facilitate the development of a vascular network is one possible cellular solution to address this restriction (Simunovic & Finkenzeller, 2021).

2.5.4 Liver Disease

The use of mesenchymal stem cells (MSCs) as a liver disease treatment has a lot of potential. MSCs can divide into hepatocytes, which can help mitigate liver inflammation, stimulate hepatic regeneration, and secrete protective cytokines (Wu *et al*., 2022).

In vivo, the differentiation of transplanted MSCs into liver cells has been shown in several experiments (Al-Dhamin *et al*., 2020; Wang *et al*., 2020). The survival rate of acute hepatic necrosis rats caused by carbon tetrachloride is greatly improved by the transplantation of human Mesenchymal Stem Cells (Khalil *et al*., 2021). The underlying pathways could include human MSCs transdifferentiating into liver cells and migrating to damaged sites in the liver (Kiseleva *et al*., 2021).

2.5.5 Regenerative Ocular Therapy

The corneal epithelium's consistency and regular operation are critical for ensuring the cornea's clarity and vision (Gómez-Fernández *et al*., 2024). The presence of a progenitor cell population in the limbus ensures a dynamic of continuous epithelial repair and regeneration (Yam, Pi, Du, & Mehta, 2023). Currently, cell-based bio-replacement approaches for limbal stem cell deficiency (LSCD) and vision restoration—cultured limbal epithelial transplantation (CLET) and cultured oral mucosal epithelial transplantation (COMET)—show promising clinical performance (Lee, Yong, & Manotosh, 2023).

Obtaining and introducing human progenitor cells from various sources in conjunction with tissue engineering approaches is another new therapeutic technique (Ntege *et al*., 2020). The advancement of cell-mediated therapies based on stem cells, such as human adult mesenchymal or induced pluripotent stem cells (IPSCs), represents a major milestone in the treatment of some eye diseases, providing a more rational, less invasive, and better clinical treatment alternative in ocular surface regenerative medicine (Cehajic-Kapetanovic, Singh, Zrenner, & MacLaren, 2023).

2.5.6 Bone Tissue Engineering

Bone, unlike many other postnatal tissues, has the ability to repair and regenerate itself; moreover, this ability can be used (Salhotra, Shah, Levi, & Longaker, 2020). Traditionally, autologous, allogeneic, and prosthetic components have been used in surgical reconstructive techniques (Pu, Zhang, Wang, Liu, & Shao, 2021). The best choice, autologous bone, is in short supply and requires an extra surgical operation. There are many concerns to consider in the development of a viable, implantable replacement tissue in regenerative tissue engineering (Battafarano *et al*., 2021).

In comparison to other stem cell outlets (adult stem cell populations or pluripotent embryonic stem cells), the apparent accessibility of an autologous osteoprogenitor population has propelled the use of skeletal stem cell therapy for orthopedic applications (Ambrosi, Longaker, & Chan, 2019; X. Li *et al*., 2022).

2.5.7 Kidney Disease

Kidney disease is a major health condition that impacts people all over the world (Kovesdy, 2022). Renal dysfunction manifests itself in a variety of ways, like acute and chronic kidney complications (Kellum *et al*., 2021). Acute kidney injury (AKI) can contribute to chronic kidney disease (CKD), which can probably result in end-stage renal disease (ESRD), which has a high mortality rate. (Yeh, Tu, Wang, & Chen, 2024) Dialysis and kidney transplantation are the only medical options currently available; furthermore, issues such as donor organ shortages, graft loss, and various complications continue to be a problem (Bastani, 2020).

2.6 Dental Stem Cell

The pulp of the tooth is close to the marrow of the bone in several ways, both are mineral-encased, heavily vascularized, and innervated soft tissues (Schmalz, Widbiller, & Galler, 2020). MSCs can differentiate into mineral-generating cells in both bone marrow and dental pulp. This work is performed by osteoblasts in bone marrow, while odontoblasts, which are produced from dental pulp stem cells, perform it in teeth (DPSCs) (Aydin & Şahin, 2019; Koh *et al*., 2021).

2.7 Sources of Dental Stem Cell

2.7.1 Dental Pulp Stem Cell

The Pulp tissue of the tooth is a connective tissue that is in direct contact with the dentin of the tooth (Farci & Soni, 2021). The dental pulp is surrounded by dentin, a porous bone-like structure (Azaryan, Emadian Razavi, Hanafi-Bojd, Alemzadeh, & Naseri, 2023). The dentin-pulp complex is represented by both tissues. Odontoblasts, the mineralizing cells of the dental pulp, trigger dentinogenesis, they can repair mild tooth decay-related hard tissue destruction, they are made up of undifferentiated cells in the dental pulp, and dental pulp stem cells (DPSCs) have also been derived from postnatal and the natal teeth which is very rarely found (Aspinall, Parker, & Khutoryanskiy, 2021; Tsutsui, 2020; Yuan, Yang, Zhang, Tian, & Yang, 2022). Various forms of somatic stem cells with varying differentiation potentials are likely to be found in the dental pulp (Staniowski, Zawadzka-Knefel, & Skośkiewicz-Malinowska, 2021). Bar, Lis-Nawara, and Grelewski (2021) isolated a subpopulation of activated dental pulp stem cells DPSCs, the granulocyte colony-stimulating factor (G-CSF) is responsible for DPSC migration. A basic cell migration assay may thus be used to enrich MDPSCs. In an ectopic tooth transplantation assay, these migrating cells exhibited more angiogenic/neurotrophic factors than DPSCs, and their ability to regenerate the dental pulp was higher (Staniowski *et al*., 2021; Yamada, Nakamura-Yamada, Kusano, & Baba, 2019).

2.7.2 Periodontal Ligament Stem Cell

Stem cells derived from mature periodontal ligaments have stem cell properties identical to MSCs (Iwayama, Sakashita, Takedachi, & Murakami, 2022). PDLSCs express MSC surface markers (CD105, CD90, and CD73) (Banavar *et al*., 2021), but lack expression of CD45, CD34, and CD14, as well as CD11b, CD79a, and CD19 (Abbasi, Iqbal, Bano, Siddiqui, & Muthiah, 2021). Furthermore, PDLSCs in the perivascular wall of periodontal ligaments have morphology, differentiation capacity, cell phenotype (expression of pericyte-associated markers CD146, neural/glial antigen-2, and CD140B), and the ability to shape capillary-like structures in vitro that are similar to pericytes (Batra *et al*., 2021).

A study by Campagna *et al*., (2024) in a meta-analysis study on tissue engineering using mesenchymal stem cells, including those originating from bone marrow and periodontal ligaments mesenchymal cells, found that the use of bone marrow-derived stem cells for cell therapy had inconsistent results, although PDLSCs consistently advocated periodontal regeneration. Yuanting Chen *et al*., (2022) concluded that PDLSCs are the best kind of mesenchymal stem cell for periodontal tissue engineering.

2.7.3 Apical Papilla Cell

Dental mesodermal tooth germ tissues, which can be derived from impacted third molars, are accessible in comparison to the human enamel organ, they may also be used to separate stem cells (Gan *et al*., 2020). The dental apical papilla, also known as the apical pad-like tissue, is one such tissue (Camassari, de Sousa, Cogo-Müller, & Puppin-Rontani, 2023). This tissue adheres to the apex of an impacted third molar's developing premature tooth base, which is regularly removed from juvenile patients for orthodontic purposes. Since the apical papilla is rich in proteoglycans, it can be histologically distinguished from the dental pulp and can proliferate and differentiate into different cell types (Al Madhoun *et al*., 2021; T. Lei, Zhang, Chen, Li, & Du, 2021).

2.7.4 Inflamed Peri-apical Cysts and Dental Follicle Stem Cell

Hertwig's epithelial root sheath is developed as an extension of the enamel organ for the initiation of tooth root growth (Rathee & Jain, 2020). A second dental mesenchymal tooth-germ tissue is separated from the dental mesenchymal pulp/dentin complex by this thin cell-sheath (Morsczeck & Reichert, 2018). The dental sac, also known as the dent follicle, is the tissue that protects the tooth germ. The dental follicle is essential for both tooth eruption and tooth root growth (G. Kumar, 2023).

The dental follicle contains multipotent ectomesenchyme stem cells, which are also known as dental follicle precursor cells, dental follicle stem cells, or dental follicle cells (Zhou *et al*., 2020).

Clinical Applications of Dental Stem Cells are:

(1) Restoration of Tooth Pulp (Xie *et al*., 2021), (2) Craniofacial Skeletal Repair (Amoupour *et al*., 2022), (3) Periodontal Tissues Regeneration (Bartold & Ivanovski, 2022), (4) Immune Modulation (P. Li, Ou, Shi, & Shao, 2023), (5) Mineral Formation (G. Lei *et al*., 2020), (6) Whole Tooth Regeneration (Zhang & Yelick, 2021).

3. CONCLUSION

Stem cell technology is proving to be a major game changer in medicine. The capabilities of stem cells increase with each experiment, but there are still many obstacles to tackle. In the not-too-distant future, stem cell therapy might be able to heal many incurable diseases.

4. RECOMMENDATION

Tissue bank establishments are recommended to save children's primary teeth and any other possible stem cell-containing tissues for future needs.

REFERENCES

- Abbasi, K., Iqbal, S., Bano, S., Siddiqui, K., & Muthiah, L. (2021). More to Explore; The Mesenchymal Stem Cells (MSCs) Major Tissue Sources, Known Surface Markers and Its Immunomodulation properties. *American Journal of*

Pure and Applied Biosciences, 3(4), 85-97. doi:https://doi.org/10.34104/ajpab.021.085097

- Abusalah, M. A. H., Abd Rahman, E. N. S. E., & Choudhary, O. P. (2024). Evolving trends in stem cell therapy: an emerging and promising approach against various diseases. *International Journal of Surgery, 110*(11), 6862-6868. doi:DOI: 10.1097/JS9.0000000000001948
- Accapezzato, D., Caccavale, R., Paroli, M. P., Gioia, C., Nguyen, B. L., Spadea, L., & Paroli, M. (2023). Advances in the pathogenesis and treatment of systemic lupus erythematosus. *International journal of molecular sciences, 24*(7), 6578. doi:https://doi.org/10.3390/ijms24076578
- Aguila, L., Osycka-Salut, C., Treulen, F., & Felmer, R. (2022). Pluripotent core in bovine embryos: a review. *Animals, 12*(8), 1010. doi:https://doi.org/10.3390/ani12081010
- Ahmed, M., Sajjad, U., Islam, R., Alghamdi, B., Iqbal, M. Z., Aljohani, I. M., . . . Awais, M. (2024). Recent advancements in stem cell-based therapies. *Pure and Applied Biology, 13*(4), 464-482. doi:DOI: 10.19045/bspab.2024.130041
- Akhtar, Z. (2024). Exploring Biomedical Engineering (BME): Advances within Accelerated Computing and Regenerative Medicine for a Computational and Medical Science Perspective Exploration Analysis. *J Emerg Med OA, 2*(1), 01-23. doi:DOI: 10.33140/JEMOA.02.01.06
- Al-Dhamin, Z., Liu, L. D., Li, D. D., Zhang, S. Y., Dong, S. M., & Nan, Y. M. (2020). Therapeutic efficiency of bone marrow-derived mesenchymal stem cells for liver fibrosis: a systematic review of in vivo studies. *World Journal of Gastroenterology, 26*(47), 7444-7469. doi:doi: 10.3748/wjg.v26.i47.7444
- Al Madhoun, A., Sindhu, S., Haddad, D., Atari, M., Ahmad, R., & Al-Mulla, F. (2021). Dental pulp stem cells derived from adult human third molar tooth: a brief review. *Frontiers in cell and developmental biology, 9*, 717624. doi:https://doi.org/10.3389/fcell.2021.717624
- Alessandrini, M., Preynat-Seauve, O., De Bruin, K., & Pepper, M. S. (2019). Stem cell therapy for neurological disorders. *South African Medical Journal, 109*(8 Supplement 1), S71-S78. doi:https://hdl.handle.net/10520/EJC-1888466f25
- Ambrosi, T. H., Longaker, M. T., & Chan, C. K. (2019). A revised perspective of skeletal stem cell biology. *Frontiers in cell and developmental biology, 7*, 189. doi:https://doi.org/10.3389/fcell.2019.00189
- Amirruddin, N. S., Low, B. S. J., Lee, K. O., Tai, E. S., & Teo, A. K. K. (2020). *New insights into human beta cell biology using human pluripotent stem cells.* Paper presented at the Seminars in Cell & Developmental Biology.
- Amoupour, M., Kebria, M. M., Hivechi, A., Peyravian, N., Ghasemian, M., Mehrabi, A., . . . Milan, P. B. (2022). Molecular mediators of vasculogenesis and angiogenesis. In *Biomaterials for Vasculogenesis and Angiogenesis* (pp. 13-37): Elsevier.
- Arora, D., & Robey, P. G. (2022). Recent updates on the biological basis of heterogeneity in bone marrow stromal cells/skeletal stem cells. *Biomaterials Translational, 3*(1), 3-6. doi:doi: 10.12336/biomatertransl.2022.01.002
- Aspinall, S. R., Parker, J. K., & Khutoryanskiy, V. V. (2021). Oral care product formulations, properties and challenges. *Colloids and Surfaces B: Biointerfaces, 200*, 111567. doi:https://doi.org/10.1016/j.colsurfb.2021.111567
- Atala, A., Lanza, R., Mikos, T., & Nerem, R. (2018). *Principles of regenerative medicine* (2nd ed.): Academic press.
- Aydin, S., & Şahin, F. (2019). Stem cells derived from dental tissues. *Adv Exp Med Bio, 1144*, 123-132. doi:DOI: 10.1007/5584_2018_333
- Azaryan, E., Emadian Razavi, F., Hanafi-Bojd, M. Y., Alemzadeh, E., & Naseri, M. (2023). Dentin regeneration based on tooth tissue engineering: a review. *Biotechnology Progress, 39*(2), e3319. doi: https://doi.org/10.1002/btpr.3319
- Aziz, N. S., Yusop, N., & Ahmad, A. (2020). Importance of stem cell migration and angiogenesis study for regenerative cell-based therapy: a review. *Current stem cell research & therapy, 15*(3), 284-299. doi:https://doi.org/10.2174/1574888X15666200127145923
- Baer, H. M. (2023). *Identification of Crohn's disease immunopathotypes.* PhD thesis, University of Glasgow,
- Bagno, L., Hatzistergos, K. E., Balkan, W., & Hare, J. M. (2018). Mesenchymal stem cell-based therapy for cardiovascular disease: progress and challenges. *Molecular Therapy, 26*(7), 1610-1623. doi:10.1016/j.ymthe.2018.05.009
- Balistreri, C. R., De Falco, E., Bordin, A., Maslova, O., Koliada, A., & Vaiserman, A. (2020). Stem cell therapy: old challenges and new solutions. *Molecular biology reports, 47*(4), 3117-3131. doi:https://doi.org/10.1007/s11033-020-05353-2
- Banavar, S. R., Rawal, S. Y., Paterson, I. C., Singh, G., Davamani, F., Khoo, S. P., & Tan, E. L. (2021). Establishing a technique for isolation and characterization of human periodontal ligament derived mesenchymal stem cells. *The Saudi Dental Journal, 33*(7), 693-701. doi:https://doi.org/10.1016/j.sdentj.2020.04.007
- Banu, S. A., Saini, S., Sharun, K., Mamachan, M., Nair, S. S., Pawde, A. M., . . . Maiti, S. K. (2024). Isolation and Characterization of Bacterial Contaminants from Bone Marrow-Derived Mesenchymal Stem Cell Cultures. *Journal of Pure & Applied Microbiology, 18*(1), 653-661. doi:DOI: 10.22207/JPAM.18.1.50

- Bar, J. K., Lis-Nawara, A., & Grelewski, P. G. (2021). Dental pulp stem cell-derived secretome and its regenerative potential. *International journal of molecular sciences, 22*(21), 12018. doi:https://doi.org/10.3390/ijms222112018
- Bartold, M., & Ivanovski, S. (2022). Stem cell applications in periodontal regeneration. *Dental Clinics, 66*(1), 53-74.
- Bastani, B. (2020). The present and future of transplant organ shortage: some potential remedies. *Journal of nephrology, 33*(2), 277-288. doi:https://doi.org/10.1007/s40620-019-00634-x
- Batra, O., Kour, S., Gulati, G., Vyassini, C. V. S., Parmar, E., & Amal, F. (2021). Periodontal Ligament Stem Cells: A Literature Review. *European Journal of Molecular and Clinical Medicine, 8*(4), 542-552.
- Battafarano, G., Rossi, M., De Martino, V., Marampon, F., Borro, L., Secinaro, A., & Del Fattore, A. (2021). Strategies for bone regeneration: from graft to tissue engineering. *International journal of molecular sciences, 22*(3), 1128. doi:https://doi.org/10.3390/ijms22031128
- Beetler, D. J., Di Florio, D. N., Law, E. W., Groen, C. M., Windebank, A. J., Peterson, Q. P., & Fairweather, D. (2023). The evolving regulatory landscape in regenerative medicine. *Molecular aspects of medicine, 91*, 101138. doi:https://doi.org/10.1016/j.mam.2022.101138
- Bhat, S., Viswanathan, P., Chandanala, S., Prasanna, S. J., & Seetharam, R. N. (2021). Expansion and characterization of bone marrow derived human mesenchymal stromal cells in serum-free conditions. *Scientific reports, 11*(1), 3403. doi:https://doi.org/10.1038/s41598-021-83088-1
- Binsila, B., Selvaraju, S., Ghosh, S., Prasad, J., Ramya, L., Ravindra, J., & Bhatta, R. (2019). Purification of spermatogonial stem cells from ram testicular isolate using ficoll density gradient separation. *The Indian Journal of Animal Reproduction, 40*(1), 7-11.
- Camassari, J. R., de Sousa, I. T. C., Cogo-Müller, K., & Puppin-Rontani, R. M. (2023). The Self-assembling peptide P11-4 influences viability and osteogenic differentiation of stem cells of the apical papilla (SCAP). *Journal of dentistry, 134*, 104551. doi:https://doi.org/10.1016/j.jdent.2023.104551
- Campagna, A., Baima, G., Romano, F., Amoroso, F., Mussano, F., Oteri, G., . . . Peditto, M. (2024). Orally Derived Stem Cell-Based Therapy in Periodontal Regeneration: A Systematic Review and Meta-Analysis of Randomized Clinical Studies. *Dentistry Journal, 12*(5), 145. doi:https://doi.org/10.3390/dj12050145
- Caplan, A. I. (2017). Mesenchymal stem cells: time to change the name! *Stem cells translational medicine, 6*(6), 1445-1451. doi:https://doi.org/10.1002/sctm.17-0051
- Cehajic-Kapetanovic, J., Singh, M. S., Zrenner, E., & MacLaren, R. E. (2023). Bioengineering strategies for restoring vision. *Nature biomedical engineering, 7*(4), 387-404. doi:https://doi.org/10.1038/s41551-021-00836-4
- Chen, Y., Huang, H., Li, G., Yu, J., Fang, F., & Qiu, W. (2022). Dental-derived mesenchymal stem cell sheets: a prospective tissue engineering for regenerative medicine. *Stem Cell Research & Therapy, 13*(1), 38. doi:https://doi.org/10.1186/s13287-022-02716-3
- Chen, Y., Shen, J., Ke, K., & Gu, X. (2020). Clinical potential and current progress of mesenchymal stem cells for Parkinson's disease: a systematic review. *Neurological Sciences, 41*(5), 1051-1061. doi:https://doi.org/10.1007/s10072-020-04240-9
- Chowdhury, S., & Ghosh, S. (2021). Stem cells an overview. *Stem Cells: Biology and Therapeutics*, 1-21. doi:DOI: 10.1007/978-981-16-1638-9_1
- Chu, D.-T., Phuong, T. N. T., Tien, N. L. B., Tran, D. K., Thanh, V. V., Quang, T. L., . . . Chu-Dinh, T. (2020). An update on the progress of isolation, culture, storage, and clinical application of human bone marrow mesenchymal stem/stromal cells. *International journal of molecular sciences, 21*(3), 708. doi:https://doi.org/10.3390/ijms21030708
- Cierpka-Kmiec, K., Wronska, A., & Kmiec, Z. (2019). In vitro generation of pancreatic β-cells for diabetes treatment. I. β-like cells derived from human pluripotent stem cells. *Folia histochemica et cytobiologica, 57*(1), 1-14. doi:DOI: 10.5603/FHC.a2019.0001
- Conese, M., Cassano, R., Gavini, E., Trapani, G., Rassu, G., Sanna, E., . . . Trapani, A. (2019). Harnessing stem cells and neurotrophic factors with novel technologies in the treatment of Parkinson's disease. *Current stem cell research & therapy, 14*(7), 549-569. doi:https://doi.org/10.2174/1574888X14666190301150210
- de Figueiredo Pessôa, L. V., Bressan, F. F., & Freude, K. K. (2019). Induced pluripotent stem cells throughout the animal kingdom: availability and applications. *World Journal of Stem Cells, 11*(8), 491-505. doi:doi: 10.4252/wjsc.v11.i8.491
- Ebrahimi, F., Pirouzmand, F., Cosme Pecho, R. D., Alwan, M., Yassen Mohamed, M., Ali, M. S., . . . Hajimortezayi, Z. (2023). Application of mesenchymal stem cells in regenerative medicine: A new approach in modern medical science. *Biotechnology Progress, 39*(6), e3374. doi: https://doi.org/10.1002/btpr.3374
- El-Ayoubi, A., Arakelyan, A., Klawitter, M., Merk, L., Hakobyan, S., Gonzalez-Menendez, I., . . . Schwab, M. (2024). Development of an optimized, non-stem cell line for intranasal delivery of therapeutic cargo to the central nervous system. *Molecular Oncology, 18*(3), 528-546. doi: https://doi.org/10.1002/1878-0261.13569

- Farci, F., & Soni, A. (2021). *Histology, tooth*: StatPearls Publishing, Treasure Island (FL).
- Fazeli, F., & Ahanjan, M. (2022). The capacity of stem cells in treatment of diabetes. *Cellular, Molecular and Biomedical Reports, 2*(4), 230-244. doi:https://doi.org/10.55705/cmbr.2022.357066.1060
- Gabriel, K. L., Sami, M., Ijishakin, O., Agyemang, S. F., Odugunwa, M. N., Miles, D. M., . . . Okezie, C. E. (2023). Efficacy and Safety of Stem Cell Therapy in the Treatment of Fistulizing Crohn's Disease and the Role of Autologous Stem Cell Transplantation: A Systematic Review. *Journal of Advances in Medicine and Medical Research, 35*(23), 189-201. doi:https://doi.org/10.9734/jammr/2023/v35i235294
- Gan, L., Liu, Y., Cui, D., Pan, Y., Zheng, L., & Wan, M. (2020). Dental tissue-derived human mesenchymal stem cells and their potential in therapeutic application. *Stem cells international, 2020*(1), 8864572. doi:https://doi.org/10.1155/2020/8864572
- Gómez-Fernández, H., Alhakim-Khalak, F., Ruiz-Alonso, S., Díaz, A., Tamayo, J., Ramalingam, M., . . . Pedraz, J. L. (2024). Comprehensive review of the state-of-the-art in corneal 3D bioprinting, including regulatory aspects. *International Journal of Pharmaceutics, 662*, 124510. doi:https://doi.org/10.1016/j.ijpharm.2024.124510
- Götz, J., Bodea, L.-G., & Goedert, M. (2018). Rodent models for Alzheimer disease. *Nature Reviews Neuroscience, 19*(10), 583-598. doi:https://doi.org/10.1038/s41583-018-0054-8
- Guo, R., Morimatsu, M., Feng, T., Lan, F., Chang, D., Wan, F., & Ling, Y. (2020). Stem cell-derived cell sheet transplantation for heart tissue repair in myocardial infarction. *Stem Cell Research & Therapy, 11*(19), 1-13. doi:DOI: 10.1186/s13287-019-1536-y
- Han, J. Y., Cho, H. Y., Kim, Y. M., Park, K. J., Jung, K. M., & Park, J. S. (2020). Production of quail (Coturnix japonica) germline chimeras by transfer of Ficoll-enriched spermatogonial stem cells. *Theriogenology, 154*, 223-231. doi:https://doi.org/10.1016/j.theriogenology.2020.05.039
- Hoang, D. M., Pham, P. T., Bach, T. Q., Ngo, A. T., Nguyen, Q. T., Phan, T. T., . . . Forsyth, N. R. (2022). Stem cell-based therapy for human diseases. *Signal transduction and targeted therapy, 7*(1), 272. doi:https://doi.org/10.1038/s41392-022-01134-4
- Hussain, A., Tebyaniyan, H., & Khayatan, D. (2022). The role of epigenetic in dental and oral regenerative medicine by different types of dental stem cells: a comprehensive overview. *Stem cells international, 2022*(1), 5304860. doi: https://doi.org/10.1155/2022/5304860
- Iwayama, T., Sakashita, H., Takedachi, M., & Murakami, S. (2022). Periodontal tissue stem cells and mesenchymal stem cells in the periodontal ligament. *Japanese Dental Science Review, 58*, 172-178. doi:https://doi.org/10.1016/j.jdsr.2022.04.001
- Johnson, N. E., & Greene, E. (2021). Neurologic therapeutics in 2035: the neurology future forecasting series. *Neurology, 97*(24), 1121-1127. doi:https://doi.org/10.1212/WNL.0000000000012976
- Kamal, M. M., & Kassem, D. H. (2020). Therapeutic potential of Wharton's jelly mesenchymal stem cells for diabetes: achievements and challenges. *Frontiers in cell and developmental biology, 8*, 16. doi:https://doi.org/10.3389/fcell.2020.00016
- Kandula, U. R., & Wake, A. D. (2022). Promising stem cell therapy in the management of HIV and AIDS: A narrative review. *Biologics: Targets and Therapy*, 89-105. doi: DOI: 10.2147/BTT.S368152
- Kangari, P., Talaei-Khozani, T., Razeghian-Jahromi, I., & Razmkhah, M. (2020). Mesenchymal stem cells: amazing remedies for bone and cartilage defects. *Stem Cell Research & Therapy, 11*(1), 492. doi:https://doi.org/10.1186/s13287-020-02001-1
- Karimi, F., Nejati, B., Rahimi, F., Alivirdiloo, V., Alipourfard, I., Aghighi, A., . . . Ghazi, F. (2024). A state-of-the-art review on the recent advances of mesenchymal stem cell therapeutic application in systematic lupus erythematosus. *Immunological Investigations, 53*(2), 160-184. doi:https://doi.org/10.1080/08820139.2023.2289066
- Kellum, J. A., Romagnani, P., Ashuntantang, G., Ronco, C., Zarbock, A., & Anders, H.-J. (2021). Acute kidney injury. *Nature reviews Disease primers, 7*(1), 1-17.
- Khalil, M. R., El-Demerdash, R. S., Elminshawy, H. H., Mehanna, E. T., Mesbah, N. M., & Abo-Elmatty, D. M. (2021). Therapeutic effect of bone marrow mesenchymal stem cells in a rat model of carbon tetrachloride induced liver fibrosis. *Biomedical journal, 44*(5), 598-610. doi:https://doi.org/10.1016/j.bj.2020.04.011
- Kiseleva, Y. V., Antonyan, S. Z., Zharikova, T. S., Tupikin, K. A., Kalinin, D. V., & Zharikov, Y. O. (2021). Molecular pathways of liver regeneration: A comprehensive review. *World Journal of Hepatology, 13*(3), 270-290. doi:doi: 10.4254/wjh.v13.i3.270
- Koh, B., Sulaiman, N., Ismadi, S. N. S. W., Ramli, R., Yunus, S. S. M., Idrus, R. B. H., . . . Yazid, M. D. (2021). Mesenchymal stem cells: A comprehensive methods for odontoblastic induction. *Biological procedures online, 23*, 18. doi:https://doi.org/10.1186/s12575-021-00155-7
- Kong, Y., Duan, J., Liu, F., Han, L., Li, G., Sun, C., . . . Liu, H. (2021). Regulation of stem cell fate using nanostructure-mediated physical signals.

Chemical Society Reviews, 50(22), 12828-12872. doi:https://doi.org/10.1039/D1CS00572C

- Kovesdy, C. P. (2022). Epidemiology of chronic kidney disease: an update 2022. *Kidney international supplements, 12*(1), 7-11. doi:https://doi.org/10.1016/j.kisu.2021.11.003
- Kumar, G. (2023). *Orban's Oral Histology & Embryology-E-BOOK*: Elsevier Health Sciences.
- Kumar, L. (2021). Engrafted stem cell therapy for Alzheimer's disease: A promising treatment strategy with clinical outcome. *Journal of Controlled Release, 338*, 837-857. doi:https://doi.org/10.1016/j.jconrel.2021.09.007
- Kumar, R., Saha, P., Kumar, Y., Sahana, S., Dubey, A., & Prakash, O. (2020). A review on diabetes mellitus: type1 & Type2. *World Journal of Pharmacy and Pharmaceutical Sciences, 9*(10), 838-850. doi:DOI: 10.20959/wjpps202010-17336
- Langlois, A., Pinget, M., Kessler, L., & Bouzakri, K. (2024). Islet Transplantation: Current Limitations and Challenges for Successful Outcomes. *Cells, 13*(21), 1783. doi:https://doi.org/10.3390/cells13211783
- Lee, Y. F., Yong, D. W. W., & Manotosh, R. (2023). A Review of Contact Lens-Induced Limbal Stem Cell Deficiency. *Biology, 12*(12), 1490. doi:https://doi.org/10.3390/biology12121490
- Lei, G., Wang, Y., Yu, Y., Li, Z., Lu, J., Ge, X., . . . Yu, J. (2020). Dentin-Derived Inorganic Minerals Promote the Osteogenesis of Bone Marrow-Derived Mesenchymal Stem Cells: Potential Applications for Bone Regeneration. *Stem cells international, 2020*(1), 8889731. doi:https://doi.org/10.1155/2020/8889731
- Lei, T., Zhang, X., Chen, P., Li, Q., & Du, H. (2021). Proteomic profile of human dental follicle stem cells and apical papilla stem cells. *Journal of proteomics, 231*, 103928. doi:https://doi.org/10.1016/j.jprot.2020.103928
- Leyendecker Jr, A., Pinheiro, C. C. G., Amano, M. T., & Bueno, D. F. (2018). The use of human mesenchymal stem cells as therapeutic agents for the in vivo treatment of immune-related diseases: a systematic review. *Frontiers in Immunology, 9*, 2056. doi:https://doi.org/10.3389/fimmu.2018.02056
- Li, J., Wu, Z., Zhao, L., Liu, Y., Su, Y., Gong, X., . . . Zhang, L. (2023). The heterogeneity of mesenchymal stem cells: An important issue to be addressed in cell therapy. *Stem Cell Research & Therapy, 14*(1), 381. doi:https://doi.org/10.1186/s13287-023-03587-y
- Li, P., Ou, Q., Shi, S., & Shao, C. (2023). Immunomodulatory properties of mesenchymal stem cells/dental stem cells and their therapeutic applications. *Cellular & molecular immunology, 20*(6), 558-569. doi:https://doi.org/10.1038/s41423-023-00998-y
- Li, X., Zhu, X., Sun, J., Yung, P. S., Tuan, R. S., & Jiang, Y. (2022). Stem Cells and Their Application in Orthopedics. *Biofabrication for Orthopedics: Methods, Techniques and Applications, 1*, 93-132. doi:https://doi.org/10.1002/9783527831371.ch4
- Liu, X.-Y., Yang, L.-P., & Zhao, L. (2020). Stem cell therapy for Alzheimer's disease. *World Journal of Stem Cells, 12*(8), 787-802. doi:doi: 10.4252/wjsc.v12.i8.787
- MacDonald, E. S., & Barrett, J. G. (2020). The potential of mesenchymal stem cells to treat systemic inflammation in horses. *Frontiers in Veterinary Science, 6*, 507. doi:https://doi.org/10.3389/fvets.2019.00507
- Marg, A., Escobar, H., Gloy, S., Kufeld, M., Zacher, J., Spuler, A., . . . Spuler, S. (2020). Human satellite cells have regenerative capacity and are genetically manipulable. *The Journal of clinical investigation, 124*(10), 4257-4265. doi: https://doi.org/10.1172/JCI63992.
- McQuade, A., Coburn, M., Tu, C. H., Hasselmann, J., Davtyan, H., & Blurton-Jones, M. (2018). Development and validation of a simplified method to generate human microglia from pluripotent stem cells. *Molecular neurodegeneration, 13*(1), 67. doi:https://doi.org/10.1186/s13024-018-0297-x
- Mendes Filho, D., dC Ribeiro, P., Oliveira, L. F., de Paula, D. R., Capuano, V., de Assunção, T. S., & da Silva, V. J. (2018). Therapy with mesenchymal stem cells in Parkinson disease: history and perspectives. *The Neurologist, 23*(4), 141-147. doi:DOI:10.1097/NRL.0000000000000188
- Mohammadi, A. T., Bagheri, H., Qahremani, R., hadi Hosnaei, M., Fazlavargharebagh, H., Salimi, M., . . . Rouzbahani, A. K. (2022). *Stem cell for researchers 1: Embryonic, Amniotic, Fetal stem cells and Neuroimaging*: Nobel TM.
- Morsczeck, C., & Reichert, T. E. (2018). Dental stem cells in tooth regeneration and repair in the future. *Expert opinion on biological therapy, 18*(2), 187-196. doi:https://doi.org/10.1080/14712598.2018.1402004
- Mummery, C. L., Van de Stolpe, A., Roelen, B., & Clevers, H. (2021). *Stem cells: scientific facts and fiction*: Academic Press.
- Naji, A., Eitoku, M., Favier, B., Deschaseaux, F., Rouas-Freiss, N., & Suganuma, N. (2019). Biological functions of mesenchymal stem cells and clinical implications. *Cellular and Molecular Life Sciences, 76*, 3323-3348. doi:https://doi.org/10.1007/s00018-019-03125-1
- Namiot, E. D., Niemi, J. V. L., Chubarev, V. N., Tarasov, V. V., & Schiöth, H. B. (2022). Stem cells in clinical trials on neurological disorders: trends in stem cells origins, indications, and status of the clinical trials. *International journal of molecular sciences, 23*(19), 11453. doi:https://doi.org/10.3390/ijms231911453

- Nikolits, I., Nebel, S., Egger, D., Kreß, S., & Kasper, C. (2021). Towards physiologic culture approaches to improve standard cultivation of mesenchymal stem cells. *Cells, 10*(4), 886. doi:https://doi.org/10.3390/cells10040886
- Nitzsche, B., Rong, W. W., Goede, A., Hoffmann, B., Scarpa, F., Kuebler, W. M., . . . Pries, A. R. (2022). Coalescent angiogenesis—evidence for a novel concept of vascular network maturation. *Angiogenesis, 25*(1), 35-45. doi:https://doi.org/10.1007/s10456-021-09824-3
- Ntege, E. H., Sunami, H., & Shimizu, Y. (2020). Advances in regenerative therapy: A review of the literature and future directions. *Regenerative therapy, 14*, 136-153. doi:https://doi.org/10.1016/j.reth.2020.01.004
- Park, E. J. (2024). *Overview of the results of clinical studies based on stem cell transplantation for patients suffering from nervous system diseases.* (Doctoral dissertation). Doctoral dissertation, University of Zagreb. School of Medicine. Department of Histology and Embryology,
- Parmar, M., Grealish, S., & Henchcliffe, C. (2020). The future of stem cell therapies for Parkinson disease. *Nature Reviews Neuroscience, 21*(2), 103-115. doi:
- https://doi.org/10.1038/s41583-019-0257-7
- Passeri, E., Elkhoury, K., Morsink, M., Broersen, K., Linder, M., Tamayol, A., . . . Arab-Tehrany, E. (2022). Alzheimer’s disease: treatment strategies and their limitations. *International journal of molecular sciences, 23*(22), 13954. doi:https://doi.org/10.3390/ijms232213954
- Pignatti, E., Maccaferri, M., Pisciotta, A., Carnevale, G., & Salvarani, C. (2024). A comprehensive review on the role of mesenchymal stromal/stem cells in the management of rheumatoid arthritis. *Expert Review of Clinical Immunology, 20*(5), 463-484. doi:https://doi.org/10.1080/1744666X.2023.2299729
- Pu, F., Zhang, Z., Wang, B., Liu, J., & Shao, Z. (2021). En bloc resection and intercalary prosthesis implantation for the treatment of humeral diaphyseal bone metastases. *International Orthopaedics, 45*, 281-288. doi:https://doi.org/10.1007/s00264-020-04845-x
- Queckbörner, S. (2020). *Endometrial Regeneration: Unraveling the Mysteries of the Stroma.* PhD thesis, Karolinska Institutet, Sweden, Retrieved from https://www.proquest.com/openview/db5cc285074 5b4df18e6096ec08ea420/1?pq-origsite=gscholar&cbl=2026366&diss=y
- Ramesh, S., & Arachchige, A. S. P. M. (2023). Depletion of dopamine in Parkinson's disease and relevant therapeutic options: A review of the literature. *AIMS neuroscience, 10*(3), 200-231. doi:doi: 10.3934/Neuroscience.2023017
- Ranjit, P., Varma, C. A. S. L., Maddela, N. R., & Reddy, K. V. (2021). Biotechnology of Twenty-First Century. *Innovations in Biotechnology for a Sustainable Future*, 17-42. doi:https://doi.org/10.1007/978-3-030-80108-3_2
- Rathee, M., & Jain, P. (2020). *Embryology, teeth*: StatPearls. StatPearls Publishing, Treasure Island (FL).
- Rebuzzini, P., Zuccotti, M., & Garagna, S. (2021). Building pluripotency identity in the early embryo and derived stem cells. *Cells, 10*(8), 2049. doi:https://doi.org/10.3390/cells10082049
- Robert, A. W., Marcon, B. H., Dallagiovanna, B., & Shigunov, P. (2020). Adipogenesis, osteogenesis, and chondrogenesis of human mesenchymal stem/stromal cells: a comparative transcriptome approach. *Frontiers in cell and developmental biology, 8*, 561. doi:https://doi.org/10.3389/fcell.2020.00561
- Rowton, M., Guzzetta, A., Rydeen, A. B., & Moskowitz, I. P. (2021). *Control of cardiomyocyte differentiation timing by intercellular signaling pathways.* Paper presented at the Seminars in cell & developmental biology.
- Ryu, N.-E., Lee, S.-H., & Park, H. (2019). Spheroid culture system methods and applications for mesenchymal stem cells. *Cells, 8*(12), 1620. doi:https://doi.org/10.3390/cells8121620
- Salhotra, A., Shah, H. N., Levi, B., & Longaker, M. T. (2020). Mechanisms of bone development and repair. *Nature reviews Molecular cell biology, 21*(11), 696-711. doi:https://doi.org/10.1038/s41580-020-00279-w
- Sarsenova, M., Kim, Y., Raziyeva, K., Kazybay, B., Ogay, V., & Saparov, A. (2022). Recent advances to enhance the immunomodulatory potential of mesenchymal stem cells. *Frontiers in Immunology, 13*, 1010399. doi:https://doi.org/10.3389/fimmu.2022.1010399
- Schmalz, G., Widbiller, M., & Galler, K. M. (2020). Clinical perspectives of pulp regeneration. *Journal of endodontics, 46*(9), S161-S174. doi:https://doi.org/10.1016/j.joen.2020.06.037
- Shang, F., Yu, Y., Liu, S., Ming, L., Zhang, Y., Zhou, Z., . . . Jin, Y. (2021). Advancing application of mesenchymal stem cell-based bone tissue regeneration. *Bioactive materials, 6*(3), 666-683. doi:https://doi.org/10.1016/j.bioactmat.2020.08.014
- Shephard, M. T., Merkhan, M. M., & Forsyth, N. R. (2022). Human mesenchymal stem cell secretome driven T cell immunomodulation is IL-10 dependent. *International journal of molecular sciences, 23*(21), 13596. doi:https://doi.org/10.3390/ijms232113596
- Shlush, L., & Feldman, T. (2021). The evolution of leukaemia from pre-leukaemic and leukaemic stem cells. *Journal of Internal Medicine, 289*(5), 636-649. doi: https://doi.org/10.1111/joim.13236
- Siddiqui, S., & Saba, I. (2020). *Stem Cells*: EduBubs Publishing House.
- Simunovic, F., & Finkenzeller, G. (2021). Vascularization strategies in bone tissue engineering.

Cells, *10*(7), 1749. doi:doi.org/10.3390/cells10071749

- Skoracka, J., Bajewska, K., Kulawik, M., Suchorska, W., & Kulcenty, K. (2024). Advances in cartilage tissue regeneration: a review of stem cell therapies, tissue engineering, biomaterials, and clinical trials. *EXCLI journal*, *23*, 1170-1182. doi:doi: 10.17179/excli2024-7088
- Snowden, J. A., Saccardi, R., Orchard, K., Ljungman, P., Duarte, R. F., Labopin, M., . . . Gordon, D. (2020). Benchmarking of survival outcomes following haematopoietic stem cell transplantation: a review of existing processes and the introduction of an international system from the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE). *Bone marrow transplantation*, *55*(4), 681-694. doi:https://doi.org/10.1038/s41409-019-0718-7
- Song, N., Scholtemeijer, M., & Shah, K. (2020). Mesenchymal stem cell immunomodulation: mechanisms and therapeutic potential. *Trends in pharmacological sciences*, *41*(9), 653-664. doi:DOI: 10.1016/j.tips.2020.06.009
- Srivastava, S., Ahmad, R., & Khare, S. K. (2021). Alzheimer's disease and its treatment by different approaches: A review. *European Journal of Medicinal Chemistry*, *216*, 113320. doi:https://doi.org/10.1016/j.ejmech.2021.113320
- Staniowski, T., Zawadzka-Knefel, A., & Skośkiewicz-Malinowska, K. (2021). Therapeutic potential of dental pulp stem cells according to different transplant types. *Molecules*, *26*(24), 7423. doi:https://doi.org/10.3390/molecules26247423
- Sun, Y., Lu, Y., Yin, L., & Liu, Z. (2020). The roles of nanoparticles in stem cell-based therapy for cardiovascular disease. *Frontiers in Bioengineering and Biotechnology*, *8*, 947. doi:https://doi.org/10.3389/fbioe.2020.00947
- Sutharshan, G., Priyadharshini, R., & Sinduja, P. (2022). Stem Cells and Its Multimodality-A Review. *Journal of Pharmaceutical Negative Results*, 1275-1282. doi:DOI: 10.47750/pnr.2022.13.S04.151
- Thowfeequ, S., & Srinivas, S. (2022). Embryonic and extraembryonic tissues during mammalian development: shifting boundaries in time and space. *Philosophical Transactions of the Royal Society B*, *377*(1865), 20210255. doi:https://doi.org/10.1098/rstb.2021.0255
- Toyooka, Y. (2020). Trophoblast lineage specification in the mammalian preimplantation embryo. *Reproductive Medicine and Biology*, *19*(3), 209-221. doi:https://doi.org/10.1002/rmb2.12333
- Triffitt, J. T. (2021). A brief history of the development of stromal stem cells (stem cells of the skeleton). *Biomaterials Translational*, *2*(4), 287-293. doi: doi: 10.12336/biomatertransl.2021.04.003
- Tripathi, H., Domingues, A., Donahue, R., Cras, A., Guerin, C. L., Gao, E., . . . Abdel-Latif, A. (2023). Combined transplantation of human MSCs and ECFCs improves cardiac function and decrease cardiomyocyte apoptosis after acute myocardial infarction. *Stem Cell Reviews and Reports*, *19*(2), 573-577. doi:https://doi.org/10.1007/s12015-022-10468-z
- Tsutsui, T. W. (2020). Dental pulp stem cells: advances to applications. *Stem cells and cloning: advances and applications*, *13*, 33-42. doi:https://doi.org/10.2147/SCCAA.S166759
- Wainstein, C., Quera, R., Fluxá, D., Kronberg, U., Conejero, A., López-Köstner, F., . . . Zarate, A. J. (2018). Stem cell therapy in refractory perineal Crohn's disease: long-term follow-up. *Colorectal Disease*, *20*(3), O68-O75. doi:https://doi.org/10.1111/codi.14002
- Wakitani, S., Mera, H., Nakamura, N., & Gobbi, A. (2024). Review of Caplan (1991) on cell-based therapeutic technology using Mesenchymal Stem Cells. *Journal of ISAKOS*, *9*(3), 426-430. doi:https://doi.org/10.1016/j.jisako.2023.08.010
- Wang, J., Hu, W. W., Jiang, Z., & Feng, M. J. (2020). Advances in treatment of neurodegenerative diseases: perspectives for combination of stem cells with neurotrophic factors. *World Journal of Stem Cells*, *12*(5), 323. doi:doi: 10.4252/wjsc.v12.i5.323
- Wilson, A., Webster, A., & Genever, P. (2019). Nomenclature and heterogeneity: consequences for the use of mesenchymal stem cells in regenerative medicine. *Regenerative Medicine*, *14*(6), 595-611. doi:https://doi.org/10.2217/rme-2018-0145
- Wong, S. W., Lenzini, S., Giovanni, R., Knowles, K., & Shin, J.-W. (2021). Matrix biophysical cues direct mesenchymal stromal cell functions in immunity. *Acta biomaterialia*, *133*, 126-138. doi:https://doi.org/10.1016/j.actbio.2021.07.075
- Wu, R., Fan, X., Wang, Y., Shen, M., Zheng, Y., Zhao, S., & Yang, L. (2022). Mesenchymal stem cell-derived extracellular vesicles in liver immunity and therapy. *Frontiers in Immunology*, *13*, 833878. doi:https://doi.org/10.3389/fimmu.2022.833878
- Xie, Z., Shen, Z., Zhan, P., Yang, J., Huang, Q., Huang, S., . . . Lin, Z. (2021). Functional dental pulp regeneration: basic research and clinical translation. *International journal of molecular sciences*, *22*(16), 8991. doi:https://doi.org/10.3390/ijms22168991
- Yam, G. H. F., Pi, S., Du, Y., & Mehta, J. S. (2023). Posterior corneoscleral limbus: Architecture, stem cells, and clinical implications. *Progress in Retinal and Eye Research*, *96*, 101192. doi:https://doi.org/10.1016/j.preteyeres.2023.101192
- Yamada, Y., Nakamura-Yamada, S., Kusano, K., & Baba, S. (2019). Clinical potential and current progress of dental pulp stem cells for various systemic diseases in regenerative medicine: a concise review. *International journal of molecular sciences*, *20*(5), 1132. doi:https://doi.org/10.3390/ijms20051132

- Yeh, T. H., Tu, K. C., Wang, H. Y., & Chen, J. Y. (2024). From Acute to Chronic: Unraveling the Pathophysiological Mechanisms of the Progression from Acute Kidney Injury to Acute Kidney Disease to Chronic Kidney Disease. *International journal of molecular sciences, 25*(3), 1755. doi:https://doi.org/10.3390/ijms25031755
- Yoshida, S., Miwa, H., Kawachi, T., Kume, S., & Takahashi, K. (2020). Generation of intestinal organoids derived from human pluripotent stem cells for drug testing. *Scientific reports*, *10*(1), 5989. doi:https://doi.org/10.1038/s41598-020-63151-z
- Yuan, S. M., Yang, X. T., Zhang, S. Y., Tian, W. D., & Yang, B. (2022). Therapeutic potential of dental pulp stem cells and their derivatives: Insights from basic research toward clinical applications. *World Journal of Stem Cells, 14*(7), 435-452. doi:doi: 10.4252/wjsc.v14.i7.435
- Zakrzewski, W., Dobrzyński, M., Szymonowicz, M., & Rybak, Z. (2019). Stem cells: past, present, and future. *Stem Cell Research & Therapy, 10*(1), 1-22. doi:https://doi.org/10.1186/s13287-019-1165-5
- Zhang, W., & Yelick, P. C. (2021). Tooth repair and regeneration: potential of dental stem cells. *Trends in molecular medicine, 27*(5), 501-511. doi:DOI: 10.1016/j.molmed.2021.02.005
- Zhao, L., Ni, B., Li, J., Liu, R., Zhang, Q., Zheng, Z., . . . Bi, L. (2024). Evaluation of the impact of customized serum-free culture medium on the production of clinical-grade human umbilical cord mesenchymal stem cells: insights for future clinical applications. *Stem Cell Research & Therapy*, *15*(1), 327. doi:https://doi.org/10.1186/s13287-024-03949-0
- Zhou, T., Li, H. Y., Liao, C., Lin, W., & Lin, S. (2020). Clinical efficacy and safety of mesenchymal stem cells for systemic lupus erythematosus. *Stem cells international, 2020*(1), 6518508. doi:https://doi.org/10.1155/2020/6518508
- Zupan, J., & Stražar, K. (2024). Synovium-Derived and Bone-Derived Mesenchymal Stem/Stromal Cells from Early OA Patients Show Comparable In Vitro Properties to Those of Non-OA Patients. *Cells, 13*(15), 1238. doi:https://doi.org/10.3390/cells13151238

