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Overview on scope and advancement in regenerative medicine

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Abstract---Regenerative medicine is the science of replacing engineering, regenerating human cells, tissues, or organs to restore or establish normal function and has now reached its potential due to its ability to deliver cell and tissue constructs to the human body thus providing therapeutic assistance of its innate healing responses. It further comprehends the cellular and molecular differences between regenerating and non-regenerating tissues thus resulting in restoring tissue structure and function in damaged, non-regenerating tissues. Replaced or repaired tissues should be indistinguishable from normal, healthy tissues in structure and function. Cellular therapy is one such strategy wherein various cell types are isolated and used that help in

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understanding their mechanism of action as well as their regenerative properties when they are utilized with different biomaterials as an extracellular matrix. As scaffolds provide targeted cell growth, stem cell delivery through scaffolding technology is another regenerative therapy that is used. The process of electrospinning is used for the generation of scaffolds. Problems like the unavailability of organs for transplantation prevails and thus regenerative medicine therapy has proved to be applicable in such cases. An overview of the regenerative mechanism approaches, strategies as well as its scope and recent evolution in the field of medicine and science has been explored in this paper.

Keywords---Regenerative Medicine, Human Stem Cells, Adipose Stem Cells, Extracellular Matrix, Scaffolding Technology, Electrospinning.

Introduction

Technology used in regenerative medicine entails attaching scaffolding materials to tissues that can regenerate. Cell scaffolds serve as an artificial extracellular matrix that creates a transient environment and aids in the infiltration, binding, multiplication, and differentiation of the cell[1]. Consequently, cell scaffolds are essential to the growth of engineered tissues[2]. The following qualities should be present in an ideal scaffolding material: biocompatibility, an appropriate microstructure, and the desired mechanical strength. Along with these qualities, it must also have a good rate of degradation and support the residence of the cell. Additionally, it must permit the continuation of metabolic processes[3]The current therapy does not seem to imply many of the idiosyncratic and genetic disorders to which regenerative medicine provides a potential panacea. In India, in the year 2020, around 5000 kidneys and 1000 liver and 50 heart donations have been carried out. Heart and lung transplants are in the range of 20 annually at a center in Chennai but the demand is much higher. Only 50,000 cornea transplantations occur whereas the demand is more than 1lakh 45.Around 17 people die each day waiting for organ transplant surgery. There were only 39,000 surgeries conducted in 2020 but the ratio of people in need of organ transplantation is much higher. Thus, regenerative medicine provides hope for the people in need of such complicated surgery.6–8

Regenerative Strategies

A figure describing different therapeutics strategies are listed below in figure 1.

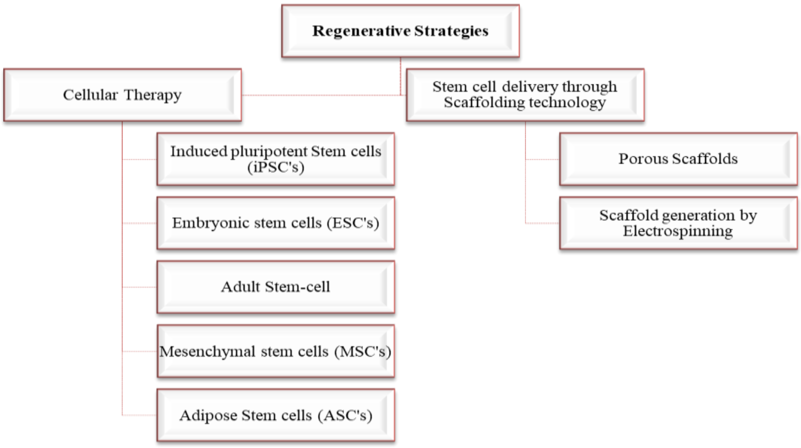

Figure 1. Regenerative Strategies

Cellular Therapy

To comprehend the mechanism underlying the process, cells are extracted from adult tissues and used. This sheds light on how cells proliferate and how their regenerative abilities are affected when combined with organic or synthetic materials or biological materials to form an extracellular matrix. These cells may be allogenic, syngeneic, or autologous. In an autologous procedure, the patient's cells could be taken out and repaired, reprogrammed, or reengineered, then placed back into the patient to study the various immunogenic reactions. No immunosuppressive reactions are seen when using patient-derived cells, but the process is still unconvinced that the cells will proliferate after being reprogrammed and reengineered into the system11. The body accepts the cells from the identical twin with ease, which is one of the benefits of syngeneic stem cell therapy. The donors go through a rigorous screening process to ensure they are free of any diseases or cancer. They consist of an extracellular matrix made of biomaterials that can be either naturally occurring or synthetic in nature, as well as a scaffold that aids in the targeted delivery of cellular components to the site of action.

Induced Pluripotent stem cells (iPSC's)

iPSC's are useful in producing cells that are suitable and acceptable to the patients and thus they can be transplanted to the injured tissue or to treat diseases that cause degeneration of tissues. Theoretically, factors that reprogram the somatic cells and methods which can be conveniently used to introduce these factors in the somatic cells can be used for the generation of iPSC. They help in the proliferation and reprogramming of cells and tissues. Prominent tissues that are related to such therapies with the conventional method are the availability of immune rejection, tissue rejection, and organ rejection.[12] Researchers have found that iPSC's protect the kidney through the induction of an anti-apoptotic, anti-inflammatory response[13]. The advanced version of iPSC's are Extracellular vesicles derived induced pluripotent stem cells (iPSC's- EV). These iPSC's- EV have now been explored in the treatment of kidney disorders. An investigation was conducted to analyze cell death rate, and changes in mitochondrial mass. The iPSC's were generated from fibroblast of a healthy volunteer via skin biopsy. Using the supernatant of iPSC's, the iPSC's- EV were generated and characterized. The cell death analysis and *In-vitro* injury study were performed on Dead Cell Apoptosis Kit using CFlow Plus Software. The extracellular vesicles proved to improve the tissue recovery. They could reduce renal cell death, macrophage infiltration. These cells prevented the damage caused by oxidative stress. Thus, iPSC's- EV have proven to be an alternative and has shown better therapeutic effect.[14]

Embryonic stem cells (ESCs)

ESCs are pluripotent cells derived from the blastocyst's inner cell mass. They are naturally pluripotent, which means they can differentiate into any of the three germ layers that make up an organism—the ectoderm, mesoderm, and endoderm. They must be pre-differentiated before transplantation. If ESCs are to be used in humans, they should be given proper immunosuppressive therapy without being differentiated first, as they can differentiate and proliferate into any type of cell. This may result in the transplanted cells being rejected or unacceptably used for therapy. To avoid rejection and other immunological effects, ESCs should be indistinguishable from the patient's genetics through cloning and the generation of various cell lineages with varying genetic backgrounds. Thus, the cell lineage can be used. One of the many applications of embryonic stem cells in the field of regenerative medicine was the restoration of cardiac activity; for this, PEGylated fibrinogen in the form of a hydrogel scaffold was introduced in an adult rat with heart lesions, i.e., infracted heart; the injection consisted of neonatal rat cardiomyocytes or human ESC. Overall, a 26 percent improvement in cell survival was observed after a 30-day period of analysis by ban echocardiogram. Embryonic stem cells are used in therapies such as cell replacement in diseases such as Diabetes, Alzheimer's, spinal cord injury, Parkinson's, and even myocardial infarction.

Adult Stem-cell

These are stem cells composed of cells that are undifferentiated and can be obtained from adult tissue. These cells have high regeneration ability, and they can differentiate themselves into specialized cells for example nerve cells, muscle tissues, and blood cells and they are multipotent. They can be found in blood, intestine, skin, muscle, brain they are less skeptical and controversial, also if obtained autologously they will be non-immunogenic. Thus, providing an enormous tool for tissue engineering although they have limited proliferation capacity for which various technologies like 3D scaffold, microfluid engineering, or surface technology methods are used. This increases the proliferation capacity to generate the desired quantity of adult stem cells. Researchers have demonstrated the use of adult somatic neural stem cell in brain repair after injury, plasticity to neuronal circuit, and hyperexcitability. Other studies have also been performed on adult stem cells unveiling its effect in the treatment of stroke, cerebral palsy blood disorders, diabetes mellitus. [15]

Mesenchymal stem cells (MSC's)

Mesenchymal stem cells (MSC's) can differentiate into bone cells and cell lineage. This property of MSC's is used strategically in various experiments and tissue engineering approaches. They also display immunosuppressive properties.[12]Thus, MSC's can suppress locally caused inflammation and tissue cell damage in a wide range of auto-immune disorders Rheumatoid arthritis. Among all the sources, bone marrow is one of the most characterized and rich sources of MSC's. These MSC's are isolated from separation of mononuclear cells from red blood cells, platelets via centrifugation. These cultured cells fraction has fibroblastic morphology which then after weeks originated from single MSC. A recent development led to development of MSC's that were derived from exosomes. These exosomes derived MSC's are found to provide physiologic function and were accountable for therapeutic effects of MSC's.[16] Patients suffering from metabolic diseases like hypophosphatasia, which is a rare heritable disease, have also been treated using the allogeneic MSC's therapy[17]. Applications of exosomes derived MSC's have been explored in the treatment of cardiac regeneration, liver fibrosis, acute kidney injury. The mechanism by which they work are autotrophic stimulation, regulation of TGF- β1 signaling pathway. These exosomes showed an increase in wound healing capacity as well. Further research about MSC's derived exosomes and its combination with other biomaterials in tissue engineering can make them a promising approach in the field of regenerative medicine.[16,18,19]

Adipose Stem cells (ASC's)

These cells are capable of differentiating themselves as they are multipotent and have self-renewal ability.3-D scaffolds produced by tissue engineering have an enhanced ability for imitating a microenvironment like the in vivo conditions This aids in the localization, adhesion, proliferation as well as differentiation of Adipose stem cells. Further studies have unfurled that use of tissues and maybe even organs from the ectodermal and mesodermal regions can be used. It is found from recent studies that there are various differentiation pathways of ASCs which are adipogenesis, chondrogenesis, osteogenesis, and other lineages. The ability of ASCs to differentiate into adipocytes is seen on a particular scaffold or when combined with a particular cue. Hence fabrication of an appropriate scaffold plays a very significant role in the differentiation of ASCs. For example, in comparison to alginate alone, the matrix composed of Gelatin-Alginate is better suited for the adipogenesis pathway. There are many sources of ASC in the human body that are localized in subcutaneous adipose tissue. A major advantage is that ASC can be obtained easily and efficiently by using liposuction which involves minimum invasion and obtaining a relatively higher percentage of cells than other stem cell sources. They can be transplanted easily in the body with fewer foreign body reactions. Such a model of rheumatoid arthritis in rats were studied. The allogenic and syngeneic transplantation of mouse or human adipose derived stem cells showed less cartilage damage and decreased antibodies. Another study demonstrated its use in the treatment of coronary disorder, osteoporosis, bone regeneration, Crohn's disease. They are found to be accessible, more flexible approach for the treatment requiring tissue regeneration [20]

Stem cell delivery through Scaffolding technology

Scaffold helps to constrain the cells in a specific area for the growth of cells and it supports the cell structurally. It also helps in the production of matrix and metabolism. Scaffolds used in tissue engineering are supposed to be analogous to the ECM concerning the physical structure and chemical composition [21]. The nanofiber matrix is polymeric and is ECM-mimetic material. It is a non-woven, fibrous nanoscale ECM protein; thus, & can be used for stem cell delivery. A polymeric scaffold in tissue engineering should be bio-compatible [17] Scaffold like 3-Dimensional structure requires nutrition and adequate oxygen supply for the proliferation of cells. Thus, scaffolds need to be provided with an optimum environment for their proliferation. Self-assembly of molecules in the scaffold acts as a backbone for the proliferation of cells and it provides a medium for soluble factor's diffusion which includes fluids and nutrients that help the cells to migrate. Various types of materials can be used for the manufacturing of scaffolds for example metal like titanium forms a titanium scaffold. These scaffolds are compatible biologically and are fit for applications on hard tissues. These applications include bone growth odontoblast-like cells from the differentiation of cells of rat dental pulp progenitor. Covering the scaffolds made up of metal with some bio-compounds increases their efficacy, for example, components of Extracellular matrix are applied as a coat on fibers of titanium scaffold. Scaffolds need an optimum environment for them to proliferate and hence porous scaffolds have proven to be highly applicable.

Porous Scaffolds

Porous scaffolds with high functional properties & are used in tissue engineering. Because of their massive 3D structures, they are used as vehicles for bioactive molecules. They provide a large spatial area for cells to proliferate due to their high porosity. This acts as a temporary skeleton, stimulating and accommodating new growing tissues. Various forms of alginate, such as foams, fibers, rods, spheres, and sponges, can be formulated in the porous scaffold's matrix and used for cell response and cell culture. As a result, it is a promising candidate for use in regenerative medicine.

Porous scaffold generation by 3D Porous Scaffolds

Natural porous scaffolds can be created through printing, freezing/lyophilization, or robocasting. A study was conducted using a natural biopolymer containing silk fibroin and -tricalcium phosphate, as well as strontium, zinc, and manganese, via salt leaching and freeze drying. The scaffolds have interconnected macro and micro porosity with sizes ranging from 500m to 1-10m. Zinc and strontium supplementation improves proliferation and osteogenic potential.[22]

Porous scaffold generation by freeze-drying method

A simple freeze-drying technique is used to easily synthesize porous sponges or porous scaffolds. The biodegradation rate and mechanical properties of the freeze-drying scaffold is adjusted as needed. The pores and the structural arrangement influence the mechanical strength. However, one of the major disadvantages of the freeze-dried scaffold is that the pore diameter is variable and not uniform. Thus, electrospinning, a technique with few drawbacks and high efficacy, used to create these scaffolds.

Scaffold generation by Electrospinning

The evolution of nanofibers has enormous potential for fabricating scaffolds capable of imitating the natural biostructure of human tissue at the nano scale for the delivery of regenerative stem cells. Because biomolecules and nanofibers have the same size range, nanofibers are the preferred scaffolding technology. Currently, three promising techniques for the development of nanofibers are available i.e., self-assembly, electrospinning, and phase separation. The most extensively experimented and documented method for tissue engineering electrospinning is as it provides exuberantly promising results for applications in a variety of fields. Some aspects of electrospinning are discussed below: The electrospinning process is used to structure synthetic scaffolds for implantation. The benefits of this process are the ability of fibers to form structures to create materials suitable for different salutary/therapeutic applications. Recently there has been an increase in the production of nano fibers by use of the technique of electrospinning, proved by patent and publication data. According to a recent publication by Nascimento et al, REF European Patent, until 2013, approximately 1,891 patents and 2,960 patents were filed globally with the expression's "electrospinning" and "nanofibers" in their abstract or title, respectively. This is still primarily academic due to the difficulties of the process involved in large-scale industrialization, as there is a need to standardize production to make it reproducible and scalable, but there is an enormous potential for novel, reasonable therapeutic products.

The general method for producing fibers by ES

A polymer solution is injected at a steady rate and fed through a blunt needle nozzle with a small diameter; the rate at which the polymer flows is controlled and influenced by various parameters. A metal plate is placed beneath the needle setup to collect the fibers produced. A circuit connects the needle and the plate. This circuit is charged to 10-30 kilovolts, which is considered extremely high. The induction of charge on the droplet surface is caused by this voltage. When this charge exceeds the surface tension charge on the liquid or polymer mixture, the charge induced on the liquid causes mutual repulsion, which is opposite to the surface tension. This causes the polymer mixture's hemispherical surface to extend, resulting in the formation of a "Taylor cone." After obtaining the optimal electric field, a jet of solution is ejected from the charged tip of the Taylor cone. Because the jet's trajectory is charged, it can be directed by using an electrical field located at a specific distance from the needle's position. During this process, the solvent from the polymer solution evaporates, resulting in the formation of a dry fiber polymer. This diameter can range from 5 to 0.05 microns. As previously stated, this incredibly small diameter provides high surface area: volume and length: diameter ratios. The increased surface area causes cell-substrate interactions such as attachment, penetration, proliferation, and differentiation. 23

Cell electrospinning

Fibers can be oriented in different alignments to promote cell growth and differentiation. The spatial arrangement (>80-95 percent) of electro spun scaffolds aids in nutrient exchange and marker expression extraction. Scaffolds made from medical-grade polymers without the use of animal products. Scaffolds can be programmed to degrade over a specific time period based on the rate of cell proliferation and differentiation. Co-axial electrospinning, a modified method in ES, can be used to create 3D scaffolds. It entails spinning two components co-axially, namely two concentrical spinnerets aligned to form a core-shell. In coaxial electrospinning, the compound spinner method is used to build core-shell structures. Different capillary channels are used to feed two components, which are integrated with a core-shell composite fiber. These hollow fibers contain polymer, which is used to immobilize the cell components to be delivered. Because they do not come into contact with the tough solvents, this methodology is primarily used for the delivery of fragile components without degrading their composition, such as proteins for cell encapsulation, bacteria, viruses, growth factors, and other similar components. Electrospray is a modification that involves the use of an aerosol created with the help of two charged electrodes. This aerosol is commonly produced between these electrodes. Association of electrospray with electrospinning we can obtain a 3-dimensional structure in which the whole environment is occupied by the cells, this is a result of scaffold fabrication in a different way which is not related to the traditional method.[24,25]

Factors affecting electrospinning

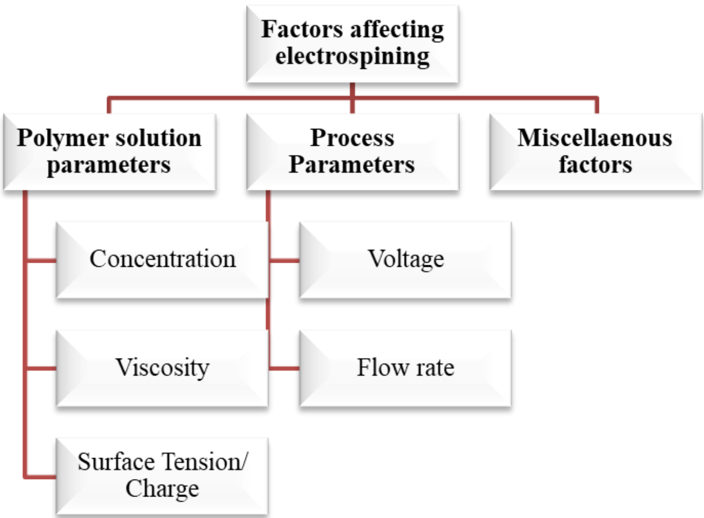

Figure 2. Factors affecting electrospinning

Polymer solution factors

- **Concentration and Viscosity:** Because the polymer solution has low viscosity at low concentrations, the polymer trajectory may be executed in the form of individual droplets rather than fiber. The elasticity of the polymer is affected by its viscosity and concentration, which in turn affects its surface tension. Thus, the polymers can be used in combination, or the concentration can be increased to increase the chain length and viscosity of the nanofibers to achieve the desired properties. It should be noted that if the concentration is not increased to the optimal level, the polymer chains will begin to overlap or cover each other, resulting in the formation of fibers with large diameters and a beaded structure.

- **Surface tension/charge:** The charge on the solution is required to overcome the surface tension of the solution for electro-spinning induction. The surface tension attempts to reduce the surface area per unit mass of a liquid by forming spherical droplets, whereas the electrical charges on the electro-spinning jet attempt to increase the surface area through elongation. While most solvents have low surface tension, solvents with high surface tension make electrospinning difficult because the jet appears to be more likely to form beaded fibers or discrete droplets. Solution conductivity is primarily determined by the polymer type and solvent type. Natural polymers are mostly polyelectrolyte by nature; thus, the ions increase the capacity of carrying charge of the polymer jet, subjecting to increased tension under electric field, thereby leading to poor formation of fiber in contrast to the synthetic counterpart.

Process parameters

- **Voltage**: In electrospinning, high voltage is applied across the spinneret and the collector plate. When the applied voltage reaches a critical value or the optimum value for the polymer used, the solution is ejected from the needle and the desired nanofibers are formed. A change in voltage or the electric field may cause the fibers to disorient. It has been observed by a few groups that an increase in the voltage gives beaded fibers, This happens because the applied voltage is more than that required for the solution to eject or is more than the surface tension, the flow, or the stream of the solution being ejected is disrupted as it cannot maintain its shape and exits like a small drop in the fibers which makes it look like beaded structure.
- **Flow rate:** Increase in the flow rate will cause the polymer to acquire less duration of time to dry before reaching the collector. If the polymer solution does not dry it may form a mass of fibers with a large diameter instead of nanofibers. It may also cause an increase in the pore size of the fibers. An increase in flow rate affects the charge of the polymer solution and may cause an increase in the surface tension thus, causing the applied voltage to not match the surface tension thus beaded fibers will be obtained. The flow rate at times can be as low as 0.1ml/hour -1 ml/hour. An extremely low flow rate may cause electrospinning to not occur efficiently or not occur at all.

Biomaterials for electrospinning

Because they will come into direct contact with the body system of a living organism, biodegradable polymers that are biologically compatible with the tissue are preferred for Tissue Engineering. The polymer selection procedure is determined by the regenerated tissue characteristics as well as the regeneration time. Polyesters, such as polylactic acid (PLA), polyglycolide (PGA), and polycaprolactone (PCL), are used in tissue engineering as synthetic materials (PLGA). To obtain optimal fibers, it is sometimes advantageous to use a material with properties of more than one polymer. In regenerative medicine, polymers such as polysaccharides and proteins are used. This is because these materials are more familiar to the cells. Hyaluronic acid, fibrinogen, natural silk, and other similar materials. This technology is applicable in the health science field, it can be used in the textile industry, optical devices, agriculture catalysis, etc.[26]

Approved drug products for regenerative medicine[27,28]

Table 1
Approved Drug Products for Regenerative Medicine

Sr. No	Cell Type	Product Name	Indication
1	Umbilical Cord Blood Stem Cell Type	Hemacord, Allocord	Disorders of hematopoietic system
2	Somatic Cell Type	GINTUIT	Wounds in the oral soft tissue defects
3	CAR-T-cell	BREYANZI	For adults with relapsed or refractory large B-cell lymphoma
		KYMRIAH	B-cell acute lymphoblastic leukemia

Clinical trials on regenerative medicine

Table 3
Clinical Trials on Regenerative Medicine

Trial Number	Study	Outcome	References
NCT03080571	Interventional; prospective randomized end observer blinded study; test group (stem cell therapy) vs. control group (standard of care)	Symptomatic intracranial hemorrhage	34
ChiCTR2000031494	Treatment of severe COVID-19 with human umbilical cord mesenchymal stem cells	IV infusion of hUC-MSCs, a safe & effective option for COVID-19.	35

Applications

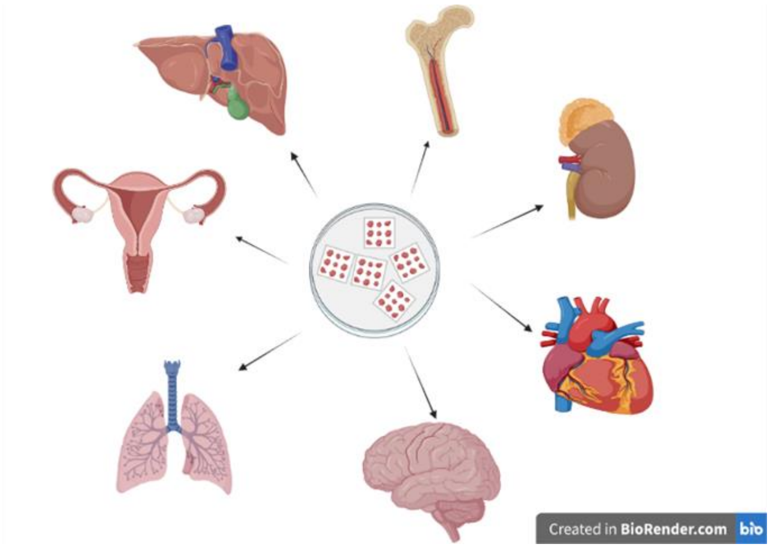

Figure 3. Applications of Regenerative Medicine

Conclusion

With the recent advancements in the field, new technologies have also been developed such as 3D technology, electrospinning, which has not only improved the treatment strategies but has also been helpful in improving the patient compliance thereby their quality of life. Regenerative medicines have the potential to treat hormonal dysfunction, neurodegenerative disorders or any infection of skin, eye with combination of stem cells.

Abbreviations

- Induced pluripotent Stem cells - iPSC's
- Embryonic stem cells -ESC's
- Mesenchymal stem cells - MSC's
- Adipose Stem cells -ASC's
- Extracellular vesicles derived induced pluripotent stem cells -iPSC's- EV

Highlights

- Regenerative Strategies including cell therapy and stem cell delivery via scaffolding technology.
- 3D scaffolds for the treatment of bone disorders.
- Applications of regenerative medicine in the treatment of liver, retinal, tracheal disorders.

Conflict of interest

The authors declare no conflict of interest.

References

1. Aly RM. Current state of stem cell-based therapies: an overview. Stem Cell Investig [Internet]. 2020 May 15 [cited 2021 Aug 11];7:8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7367472/
2. Barreca MM, Cancemi P, Geraci F. Mesenchymal and Induced Pluripotent Stem Cells-Derived Extracellular Vesicles: The New Frontier for Regenerative Medicine? Cells. 2020 May 8;9(5):E1163.
3. Collino F, Lopes JA, Tapparo M, Tortelote GG, Kasai-Brunswick TH, Lopes GMC, et al. Extracellular Vesicles Derived from Induced Pluripotent Stem Cells Promote Renoprotection in Acute Kidney Injury Model. Cells. 2020 Feb 17;9(2):E453.
4. Design Parameters of Tissue-Engineering Scaffolds at the Atomic Scale - Jekhmane - 2019 - Angewandte Chemie International Edition - Wiley Online Library [Internet]. [cited 2021 Jul 23]. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/anie.201907880
5. Engineering of the Embryonic and Adult Stem Cell Niches [Internet]. [cited 2021 Jul 23]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3652509/
6. Golchin A, Farahany TZ. Biological Products: Cellular Therapy and FDA Approved Products. Stem Cell Rev Rep. 2019 Apr;15(2):166–75.
7. Gurusamy N, Alsayari A, Rajasingh S, Rajasingh J. Chapter One - Adult Stem Cells for Regenerative Therapy. In: Teplow DB, editor. Progress in Molecular Biology and Translational Science [Internet]. Academic Press; 2018 [cited 2021 Aug 11]. p. 1–22. Available from: https://www.sciencedirect.com/science/article/pii/S1877117318301121
8. Hsia GSP, Esposito J, da Rocha LA, Ramos SLG, Okamoto OK. Clinical Application of Human Induced Pluripotent Stem Cell-Derived Organoids as an Alternative to Organ Transplantation. Stem Cells Int [Internet]. 2021 Feb 24 [cited 2021 Jul 24];2021:e6632160. Available from: https://www.hindawi.com/journals/sci/2021/6632160/
9. Jani, J. R., Bajamal, A. H., Utomo, S. A., Parenrengi, M. A., Fauzi, A. A., Utomo, B., & Dwihapsari, Y. (2021). Correlation between magnetic resonance imaging (MRI) and dynamic mechanical analysis (DMA) in assessing consistency of brain tumor. International Journal of Health & Medical Sciences, 4(2), 260-266. https://doi.org/10.31295/ijhms.v4n2.1737
10. Jun I, Han H-S, Edwards JR, Jeon H. Electrospun Fibrous Scaffolds for Tissue Engineering: Viewpoints on Architecture and Fabrication. Int J Mol Sci [Internet]. 2018 Mar 6 [cited 2021 Aug 11];19(3):745. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5877606/
11. Knoepfler PP, Ph.D. List of FDA Approved Stem Cell Therapies [Internet]. The Niche. 2021 [cited 2021 Aug 7]. Available from: https://ipscell.com/2021/03/list-of-fda-approved-stem-cell-therapies/
12. Kuo Y-C, Chung C-Y. TATVHL peptide-grafted alginate/poly(γ-glutamic acid) scaffolds with inverted colloidal crystal topology for neuronal differentiation of iPS cells. Biomaterials. 2012 Dec;33(35):8955–66.
13. Lim WF, Inoue-Yokoo T, Tan KS, Lai MI, Sugiyama D. Hematopoietic cell differentiation from embryonic and induced pluripotent stem cells. Stem Cell Res Ther. 2013 Jun 18;4(3):71.

14. Liverani L, Raffel N, Fattahi A, Preis A, Hoffmann I, Boccaccini AR, et al. Electrospun patterned porous scaffolds for the support of ovarian follicles growth: a feasibility study. Sci Rep [Internet]. 2019 Feb 4 [cited 2021 Aug 11];9(1):1150. Available from: https://www.nature.com/articles/s41598-018-37640-1
15. Maqsood M, Kang M, Wu X, Chen J, Teng L, Qiu L. Adult mesenchymal stem cells and their exosomes: Sources, characteristics, and application in regenerative medicine. Life Sci [Internet]. 2020 Sep 1 [cited 2021 Aug 9];256:118002. Available from: https://www.sciencedirect.com/science/article/pii/S0024320520307529
16. Maribel Mata-Miranda M, Jacobo Delgado-Macuil R, Rojas-Lopez M, Martinez-Flores R, Jesus Vazquez-Zapien G. Potential Therapeutic Strategies of Regenerative Medicine for Renal Failure. Curr Stem Cell Res Ther. 2017 Jul 1;12(5):423–31.
17. Miana VV, González EAP. Adipose tissue stem cells in regenerative medicine. ecancermedicalscience [Internet]. 2018 Mar 28 [cited 2021 Aug 8];12:822. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5880231/
18. Miceli V, Bulati M, Iannolo G, Zito G, Gallo A, Conaldi PG. Therapeutic Properties of Mesenchymal Stromal/Stem Cells: The Need of Cell Priming for Cell-Free Therapies in Regenerative Medicine. Int J Mol Sci. 2021 Jan 14;22(2):E763.
19. Organ Donation Statistics | organdonor.gov [Internet]. [cited 2021 Jul 24]. Available from: https://www.organdonor.gov/learn/organ-donation-statistics
20. Pacheco DF, Pinheiro D, Cadeiras M, Menezes R. Characterizing Organ Donation Awareness from Social Media. In 2017.
21. Pina S, Ribeiro VP, Marques CF, Maia FR, Silva TH, Reis RL, et al. Scaffolding Strategies for Tissue Engineering and Regenerative Medicine Applications. Materials [Internet]. 2019 Jan [cited 2021 Aug 16];12(11):1824. Available from: https://www.mdpi.com/1996-1944/12/11/1824
22. Polak DJ. Regenerative medicine. Opportunities and challenges: a brief overview. J R Soc Interface. 2010 Dec 6;7 Suppl 6:S777-781.
23. Politi S, Carotenuto F, Rinaldi A, Di Nardo P, Manzari V, Albertini MC, et al. Smart ECM-Based Electrospun Biomaterials for Skeletal Muscle Regeneration. Nanomaterials [Internet]. 2020 Sep [cited 2021 Aug 11];10(9):1781. Available from: https://www.mdpi.com/2079-4991/10/9/1781
24. Qu H, Fu H, Han Z, Sun Y. Biomaterials for bone tissue engineering scaffolds: a review. RSC Adv [Internet]. 2019 Aug 19 [cited 2021 Jul 23];9(45):26252–62. Available from: https://pubs.rsc.org/en/content/articlelanding/2019/ra/c9ra05214c
25. Sachdeva S. Organ donation in India: Scarcity in abundance. Indian J Public Health [Internet]. 2017 Oct 1 [cited 2021 Jul 23];61(4):299. Available from: https://www.ijph.in/article.asp?issn=0019-557X;year=2017;volume=61;issue=4;spage=299;epage=301;aulast=Sachdeva;type=0
26. Stratton S, Selke NB, Hoshino K, Rudrama S, Kumbar SG. Bioactive polymeric scaffolds for tissue engineering. Bioact Mater [Internet]. 2016 Dec 1 [cited 2021 Jul 23];1(2):93–108. Available from: https://www.sciencedirect.com/science/article/pii/S2452199X16300238

27. Suryasa, I. W., Rodríguez-Gámez, M., & Koldoris, T. (2021). Get vaccinated when it is your turn and follow the local guidelines. *International Journal of Health Sciences*, *5*(3), x-xv. https://doi.org/10.53730/ijhs.v5n3.2938
28. Tan H, Zhou Q, Qi H, Zhu D, Ma X, Xiong D. Heparin interacting protein mediated assembly of nano-fibrous hydrogel scaffolds for guided stem cell differentiation. Macromol Biosci. 2012 May;12(5):621–7.
29. Tsiapalis D, O'Driscoll L. Mesenchymal Stem Cell Derived Extracellular Vesicles for Tissue Engineering and Regenerative Medicine Applications. Cells [Internet]. 2020 Apr [cited 2021 Jul 24];9(4):991. Available from: https://www.mdpi.com/2073-4409/9/4/991
30. World Organ Donation Day 2020: COVID-19 And The Impact Of Organ Donation [Internet]. [cited 2021 Jul 24]. Available from: https://www.netmeds.com/health-library/post/world-organ-donation-day-2020-covid-19-and-the-impact-of-organ-donation
31. Zhou Y, Chyu J, Zumwalt M. Recent Progress of Fabrication of Cell Scaffold by Electrospinning Technique for Articular Cartilage Tissue Engineering. Int J Biomater [Internet]. 2018 Mar 25 [cited 2021 Aug 11];2018:e1953636. Available from: https://www.hindawi.com/journals/ijbm/2018/1953636/
32. 徐太元, S·侯赛因卡恩. Method for preparing exosomes for any clinical use from ipscs and derivatives thereof [Internet]. CN113166724A, 2021 [cited 2021 Aug 11]. Available from: https://patents.google.com/patent/CN113166724A/en?q=regenerative+medicine&after=priority:20210101