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Regenerative Medicine: A Broad Analysis of Innovations and Therapeutic Applications

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Abstract

Regenerative medicine is an interdisciplinary, adventurous aspect which empowers to heal, substitute and regeneration of doomed tissues, cells, and organs by the use of innovative technologies and network of modern therapeutics. Here, a comprehensive overview of basic principles, key technologies and diverse applications of regenerative medicine is presented. As such, this field harnesses the knowledge obtained from stem cell biology, gene therapy, tissue engineering and cellular therapies to design new treatment strategies for numerous diseases. Notably for neuro degenerative disorders, cardiovascular disorders and organ failure. It outlines the regenerative capacity and relevance of pluripotent and induced pluripotent stem cells (PSCs and iPSCs) as well as the specificity and capabilities of the CRISPR-Cas9 gene editing technique for the correction of genetic defects. Moreover, it highlights advances in tissue engineering approaches such as 3D bioprinting and scaffold design that are laying the groundwork toward generating functional tissues and organs. Their therapeutic use from CAR-T cells to exosomes as well as their emerging roles in the fields of regenerative medicine and cancer immunotherapy are also reviewed. The report also spotlights the clinical advances that have been made in addition to challenges that remain for regenerative medicine, including immune rejection, scalability and economic viability for broader use. Ultimately serves as a widely scoped review of the emerging field of regenerative medicine that is certain to be indispensable in the future of patient care, integrating advances in gene therapy, tissue engineering, stem cell research that offer new opportunities for discovering and implementing novel therapies predicated on tissue regeneration.

Keywords: Regenerative Medicine, Stem Cell Therapy, Tissue Engineering, Gene Editing, CAR-T Cell Therapy, 3D Bioprinting

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Introduction

Regenerative Medicine is a new and rapidly developing field of science that is repairing, replacing or rewiring damaged tissues, cells and organs.Gene therapies are changing the landscape of modern therapeutics, offering hope for diseases that had no effective treatments before. The multidisciplinary premise of regenerative medicine relies on advances in stem cell biology, tissue engineering, gene therapy, and biomaterials science. By combining these cutting-edge technologies, engineers can fundamentally change the practice of medicine. In recent years, researchers have accelerated the development of new biomanufacturing techniques and designed technological solutions that support healing by employing the body's own natural repair systems and components. This feat of regrowth, the ability to restore or recreate damaged tissues and organsrepresents a huge advance in the field and a light of hope for many patients with chronic, degenerative, or traumatic diseases (Jones & Lee, 2022; Gupta et al., 2021);(Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). This fast-growing field is a revolution not only in therapeutic approaches but in the conception, development, and delivery of medicine globally(Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Stem cell therapy is one of the main pillars of regenerative medicine. Stem cells, especially pluripotent and induced pluripotent stem cells (iPSCs), can differentiate into a wide range subset of specialized cell types and offer a potential treatment for many medical conditions. Neural tissue regeneration for Parkinson's disease, spinal cord injuries, or other neurological disorders can be accomplished by the use of stem cells and the application of these cells by researchers and clinicians (Zhang et al., 2020; Harris et al., 2021; Park et al., 2021;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024).Similarly, stem cell-derived therapies are being adopted for cardiovascular diseases, using stem cells to regenerate damaged cardiac tissue, thereby improving functional recovery and reducing the likelihood of developing heart failure (Schoen et al., 2020; Lee et al., 2020). Other stem cell therapies are now being studied to rescue the

damaged liver cells, promise cures for patients with chronic liver disease and cirrhosis (Poudel et al., 2021; Kimet al., 2021);(Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). At the same time, tissue engineering has advanced in the direction towards functionally relevant, biocompatible scaffolds to either repair or replace damaged tissue. Researchers have introduced scaffolds composed of synthetic or natural biomaterials that can support cellular growth and transiently replicate morphological and mechanical properties of native tissues (Borselli et al., 2020; Zhang et al., 2021). The proposed scaffolds are the most apparent in the tissue regeneration (Koh et al., 2020; Zhang et al., 2021) along in bone, cartilage and skin. Furthermore, developments in 3D bioprinting have expanded the horizons of tissue engineering and enabled three-dimensional, patient-specific tissue-volume for personalized therapy (Sharma et al., 2023). Moreover, due to its ability to generate in vitro models accurately mimicking human physiology, this technology has tremendously accelerated drug discovery by not only allowing better understanding of pathophysiological mechanisms, but also through new insights of drug'smechanism of actions (Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024).Gene therapy has also come to represent a very powerful weapon in the arsenal of regenerative medicine, and the discovery of CRISPR-Cas9 technology has surely accelerated that revolution. CRISPR-Cas9 generates accurate and precise mutations into the genome which corrects molecular errors driving the pathogenesis of several inherited disorders (Williams et al., 2019; Lee et al., 2020). Moreover, it has already been applied in clinical trials for the treatment of sickle cell anemia, cystic fibrosis, and Duchenne muscular dystrophy through correcting of genetic mutations to return normal functions of those cells (Liu et al., 2020; Zhao et al., 2021). Genetic manipulation and delivery technologies (including gene editing therapies, viral and non−viral vectors) which promote *in vivo* and *in vitro* stem cell differentiation as well as tissue regeneration (Shao et al., 2020; Guo et al., 2021). At the same time, the great burden of chronic and degenerative diseases drives the relevance of regenerative medicine approaches. In 2020, over 60 million people across the globe were afflicted with chronic ailments including organ failure, neurodegenerative disorders, and severe trauma (Smith et al., 2021). Such patients have longstanding, limited recourse to conventional therapeutic modalities that nevertheless often fail to be long-lasting solutions. Regenerative medicine indeed offers such symptomatic relief for these patients but also offers the promise of complete functional recovery, alternative for organ transplantation or cure for previously irreversible conditions (Borselli et al., 2020; Harris et al., 2021). For instance, the ability to regenerate entire organs including liver, kidney, and heart can significantly decrease reliance on organ donors and waiting lists, hence eliminating a part of the major ethical implications of organ transplantation (Poudel et al., 2021; Kim et al., 2021). New technologies such as 3D bioprinting and organ-on-a-chip (OOC)models are taking regenerative medicine into the next phase(Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). These technologies permit building functional tissues/organ models that recreate the intricate physiological environment of the human body. As a result, 3D bioprinting and organonachip system not only help develop personalized treatments by allowing more accurate testing in preclinical studies, but they also increase efficiency in drug discovery processes and decrease dependence on animal testing (Sharma et al., 2023; (Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Besides, organ-on-a-chip models could model the disease progression, thus serving as a more efficient tool than traditional literature approaches for studying pathologies and testing therapeutic interventions in real time (Huang et al., 2021; Zhang et al., 2020). Piecing together the potential of regenerative medicine has its challenges as well. Ethical issues in stem cell origin, including stem cells originating from embryos, persist as a controversial topic among scientists and the broader public (Gupta et al., 2021; Lee et al., 2020). The widespread clinical applications of regenerative therapies are hindered by regulatory challenges, particularly in approving new treatments and monitoring their safety and effectiveness. Moreover, the expensive development and manufacturing costs of

regenerative therapies also pose a barrier to widespread accessibility, especially in low-income areas with fragile health care infrastructure (Harris et al., 2021; Poudel et al., 2021). Overcoming these ethical, regulatory, and economic hurdles is vital to realizing the potential of regenerative medicine and making it available to a worldwide population. Still, regenerative medicine has been moving fast, thanks in part to partnerships between academic scientists, physicians, and companies. With advances in stem cell research, gene editing, and tissue engineering, the possibilities for regenerative medicine and healing have never been greater. Through ongoing advancements and cross-disciplinary efforts, regenerative medicine will reimagine the landscape of medical therapies, holding promise for countless patients around the globe (Jones & Lee, 2022; Gupta et al., 2021; Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024).

Historical Background

Regenerative medicine traces its history to earlier medical treatments that attempted to make repairs or replacements to damaged tissue, like skin grafting and organ transplants. A bridge towards that goal was those early tissue repairgoesback to maintain function of those body organs already. Proven use of grafts would usher in a major milestone in the development of regenerative therapies, facilitating the replacement of lost or compromised tissue. Early "unnatural" organ transplantations used surgical measures to implant those organs into patients and paved the way for organ transplantations as moments in medical history, highlighting the applicability of external manmade interventions to restore function to damaged organs (Jones & Lee, 2022), e.g., kidney and liver transplants. Nevertheless, these approaches faced challenges due to donor availability, rejection problems, and the complexity of the surgical procedures, underscoring the importance of a more sustainable and scalable solution. Tissue regeneration moved forward in a big way mid-20th century upon the discovery of stem cells(Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Hematopoietic stem cells (HSCs), were discovered by scientists in the 1960s, and they are able to generate all blood cell types in the body. This led to a revolution in regenerative medicine, showing that particular cells can self-renew as well as differentiate into specialized tissues (Borselli et al., 2020). This called the attention of scientists towards pluripotent stem cells, which can differentiate into any cell type in the body, so they can be even more effective for stem cell research (Evans & Kaufman, 1981)(Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024) which increased making stem cell research become a hot topic of interest during the 1990s. The discovery of pluripotent stem cells, particularly the isolation of human embryonic stem cells in 1998, is a milestone event in the field of regenerative medicine (Thomson et al., 1998). These breakthroughs laid the foundation for a more precise perspective on tissue regeneration that led the researchers to believe that stem cells could be redirected to mend or replace injured organs and tissues in a well-controlled and streamlined fashion. In the 2000s breakthroughs in stem cell technologies such as induced pluripotent stem cell (iPSC) development opened significant places for regenerative medicine. Human embryonic stem cells are known to have limitations, mainly due to the ethical concerns regarding the embryonic development process, hence the alternative of iPSCs, human adult cells “reprogrammed” to an embryonic-like state (Takahashi & Yamanaka, 2006). The advent of induced-pluripotent stem cells (iPSCs), presented a significantly simpler and more ethically favorable pluripotent cell type for use in regenerative therapies (Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). As such, iPSCs have been very widely studied for their potential therapeutic application in diseases such as Parkinson's disease, heart disease, and many genetic disorders (Kim et al., 2020; Zhao et al., 2021). The past 10 years of gene editing technologies have brought regenerative medicine into uncharted territory. Then CRISPR-Cas9 appeared in 2012, providing scientists a powerful tool to perform genetic modifications at the DNA sequence level (Jinek et al., 2012). This groundbreaking advancement has enabled gene editing as well as a new door for

regenerative medicine to treat genetic disease which we were unable to treat before. Therapeutic CRISPR-Cas9 applications in clinical trials to treat sickle cell anemia, one of the most well-studied applications of this potential, are directly correcting the causal mutation in patients' stem cells (Williams et al., 2019; Lee et al., 2020). CRISPR-based techniques have also been explored for their ability to promote tissue regeneration by promoting stem cell differentiation and enhancing the regenerative capacity of damaged tissues and organs (Gupta et al., 2021; Harris et al., 2021). Gene editing developments are involving regenerative medicine path to target pathologies by correcting gene mutations and enhancing cellular-level tissue repair.Applications of stem cell research combinations with gene editing and tissue engineering have converged the regenerative medicine area into a fast-growing field with great therapeutic potential. The evolution of regenerative medicine has moved from early concepts in transplantation medicine to the subsequent development of stem cell therapies and most recently gene editing technologies. It has the potential to revolutionize disease therapy, providing curative solutions for previously elusive diseases (Jones & Lee, 2022; Gupta et al., 2021; Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024).

Fundamental Technologies and Methods

Stem Cell Therapy

Stem cell therapy is viewed as one of the cornerstone technologies for regenerative medicine. The identification and characterization of pluripotent stem cells (PSCs) was a game-changer in this domain; being capable of differentiating into nearly every cell in the human body, PSCs were thought to hold promise in tissue repair and regeneration in a variety of diseases (Gupta et al., 2021). Some of the most studied forms of stem cells are induced pluripotent stem cells (iPSCs) which are obtained by reprogramming adult somatic cells back to an embryonic-like state. This reprogramming technology is not only an unlimited source of Patient specific stem cells but also an alternative of embryonic stem cells which has a lot of ethical problems (Borselli et al., 2020). These iPSCs have significant potential for applications in disease-specific modeling and possible autologous treatment of neurodegenerative diseases, such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis (ALS) (Zhang et al., 2020; Williams et al., 2020). There has been emerging potential to harness the regenerative capabilities of stem cells in the treatment of spinal cord injury, heart failure, and stroke. Stem cells have the ability to be differentiated into specific cell lineages, researchers are attempting to regenerate or replace damaged tissues, offering optimism for patients with once deemed intractable pathologic states (Harris et al., 2021; Lee et al., 2021). New clinical studies have also explored the usage of stem cell transplantations into the heart muscle following myocardial infarction(Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). These investigations have proposed a successful application in terms of cardiac tissue regeneration and recovery (Huang et al., 2022; Chen et al., 2023). Both these discoveriesfor heart muscle derive either from cardiomyocyte, fibroblast, or even satellite stem cell cells, show the ability stem cell-based therapies to reduce and regenerate heart muscle and ameliorate function after ischemic injury (Borselli et al. 2020; Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). The regenerative potential of bone marrow or adipose-derived stem cells in cartilage or bone have been shown both preclinically and clinically to improve cartilage repair (Yuan et al., 2020; Zhang et al., 2021), providing a potential adjunctive treatment to joint replacements. Neural stem cells are being explored for potential use in spinal cord injuries and other central nervous system disorders, and early research suggests that they could help improve function and quality of life (Harris et al., 2021; Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Stem cell treatment in neurological disorders is one of the most widely discussed fields of interest. Parkinson's disease is a progressive disorder of the movement system resulting from degeneration of dopaminergic neurons in the

brain leading to devastating motor symptoms. In an attempt to ease symptoms and help restore the lost motor function, stem cells, particularly dopaminergic-producing stem cells are maturing to replace the missing neurons. Despite these advances, many critical barriers persist, notably with respect to risk of immune rejection, and engraftment and survival of transplanted cells (Lee et al., 2020; Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Regenerative medicine is essential in spinal cord injuries, which commonly result in paralysis and permanent damage. Bioengineered scaffolds are being utilized to promote cell growth and tissue rebuilding and ongoing studies have demonstrated positive results in pre-clinical studies (Smith et al., 2021; Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Stroke, a leading cause of chronic disability. It is also benefit from regenerative therapeutics. Stem cells and biomaterials are also being explored to facilitate the repair of damaged brain tissues (Zhang et al., 2022; Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Advances in regenerative stem cell therapies are promising for heart failure, which is a condition in which the heart fails to pump blood properly. These therapies are designed to stimulate tissue repair and enhance cardiac function as an alternative to conventional treatments such heart transplantation. Myocardial infarction causes irreversible damage due to scarring or fibrosis in heart tissue and essential aim of regenerative therapies to replace non-functional muscle or scar tissue with healthy contractile cardiac muscle cells and some studies report significant improvements in heart tissue regeneration (Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024).Regenerative therapy is also anticipated to hold promise for vascular diseases such as peripheral artery disease. Scientists have been implementing strategies through blood vessel rehabilitation (tissue engineering) and growth factors to restore adequate blood flow and prevent the need for invasive surgical therapies (Kumar et al. 2022; Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Osteoarthritis is a degenerative joint disease characterized by the degeneration of cartilage and one avenue of research is investigating how arthropods utilize mesenchymal stem cells (MSCs) to repair cartilage and modulate joint inflammation. MSCs have been commonly used in treating bone fractures and the development of engineered scaffolds has fostered rapid healing of fractures and bone formation (Bohm et al., 2023; Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Two stem cell therapies are being developed to repair these injuries; one is aimed at repairing damaged muscle fibers, while the other is designed to promote site-specific myogenesis and therefore enhance the overall effectiveness of muscle regeneration. Regenerative medicine has been explored to address those challenges of patients with Type I diabetes, whose pancreatic tissue in the pancreas is deficient in insulin-producing beta cells. Beta cell replacement from pluripotent stem cells represents a potential mean of replenishing the lost cells and restoring insulin secretion. Regenerative procedures are being made to offer generous pools of islet cells for transplantation, which could serve as chronic treatments for people with Type 1 diabetes. Such a success here could radically change the therapeutic landscape for diabetes decreasing dependence on insulin injections and improving quality of life. In the case of liver cirrhosis, in which liver tissue gets replaced by fibrous scar tissue. who would otherwise need a liver transplant. Stem cells and bioartificial liver devices are being investigated as methods to restore liver function and improve patient outcomes for acute liver failure (Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). kidney diseases like chronic kidney disease (CKD) and acute kidney injury (AKI), regenerative medicine can be useful. *Rejuvenating Damaged Kidneys with Stem Cells:* Stem cells are being investigated to facilitate damaged renal tissues repair, thus improving kidney function and possibly postponing the requirement of dialysis or transplantation. These individual drugs may help in improving the quality of life for these individuals with chronic diseases (Zhao et al., 2021; Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). The topical application of regeneration techniques in dermatology has provided evidence

for accelerated healing of burns and chronic wounds. The development of skin grafts through the use of tissue engineering and stem cells has accelerated healing times and produced less complications from skin grafts. Specifically for chronic wounds, growth factors and cell therapies are being redeployed to enhance tissue repair, offering much-desired alternatives to traditional wound healing practices (Norton et al., 2022; Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Regenerative medicine is also having an impact on cancer treatment. In the past few decades bone marrow (BM) or hematopoietic stem cell (HSC) transplantation has established itself as a standard treatment option for patients suffering from both leukemia and lymphoma, allowing for the replenishment of the immune system and cure of hematological malignancy. Regenerative medicine unlike cytotoxic treatments (chemo, radiation) cannot only be helpful in repair of the injured tissues by the cytotoxic treatments but can potentially regenerate tissues post -cancer treatment as well (Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). In ophthalmology, regenerative medicine could offer hope for treating diseases such as macular degeneration, which leads to vision loss caused by the death of cells in the retina. Patients who are rendered blind by this age-related condition are now being given stem cells to regrow their retinal cells and restore their vision. Considering that visual impairment due to corneal scarring is a significant problem, stem cell therapies to repair corneal damage are also being investigated (Lee et al., 2020; Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Regenerative approaches are increasingly being applied to autoimmune diseases like multiple sclerosis (MS) and rheumatoid arthritis. Both MSCs are now being utilized in rheumatoid arthritis for the regulation of the immune system and joint tissue repair for what it alleviates symptoms and prevents joint tissue damage. In MS, stem cell therapies seek to restore the myelin sheaths destroyed in the neurological system and to modify the immune response, which may help slow disease progression and promote recovery. Regenerative medicines also have applications in treating respiratory illnesses such as chronic obstructive pulmonary disease (COPD) and cystic fibrosis. In COPD, stem cells are explored to isolate an approach for the regeneration of degenerated pulmonary tissue with the hope to postpone or even reverse the spread of the disease (Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). In cystic fibrosis, an inherited disease that leads to debilitating lung degradation, it has been demonstrated that using stem cell therapies significantly improve lung function (Smith et al. 2022; Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Regenerative medicine is currently being used includes hematological disorders such as anemia, thalassemia and sickle-cell disease. The regenerative therapies in anemia promote the development of red blood cells (RBCs) and therefore oxygen-transports throughout the body. Applications of stem cells having been proven useful in treating gastrointestinal diseases like inflammatory bowel disease (IBD) and esophageal and intestinal disorders (Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). In IBD, researchers have identified mesenchymal stem cells as promising agents to reduce inflammation and heal damaged intestinal tissue and they may serve as an effective alternative to more invasive approaches such as surgery (Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Stem cells therapy use is also remarkable in dental and oral health. Regenerative techniques for periodontal disease, where clinical procedures aim to regain lost tissue and bone to prevent tooth loss and recapture overall oral health status are under investigation (Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Another area of research for tooth regeneration is using stem cells to regenerate dental pulp and enamel as this may have the potential to provide an alternative to traditional dental treatments (Lee et al., 2020; Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). In reproductive health, regenerative medicine holds promise for infertility and uterine or endometrial conditions. This is in order to repair or replace ovarian or testicular tissues, with several potential treatments already being investigated, helping patients who

may be concerned about their future fertility(Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Regenerative approaches are also being investigated to regain uterine function in women with uterine diseases (Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024), renewing hope for women who have difficulties with fertility when their reproductive organs are damaged(Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Regenerative medicine has a lot of potentials within diseases with inadequate treatments. Many of these therapies are still in research or even clinical trials but they could clearly change health care (Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Stem cell therapies hold exciting promise in applications, but challenges remain. To prevent rejection of the transplanted organ, immunosuppressive therapies are used, which can increase susceptibility to opportunistic infections and malignancy (Lee et al., 2020; (Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). The production of stem cells at scale is also costly, and it is difficult to maintain their quality and ensure their safety. Overcoming these challenges is crucial for the accessibility and cost-effectiveness of stem cell-based therapies for patients (Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024; Jones & Lee, 2022). Ethical issues for the use of stem cells from certain sources, especially human embryos, are still an area of much debate between people, although the recent discovery of the iPSCs is helping reduce these concerns (Borselli et al., 2020; Zhang et al., 2020). In addition, with the development of stem cell therapies, it is necessary to be careful about the long-term safety, tumor formation ability and gene mutation risk of transplanted cells. *Genomic engineeringtools*: In December 2023, scientists derived human cells from pluripotent stem cells using genome-editing tools like CRISPR-Cas9 which provide valuable control over stem cell differentiation and reduce the potential for adverse effects; however, these tools need extensive vetting before being used clinically (Williams et al., 2019; Amin, 2023). Multidisciplinary collaborations between stem cell biologists, engineers, clinicians, and ethicists will be essential as the field develops to tackle these challenges and help uncover the full therapeutic promise of stem cell-based regenerative medicine (Gupta et al., 2021; Harris et al., 2021; Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024).

Fig: 1 (USFDA Approved Cellular and Gene Therapy Products)

Proper Name	Indications
IdecabtageneVicleucel	Treatment of adult patients with relapsed or refractory multiple myeloma
NadofarageneFiradenovec-vncg	Treatment of adult patients with high-risk Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors.
HPC, Cord Blood	Used in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment.
Lifileucel	Treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.
ObecabtageneAutoleucel	For the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)

ExagamglogeneAutotemcel (exa-cel)	Treatment of sickle cell disease (SCD) in patients 12 years and older with recurrent vaso occlusive crises (VOCs). Indicated for the treatment of patients aged 12 years and older with sickle cell disease (SCD) with recurrent vaso occlusive crises (VOCs) and transfusion-dependent ß-thalassemia (TDT).
DelandistrogeneMoxeparvovec-rokl	For the treatment of Duchenne muscular dystrophy (DMD) in patients who are ambulatory and have a confirmed mutation in the *DMD* gene.
Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen	Indicated for topical (non-submerged) application to a surgically created vascular wound bed in the treatment of mucogingival conditions in adults.
EtranacogeneDezaparvovec-drlb	Indicated for the treatment of adults with Hemophilia B (congenital Factor IX deficiency) who: Currently use Factor IX prophylaxis therapy, or Have current or historical life-threatening hemorrhage, or Have repeated, serious spontaneous bleeding episodes.
TalimogeneLaherparepvec	For the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.
EladocageneExuparvovec-tneq	For the treatment of adult and pediatric patients with aromatic L amino acid decarboxylase (AADC) deficiency.
Tisagenlecleucel	Indicated for the treatment of: Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. Adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma. Limitations of Use: KYMRIAH is not indicated for treatment of patients with primary central nervous system lymphoma. Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).
Donislecel-jujn	In the treatment of adults with Type 1 diabetes who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education.
Azficel-T	Indicated for improvement of the appearance of moderate to severe nasolabial fold wrinkles in adults.

AtidarsageneAutotemcel	Indicated for the treatment of children with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ) or early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD)
VoretigeneNeparvovec-rzyl	For the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy.
LovotibeglogeneAutotemcel (lovo-cel)	Treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events (VOEs).
Autologous Cultured Chondrocytes on Porcine Collagen Membrane	Indicated for the repair of symptomatic, single or multiple full-thickness cartilage defects of the knee with or without bone involvement in adults.
Omidubicel-onlv	For use in adults and pediatric patients 12 years and older with hematologic malignancies who are planned for umbilical cord blood transplantation following myeloablative conditioning to reduce the time to neutrophil recovery and the incidence of infection.
Sipuleucel-T	For the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.
Allogeneic Processed Thymus Tissue–agdc	For immune reconstitution in pediatric patients with congenital athymia.
ValoctocogeneRoxaparvovec-rvox	Indicated for the treatment of adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity <1 IU/dL) without pre-existing antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test.
Remestemcel-L-rknd	Indicated for the treatment of steroid-refractory acute graft versus host disease (SR-aGvHD) in pediatric patients 2 months of age and older.
Acellular Tissue Engineered Vessel-tyod	Indicated for use in adults as a vascular conduit for extremity arterial injury when urgent revascularization is needed to avoid imminent limb loss, and autologous vein graft is not feasible.
ElivaldogeneAutotemcel	Indicated to slow the progression of neurologic dysfunction in boys 4-17 years of age with early, active cerebral adrenoleukodystrophy (CALD). Early, active CALD refers to asymptomatic or mildly symptomatic (neurologic function score, NFS ≤ 1) boys who have gadolinium enhancement on brain magnetic resonance imaging (MRI) and Loes scores of 0.5-9. This indication is approved under accelerated approval based on 24-month Major Functional Disability (MFD)-free survival *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).
Allogeneic Cultured Keratinocytes and Dermal Fibroblasts in Murine Collagen-dsat	To promote durable wound closure & regenerative healing in the treatment of adult patients with debrided thermal burns that contain intact dermal elements, and for which surgical intervention is clinically indicated.

BrexucabtageneAutoleucel	Indicated for the treatment of: Adult patients with relapsed or refractory mantle cell lymphoma (MCL). This indication is approved under accelerated approval based on overall response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. Adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).
AfamitresgeneAutoleucel	Treatment of adults with unresectable or metastatic synovial sarcoma who have received prior chemotherapy, are HLA-A*02:01P, -A*02:02P, -A*02:03P, or -A*02:06P positive and whose tumor expresses the MAGE-A4 antigen as determined by FDA-approved or cleared Companion Diagnostic devices.
BeremageneGeperpavec	For the treatment of wounds in patients 6 months of age and older with dystrophic epidermolysis bullosa with mutation(s) in the *collagen type VII alpha 1 chain (COL7A1)* gene.
AxicabtageneCiloleucel	Indicated for the treatment of: Adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy. Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Limitations of Use: YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma. Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).
AxicabtageneCiloleucel	Indicated for the treatment of: Adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy. Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Limitations of Use: YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma. Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

BetibeglogeneAutotemcel	For treatment of adult and pediatric patients with ß-thalassemia who require regular red blood cell (RBC) transfusions
OnasemnogeneAbeparvovec-xioi	For the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi allelic mutations in the *survival motor neuron 1 (SMN1) gene.*

Table 2: Approved cell therapy products by the US FDA, EU EMEA, and non-third-world countries

Approval	Generic Names	Condition
1997 US FDA approval	Glucosamine sulfate + chondroitin	Articular cartilage damage in the knee
1998 US FDA approval	Living cellular skin substitute	Diabetic foot ulcers and venous leg ulcers
2009 EU EMEA approval	Autologous cultured chondrocytes	Single symptomatic cartilage defects in the knee
2010 US FDA approval	Sipuleucel-T	Asymptomatic or hormone refractory prostate cancer
2010 US FDA approval	Allogeneic cultured keratinocytes and fibroblast in bovine collagen	Asymptomatic or hormone refractory prostate cancer
2011 Korean approval	Autologous bone marrow derived mesenchymal stem cells(BM-MSCs)	Heart repair postmyocardial infarction
2011 US FDA approval	Allogenic cord blood	Disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment
2011 US FDA approval	Azficel-T	Moderate-to-severe nasolabial fold wrinkles in adults
2012 US FDA approval	Allogeneic cultured keratinocytes and fibroblast in bovine collagen	Topical application to a surgically created vascular wound bed in the treatment of mucogingival conditions in adults
2012 US FDA approval	Azficel-T	Moderate-to-severe nasolabial fold wrinkles
2012 Health Canada New Zealand	Remestemcel-L	Graft vs host disease in children who are refractory to steroid therapy post-BMT
2012 Korean approval	Human umbilical cord blood-derived mesen-chymal stem cells (HUCB-MSCs)	Traumatic and degenerative osteoarthritis
2012 Korean approval	Allogenic adipose-derived mesenchymal stem cells (AD-MSCs)	Anal fistula in Crohn's disease
2012 US FDA approval	Hydroxprogesterone caproate	Disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment
2012 US FDA approval	Hematopoietic progenitor cells (HPCs)	Disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment
2013 US FDA approval	Hydroxprogesterone caproate	Disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment

2013 US FDA approval	allogeneic cord blood	Disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment
2015 EU EMEA approval	Ex vivo expanded autologous human corneal epithelial cells containing stem cells	Corneal diseases

Abbreviations: US FDA, US Food and Drug Administration; EU EMEA, EU European Medicines Agency; BMT, blood and marrow transplantation

Tissue Engineering

Tissue engineering is one of the critical technologies in regenerative medicine and has been applied to generate functional tissues by utilizing biomaterials, scaffolds, and cellular components for transplantation and tissue repair. It has the ability totreat tissue loss caused by skin burn, cartilage degeneration, and organ failure (Gupta et al., 2021; Zhang et al., 2020), also many other medical conditions. *Biomaterial:* Biomaterials are necessary components for tissue engineering, as they are utilized to provide structural support and conducive environments for cell growth and differentiation. To create a three-dimensional scaffold, synthetic,natural biomaterials are used to recapitulate the mechanical and biochemical environment of native tissues (Borselli et al., 2020; Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). In the past decade, bioprinting has emerged as an innovative technology for the layer-by-layer deposition of cells, biomaterials and growth factors for the fabrication of three-dimensional (3D) constructs that recapitulate human tissues. It is suggested that this technology could have a major potential in not only regenerating simple tissues such as skin, cartilage, and bone, but also more complex organs like the liver, kidney, and heart (Jones & Lee, 2022; Williams et al., 2020). Using bioprinting, custom-engineered tissue constructs can be produced in accordance with the specific needs of the patient. Vascular structure printing is particularly critical, as once grafted into the organism, blood vessels are required to provide both nutrients and oxygen to the tissue (Sharma et al., 2023; Harris et al., 2021;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024).These complex 3D structures are one of the major challenges in tissue engineering, particularly when it comes to developing functional vascular networks. The vascularization is very important to the life of generated tissue, since tissues without vascularization will cause the death of the cells in the tissues, due to oxygen and nutrient deficiency (Zhang et al., 2021;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Thus, strategies for vascularization through bioprinting or with methods such as the inclusion of endothelial cells to induce blood vessel formation represent a significant focus of research (Gupta et al., 2021; Lee et al., 2020; Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). While it is possible to bio print small blood vessels (Chen et al., 2022;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024), the challenge of scaling this up for larger tissues persists. Besides bioprinting scaffolds designs is also a core field in tissue engineering. Scaffolds can support cells to grow and arrange into the functional tissue by providing a three-dimensional structure. These scaffolds may be created from multiple methods including but not limited to electrospinning, 3D print, and freeze-drying and they are often made from biodegradable material to allow the final engineered tissue to integrate into the body (Borselli et al., 2020;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). These cascade from the design of scaffold materialssuch as hydrogels, decellularized matrices and polymeric materials, which can be engineered to yield the native structure mechanical properties, whilst also

allowing for subsequent cell adhesion, proliferation and differentiation (Jones & Lee, 2022;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). These advancements in cellular sourcing for tissue engineering have also led to novel therapeutic applications. As examples, stem cells, in particular iPSCs and MSCs, have been used as the cellular components of engineered tissues due to their ability to differentiate into various cell lineages and the secretion of factors that promote tissue repair (Gupta et al., 2021; Zhang et al., 2020; Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Immune attack against transplanted cells and tumorigenicity pose additional risks that require evaluation, particularly when utilizing cells obtained from allogeneic sources (Zhang et al., 2020;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Therefore, many researchers have paid much attention on the design and preparation of new smart scaffolds, which have the properties of stimulus-triggered systems sensitively responding to environmental changes, such as pH, temperature, and electric signals. By promoting certain cellular response, the dynamic properties of these smart scaffolds can provide an ideal induction for tissue regeneration (Chen et al., 2021;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). The combination of gene therapy strategies, including the release of growth factors and signaling molecules, with tissue engineering approaches is likely to play a role in enhancing restoration of tissue and their functional integration (Sharma et al., 2023;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024).The relatively, frontier approach to tissue engineering of organ-on-a-chip technologies is designed to *in vitro* replicate human organs and has the potential to disrupt preclinical development in drug discovery and toxicology testing.Those microfluidic devices that are designed to replicate organ-level physiology can also be applied for drug testing, modeling of particular disease and generation of transplantable tissue constructs (Borselli et al., 2020;Amin, Abyaz, et al. 2024; Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Organ-on-a-chip systems can more adequately emulate the physiology of human organs compared to conventional 2D cell cultures, paving the way for improved drug screening and personalized medicine strategies (Gupta et al., 2021;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024).However, for wide-scale clinical applications, one needs to tackle the challenges posed by vascular supply to the engineered tissues, source of cells for tissue constructs and long-term survival of tissues. Thereby, the field has the potential to completely transform the care of many diseases and injuries that were previously considered incurable (Gupta et al., 2021; Sharma et al., 2023; Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024), as the field is constantly being propelled forward by significant developments in materials science, cellular biology and bioengineering.

Gene Therapy

Gene therapy falls under the umbrella of regenerative medicine and is an innovative method of treating, or even preventing, disease, by altering the genetic material within a person's own cells. Gene-editing technologies, notably CRISPR-Cas9, have significantly enhanced the accuracy of genomic modifications, rendering gene therapy more practical and cost-effective for clinical application (Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). CRISPR-Cas9 is also widely regarded to hold great potential for treating genetic diseases, including cystic fibrosis, sickle cell disease and muscular dystrophy, which are caused by deletions or mutations of specific genes (Gupta et al., 2021; Zhang et al., 2020). Gene therapy manipulates a patient’s genetic material to repair, restore or augment damaged function of tissues. One of the more promising approaches is the manipulation of stem cells, which can be genetically engineered outside the body and later put back into the body to develop or regenerate damaged tissues. For instance, investigators were able to cure and treat sickle cell anemia using gene therapy by modifying hematopoietic stem cell genes to remedy the mutation that occurs in

the disease (Williams et as al., 2019). Moreover, gene therapy has been used to repair or replace defective genes in retinal cells, which is promising for treatment against inherited blindness (Lee et al., 2020; Borselli et al., 2020;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Another strategy for gene therapyin vivo editing is the direct introduction of therapeutic genes into the patient's body, most frequently with the use of viral vectors. An example of this vector type is the adenoviral-associated viruses (AAVs) and lentiviruses, both of which can transmit genetic material into a host cell while minimizing immune response (Harris et al., 2021). This method has thus far been successfully applied to treat some genetic diseases, including spinal muscular atrophy (SMA), a serious genetic disease characterized by progressive muscle weakness.On this front, Zolgensma, a gene therapy for SMA, was a big success and was approved for clinical use (Sharma et al., 2023). However, there are still many challenges that need to be overcome before gene therapy can be a widely available treatment option. Including CRISPR/Cas9 systems, are widely used in genetic analysis, agriculture, animal breeding, and plant breeding, triggering enormous expectation in genetically-modified related research and commercial applications; however, public concern about the safety of such technologies has not been eliminated, especially to the off-target effect, unintended genetic alterations that may lead to harmful consequences such as tumorigenesis (Zhang et al., 2021;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Moreover, there are issues regarding the delivery mechanisms, as it is still a major issue to deliver the right toxic or immune-modulatory genetic material upon the target cells without producing an exaggerated immune response (Gupta et al., 2021;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024).In some instances, the effects of gene therapy have diminished over time, requiring further treatments to sustain therapeutic effects (Borselli et al., 2020; Zhang et al., 2020;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Immune responses to viral vectors used for gene delivery and also immune rejection of edited cells themselves are crucial barriers to overcome to achieve durable therapeutic effects. Gene editing has moved beyond CRISPRCas9 to encompass a very large number of other technologies, including base editing and prime editing, which allow more specificity in correcting genetic mutations (Williams et al., 2019). Base editing is a gene editing technology that allows the direct conversion between one DNA base pair to the other, which is a break-free gene editing mechanism so that the base editing can achieve lower error-prone (Harris et al., 2021;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Another promising tool for precise correction of numerous genetic mutations is the “search-and-replace” prime editing technology (Sharma et al., 2023). These emerging technologies could have significant advantages over CRISPR-Cas9 as they improve the precision of gene edits and reduce potential side effects. Gene therapy is also used for gene enhancement, which means to enhance or supplement a healthy cell biological function instead of correcting a mutation. Common treatment and regenerative strategies involve loading genes coding for growth factors or cytokines, to stimulate tissue regeneration in heart failure or neurodegeneration by gene therapy (Lee et al., 2020; Gupta et al., 2021;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Regenerative medicine, it is being studied as a way to stimulate healing and functional restoration in tissues injured by trauma, disease or illness. As more and more therapies are developed, the advantages of gene therapy as a type of personalized medicine are becoming clear.The ability to edit the genome of a patient’s own cells opens a new era of personalized medicine, where treatments can be designed to be as unique as the individual (Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Especially in genetic disease, this personalized method can help bring about better treatment and less side effects. Overall, gene therapy is a technique that can provide an astonishing boost to regenerative medicine, as it allows the treatment or even cure of genetic diseases through genetic modification. Although the technology has demonstrated significant

potential in animal models and preliminary clinical trials, safety, delivery and long-term efficacy concerns must be reconciled (Lal et al., 2022) before they can become more broadly implemented. Moreover, advances in next-generation gene-editing techniques, including base editing and prime editing, could offer new avenues toward the precision and safety of gene therapy interventions (Borselli et al., 2020; Harris et al., 2021;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). As research continues to evolve and more clinical applications emerge, gene therapy will make up a significant part of regenerative medicine and a revolutionary method of treating numerous genetic and degenerative diseases (Gupta et al., 2021; Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024).

Cellular Therapies

Cellular therapies are one of the most promising areas of regenerative medicine, especially with respect to cancer treatment, and perhaps the most prominent example from this area is Chimeric Antigen Receptor T (CAR-T) cell therapies. CAR-T cell therapies entail genetically altering a patient's own T cells to express a receptor that recognizes specific proteins found on the surface of cancer cells. This alteration allows the T cells to better recognize and kill the cancer cells than they would naturally (Jones and Lee, 2022). CAR-T therapy has emerged as a powerful tool in destroying cancer cells similar to how the body's own immune system operates (Borselli et al., 2020; Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024), with unprecedented efficacy in hematologic cancers, especially in acute lymphoblastic leukemia and non-Hodgkin lymphoma. This class of drugs was pioneered by the first FDA-approved CAR-T therapies, like Kymriah (tisagenlecleucel), Yescarta (axicabtageneciloleucel), which provided a novel approach to cancers, enabling extended remission in patients previously unresponsive to conventional therapies (Gupta et al., 2021). While blood cancers have successfully implemented CAR-T cell therapies, solid tumor applications are still an area of study. *Tumors*:solid tumors complications include the tumor micro environment, a potentially suppressive environment for immune cell activity that may affect the efficacy of a malaria therapy and, Maximal-IFN-α CAR-T (Borselli et al., 2020; Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Another challenge for the ability to target the entire tumor is tumor heterogeneity, where different cancer cells within the same tumor may express different antigens, making it difficult for CAR-T cells to recognize and kill all cancer cells (Gupta et al., 2021;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). In addition, researchers are focusing on better strategies for CAR-T cell therapy, such as trying to change CAR-T cells to prevent being affected by the inhibitory effect caused by the tumor microenvironment, and designing therapeutic proteins bispecific CAR-T cells that attack multiple antigens (Jones & Lee, 2022;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). In addition to cancer treatment, CAR-T and other cellular therapies are being explored in the realm of regenerative medicine. Another area of real promise is modified T cells for autoimmune disease. In diseases like rheumatoid arthritis and multiple sclerosis, the immune system mistakenly attacks the body's own tissues. Researchers develop these CAR and TCR based therapies for autoimmune disorders through reprogramming T cells to selectively attack and inactivate the immune response driving cells while avoiding killing other normal immune cells; ultimately reestablishing normal immune engagement without the risk of further damage (Borselli et al., 2020; Gupta et al., 2021). Such an approach could potentially provide a long-term cure for autoimmune disease without immunosuppression and the associated side effects. Outside of autoimmune diseases, cellular therapies are being researched for a potential role in regeneration of tissues. One intriguing option are mesenchymal stem cells (MSCs) with the ability to differentiate into multiple cell types, including bone, cartilage and adipocytes, that support tissue healing (Borselli et al., 2020;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Osteoarthritis, spinal cord injury, and heart failure are some of the conditions spoken

about so far with the need for tissue regeneration to restore function and MSCs have been explored for this (Gupta et al., 2021). MSCs are known to secrete growth factors that help in healing and recovering tissues and have been tested in clinical trials to increase regenerative potential of damaged tissues. Another potential application of gene-editing approaches is in stem cell-based regenerative medicine. Genetic modification is able to enhance the regenerative capacity of stem cells and assist them to be nearer to realizing the wished tissue restore processes. Scientists have for example, been using gene editing to engineer iPSCs to enhance their efficiency in differentiating into certain cell types, such as neurons for treatments of Parkinson's disease or cardiomyocytes for regenerating cardiac tissue (Gupta et al., 2021;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). The thinking behind this approach is that if future treatments were created from the patient's own tissue, they would be more personalized and effective while also reducing the risk of immune rejection.Though cellular therapies had great potential, numerous obstacles still need to be overcome for the widespread application of cellular therapies for regenerative medicine. One of the greatest challenges facing cell-based therapies is scalability. One of the biggest challenges to the use of stem cells therapeutically, particularly for diseases that damage tissue that is more substantial in scale, is the ability to generate sufficient numbers of functional cells (Jones & Lee, 2022;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Moreover, safety is of utmost concern for these therapies. This type of therapy, however, may not be without risks, as unanticipated biological consequences of genetic alteration may occur, amongst other things, and be able to provoke an immune activation with activation of T cells and possibly cytokine storms where excessive immune reaction triggers extensive inflammation and damage to organs (Gupta et al., 2021). Longer term follow-up is required to assess the longevity of cellular therapies and the potential for negative events such as tumorigenesis or immune dysregulation (Borselli et al., 2020;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024).*Cellular therapies at the cutting edge:* CAR-T cell therapies and stem cell-based therapies for treatment of cancer and regenerative medicine while CAR-T has performed wonders for blood cancers, it is still being actively researched for solid tumors and autoimmune diseases. Due to its potential for tissue regeneration mediated through these stem cells (especially MSCs) and gene-edited iPSCs, it is considered as a potential therapy. Nevertheless, several challenges associated with scalability, safety and long-term efficacy remain before these therapies will be applied in standard clinical practice. If cellular therapeutic approaches continue to be developed, and strategies to resolve potential complications (Borselli et al., 2020; Gupta et al., 2021; Jones & Lee, 2022; Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024) are implemented, these therapies could represent success for regenerative medicine.

Extracellular Vesicles and Exosomes

One of the most extensively studied classes of Extracellular Vesicles and Exosomes(EVs)is exosome, vesicles range from 30–150 nm in diameter that are released from diverse cell types within the extracellular space, which may play a key role in cell-to-cell communication and tissue regeneration. As a result, these vesicles are packed with a range of bioactive agents including proteins, lipids, RNA (mRNA and non-coding RNAs) and DNA that can directly influence an array of cellular processes, modify immune responses and drive tissue regeneration (Harris et al., 2021). Exosomes play a role in intercellular communication by transferring their contents to near or distant cells and affecting critical cellular functions including proliferation, differentiation, apoptosis, and immune response (Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). A more recent technology garnering a prospect in regenerative medicine is exosome therapy wherein exosomes are now actively being investigated for use in drug delivery, tissue repair, or immune modulation. Moreover, exosomes can be used in treatment strategies as they contain bioactive molecules and they could be a targeted delivery system for drugs, since the

therapeutic compound can be delivered to the tissue or cell of interest. Their unique nature of transcending biological barriers in the body, most notably the blood-brain barrier (BBB), they become one of the potential alternatives for conventional drug delivery systems for disorders such as cancer and neurodegenerative diseases (Gupta et al., 2021; (Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). The exosomes with therapeutic agents, such as small molecules, nucleic acids or proteins, researchers are exploring the possibility that exosomes can effectively transport the aforementioned agents to specific tissues of the body or even alter the genetic material of certain cells in a targeted manner (Borselli et al., 2020;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). In addition, exosomes have been shown to have an ability to modulate immune responses, which makes them a promising therapeutic target in the case of various immune dysregulatory diseases like autoimmune diseases or chronic inflammation. Just like that, mesenchymal stem cell (MSC)exosomes have shown anti-inflammatory properties and can thus be applied against immune action or can be used for regeneration of tissue with no risk of immune rejection as in whole cell therapies (Gupta et al., 2021). Further, exosomes are known to shuttle signaling molecules and promote the survival and proliferation of regenerative cells within affected tissues (Harris et al., 2021;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Stem cell exosome, showing that they could aid in the promotion of tissue repair boosting cell migration, collagen deposition and angiogenesis in the healing processes of wounds (Borselli et al., 2020). Exosomesare known to enhance myocardial repair following heart attacks by promoting the survival of cardiomyocytes, reducing the inflammatory response as well as neovascularizing the damaged site (Gupta et al., 2021;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Exosomes have been shown to contribute to neural tissue reparation. The studies that have tested the effectiveness of exosomes on neuroprotection, they have proven to enhance the effects of the NSC-derived exosomes on neural injury, exosomes are very effective, especially in reducing neuroinflammation and neuroprotection and also in promoting these healing are the most remit treatment methods to neural disease of one of the new high-tech (Harris et al., 2021;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024).especially on Parkinson's,Alzheimer's disease (AD), spinal cord injury and neural disease treatment has been to become one of the new effective strategies. Currently, numerous exosome-based therapies are under clinical trial investigation for different diseases. Exosomes from MSC are studied to enhance diabetic ulcers, chronic wounds and myocardial infarction. These trials aim to assess exosomesa potential new class of regenerative medicinefor safety, efficacy and promise (Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Still, some challenges continue to exist such as the incorporation of standardized protocols for the isolation, characterization, and large-scale production of exosomes, and the determinants of specific biomarkers to monitor and trace their therapeutic actions (Gupta et al., 2021; Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). In addition to their therapeutic potential, exosomes are also being explored as diagnostic biomarkers. Exosomes are used to deliver various types of molecular payload from their parent cell, thus making their content a reflection of the physiological state of their loading cell. Thus, exosomes have also been proposed as biomarkers for diverse diseases, including cancer, neurodegenerative diseases and cardiovascular pathology. Contents extracted from exosomes can be efficient biomarkers for early diagnosis, treatment response evaluation and outcome prediction (Harris et al., 2021;Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024). Exosomes are a powerful factor in regenerative medicine because of their participation in cell signaling, immune regulation and tissue repair. Clinical trials are currently investigating their potential uses in drug delivery, wound healing, myocardial repair and neural tissue regeneration. Although this is undoubtedly exciting, exosome-based therapies must be carefully scrutinized regarding their scalability, standardizationand safety. It is clear that

continued investigation into the underlining mechanisms regulating exosome function and their future uses as regenerative therapies will lead to groundbreaking innovations(Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024; Borselli et al., 2020; Gupta et al., 2021; Harris et al., 2021).

Conclusion

Regenerative medicine is a promising breakthrough in treating a wide range of diseases and injuries. The field envisions creating ways to re-generate, restore or replace impaired or missing tissues and organs, which together with stem cell therapy, gene editing, tissue design, engineering and cellular therapies give regenerative medicine the potential to cure diseases once deemed impossible to treat. Clearly, these emerging humanities promises to be capable of managing acute injuries such as burns and fractures, as well as chronic diseases such as neurodegenerative diseases (Parkinson's and Alzheimer's diseases), cardiovascular diseases and autoimmune diseases a miracle indeed of not merely surviving but recovering, with re-acquired functions. As one of the many exciting technologies, stem cell-based therapies represent a leading paradigm due to their potential to regenerate damaged tissues and organs. Stem cell therapies are leading the charge, with potential indications in neuroscience with Parkinson's disease and spinal cord injuries, as well as heart failure, stroke and other cardiovascular diseases. These therapies focus on generating new tissues and restoring lost function to lessen the need for invasive surgeries such as transplants. Further, regenerative methods are reported to have shown potential for diseases including but not limited to osteoarthritis, bone fractures, bone formation,Type 1 diabetes, liver cirrhosisand renal scale as well as organ regeneration and tissue repair. In other areas, such as post-care and recovery from cancer, treatment of autoimmune diseases, gastrointestinal disease, peripheral artery disease, hematological disorders, dental and oral health, healing of burns and chronic wounds,respiratory disease and reproductive health, these therapies may provide options that are safer and more effective than traditional therapies. Though many therapies remain in the research or clinical trial stages, their ability to change the face of healthcare is no less compelling, offering integrative solutions for chronic and degenerative conditions. Embryonic stem cell line division creates pluripotent stem cells (PSCs) and eventually differentiate into most human cell types, thus paving the way for remarkable organ regeneration potential. Pairing with targeted genome editors like CRISPR-Cas9, these breakthroughs are giving scientists the power to repair the gene mutations that cause hereditary disease,the eventual tantalizing prospect of curing sickle cell disease and cystic fibrosis. Tissue Engineering is afuture for 3D Bioprinting, human bioengineering organs and match them with patients. Bioengineering material development, tissue engineering and bioprinting is a field with great potential, we are creating functional tissues and organs that can be used in humans. which may someday lead to bioengineered organs that match our patients and compensate for organ donors. CAR-T cell therapies are evolving based on strong results in treating blood cancers (like leukemia and lymphoma). This breakthrough enables us to genetically modify the patient's own immune cells so they will target and destroy cancerous cells;these therapies can be deployed to treat solid tumors and other diseases. While CAR-T therapy was started for several types of cancer, other areas such as immune-mediated diseases and even regenerative of the tissues is under research on CAR-T therapy (Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024; Gupta et al., 2021; Jones & Lee, 2022), which is a strongpoint to regenerative medicine. Regenerative medicine shows great promise, but there are numerous important hurdles that need to be addressed before these technologies can achieve widespread adoption in the clinic. However, the cross-reactivity of iPSCs with the immune system is one of the challenges that must be overcome to realize applications of iPSC in therapy and it is hit in stem cell therapy that has been requiring precision in terms of immune response management and safety profile. Furthermore, while greater numbers of stem cells can be relatively challenging to produce and deliverthe production with delivery costs are

additionally high, making widespread use as a challenge (especially in resource-limited settings). In addition, reconstructing the complexity of human tissues poses challenges for tissue engineering, particularly the generation of vascularized tissues, such as those containing functional vasculature and nuanced cellular interactivity. If regenerative medicine is ever going to attain its potential in the clinical setting, these challenges need to be addressed and overcome. In addition, the long-term safety and effectiveness of gene editing and stem cell therapies are under investigation, with clinical trials being conducted to assess the effects and risks of these instruments over the long term (Harris et al., 2021). In spite of all the challenges, regenerative medicine is becoming more and more appealing. Ultimately, observed advances and uses of partition, flourishing innovations are positioning the field of medication for a transformative shift towards more precise analytic devices and focused on intercessions for distinct patients. Advanced biomaterials are used to provide scaffolding for tissue repair, and our growing ability to tailor therapy to a person's genetic makeup will enhance the effectiveness of treatment. These advances could reduce the demand for organ transplants and successful treatments for a range of medical conditions. Future healthcare ecosystem whose passions include personalized approaches using regenerative therapies, which would permit physicians to capitalize on the body's regenerative potential to heal not only injuries but also the etiologies of chronic diseases and beyond (Amin, Abyaz, et al. 2024;Amin, Chowdhury, et al. 2024; Al Amin et al., 2024; Gupta et al., 2021; Jones & Lee, 2022).

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