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Gene And Cell Therapy In Regenerative Medicine

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Abstract

Regenerative medicine is a novel multidisciplinary approach that is quickly evolving and aims to repair, replace, and regenerate damaged organs and tissues. It has progressed over the last few decades from simple tissue engineering principles to complicated therapeutic approaches that mix gene and cell-based products. This advancement is critical to the function of gene and cell treatments, which enable fine-tuning of cellular activity, improved tissue re-modeling, and the correction of genetic abnormalities that underlie many illnesses. New improvements in gene delivery technologies have significantly improved therapeutic efficacy and safety. Adenoviral, adeno-associated viral, and lentiviral systems are thought to be particularly effective in transfection, although non-viral carriers, such as lipid nanoparticles and polymers, are safer and more flexible. Embryonic stem cell-based, induced pluripotent stem cell-based, and mesenchymal stem cell-based stem cell technologies have all demonstrated exceptional regeneration capabilities. Furthermore, the introduction of genome editing devices such as CRISPR-Cas9 has resulted in great precision in gene editing, allowing for tailored and focused treatment. The study focuses on key advances in gene and cell therapy in the field of regenerative medicine, including clinical applications and technological achievements. Despite the constraints of delivery efficiency, safety, and cost, continuing research continues to push the development of increasingly efficient, scalable, and accessible regenerative treatments.

Keywords: Cell therapy**;** Gene therapy**;** Regenerative medicine**;** Non-viral delivery systems**;** Tissue engineering.

1. Introduction

Regenerative medicine is a fast evolving science aimed at restoring, replacing or regenerating damaged organs and tissues to perform normal physiological functions [1]. It is a multidisciplinary methodology that combines biological, medical, and engineering to come up with novel therapeutic measures. “Regenerative medicine seeks to correct the causes of disease rather than just alleviating the symptoms as is the case with conventional treatments. Its spectrum is between arousing natural healing processes in the body to the creation of bioengineered tissues and functional organ replacements [2].

The history of regenerative medicine is inextricably linked to the advancements of gene therapy and cell-based therapeutics. Gene therapy was created as an experimental treatment for genetic abnormalities by inserting functioning genes into target cells. The use of viral vectors for effective gene delivery was an early method that yielded considerable results in the treatment of hereditary disorders [3]. Gene transfer has become more safe and efficient as molecular biology and vector design have advanced. At the same time, cell therapy is no longer a simple transplantation operation like bone marrow transplantation, but has evolved to more complicated applications using stem cells that can be differentiated into many types of tissues. These simultaneous developments have established the groundwork for modern regenerative techniques [4].

The growing need in more sophisticated therapeutic approaches has also contributed to the development of this area. The traditional therapies are usually unable to offer any long-term remedies to chronic, degenerative, and genetic diseases due to the fact that they cannot offer complete healing and cannot bring back full functionality. Regenerative medicine overcomes these drawbacks by enhancing long-term tissue remedies and functional restoration. It does not involve frequent administration of drugs or synthetic replacements, but the regeneration of living tissues, which become a part of the host system [5]. One of the characteristics of regenerative medicine is the combination of cell-based treatment with gene therapy. Gene therapy is the direct or indirect insertion of genetic material into the body (in vivo) or in genetically engineered cells (ex vivo) and cell therapy is the use of living cells to repair tissues [6]. Their combination allows the use of advanced strategies like engineered stem cells that contribute to a better regeneration and therapeutic outcome. This review will set the objective of offering a summary of regenerative medicine focusing on gene and cell therapies, recent developments, uses and prospective advances in this potential therapy.

2. Gene Therapy Systems

Gene therapies are one of the foundations of current regenerative medicine, which provides the possibility to introduce therapeutic genetic material into the target cells to cure or alter the pathogenesis [7].

These systems can be generally divided into viral and non-viral systems, but viral vectors are the most efficient and the most studied ones because they have a natural capacity to infect host cells. Selection of the gene delivery system is based on various aspects, such as type of disease, target tissue, length of gene expression and safety. Among them, viral gene therapy-based systems have shown impressive success both

in preclinical and clinical applications, yet safety, immunogenicity and scalability issues continue to be a challenge [8].

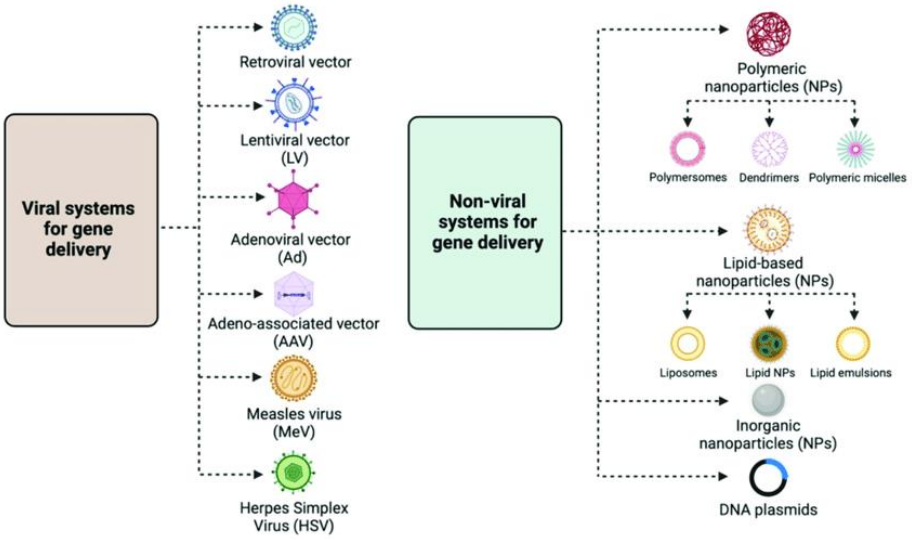

Figure 1: Gene Therapy Systems

2.1 Viral Gene Therapy-Based Systems

Viral vectors are very effective vectors used in the transfer of genes since they use the natural capacity of the viruses to get inside the cells and transfer the genetic material. These vectors can be delivered either topically or systemically and they are therefore flexible to a variety of therapeutic uses. Nevertheless, viral vectors have various limitations despite their high transfection efficiency that limits the use of viral vectors in clinical applications [9]. The fact that they may cause immune and inflammatory reactions and result in either toxicity or decreased therapeutic efficacy is one of the key issues. Also, there is a theoretical risk of recombination events which may produce replication competent and potentially pathogenic viruses. Limits such as limited capacity of carrying DNA, difficulties in mass production, and possibilities of insertional mutagenesis or carcinogenesis are other limitations [10].

In spite of these disadvantages, viral gene therapy has made major milestones, such as clinical approvals on diseases like melanoma, head and neck cancers, and lipoprotein lipase deficiency. Adenoviruses, adeno-associated viruses (AAV), retroviruses, and lentiviruses are among the most often used viral vectors. These systems vary in terms of their structure, gene delivery mechanism and application in particular therapeutic situations. Overall, viral vectors are highly efficient and have favorable gene expression profile but the current research is directed at improving its safety profile and overcoming the biological barriers [11].

2.2 Non-Viral Gene Delivery Systems

In gene therapy, non-viral gene delivery technologies have emerged as a safer and more versatile alternative to viral vectors. Such techniques involve the synthetical or physical injection of genetic material into target cells without the requirement for viral components. Routine alternatives to the virus involve liposomes, nanoparticles, vectors made of polymer, and physical methods like electroporation. Non-viral systems are becoming more and more attractive in the fields of regenerative medicine and therapeutics due to their low immunogenicity, simplicity of manufacturing, and ability to transport larger genetic payloads [12].

One of the earliest and most commonly used non-viral carriers is the liposomes. They are vesicles made of lipids and contain DNA or RNA and are then incorporated by the cells through membrane fusion or endocytosis. Gene transfection in vitro has been extensively used and commercial transfection preparations such as Lipofectin are used. Similarly, nanoparticles, particularly those that are based on either the calcium phosphate or the polymeric materials enable the formation of stable DNA complexes which can be conveyed to the cells. Polymers, e.g. polycationic vectors, are also based on the electrostatic forces between positively charged polymers and negatively charged nucleic acids to produce complexes called polyplexes. These systems can also be further engineered with biodegradable materials, which are polysaccharide-derived polycations, so that they have high biocompatibility and transfection efficiency. Physical techniques such as electroporation briefly destabilize the cell membrane with electrical pulses, permitting genetic material to directly enter the cytoplasm [13].

Although they have their benefits, non-viral systems have a number of delivery challenges. Their transfection efficiency is relatively low when compared to viral vectors, one of the significant limitations. Moreover, genetic material is prone to be degraded by extracellular nucleases, decreasing the effectiveness of treatment. Nucleic acids are encapsulated in nano-carriers to ensure their protection and extend their circulation [14]. Nevertheless, it is still challenging to attain targeted delivery because there is non-specific interaction with serum proteins and non-target cells. Other barriers include poor cellular uptake, limited endosomal escape and body clearance. To avoid these, approaches such as surface modification with polyethylene glycol (PEG) and receptor-mediated targeting are being studied. Also, intracellular delivery of large and negatively charged molecules like mRNA requires advanced carrier systems to stabilize, avoid immunogenicity and enhance intracellular delivery [15].

Non-viral gene delivery systems have a better safety profile when compared to viral systems as they lack the risks of viral infection, insertional mutagenesis and immune responses. They are also less expensive, simple to produce, and can accommodate bigger genes. However, their reduced efficiency and failure to provide long-term gene expression better hamper their clinical translation in an efficient manner. Viral vectors on the other hand have a high transfection efficiency and long-term expression and are associated with safety concerns and heightened complexity in production [16].

Overall, non-viral delivery systems of genes are a potentially exciting and rapidly evolving area of gene therapy. The biomaterials, nanotechnology, and targeted delivery methods will be further developed and will improve their efficacy and be used in the clinical practice more extensively.

Gene therapy has undergone a revolution because to the use of genome editing technologies, which enable precise and targeted changes to the genetic composition of live cells. Among the finest are CRISPR-Cas9, TALENs (Transcription Activator-Like Effector Nucleases), and ZFNs (Zinc Finger Nucleases). The technology is facilitated by the formation of site-specific double-stranded breaks within the DNA that are repaired by cellular processes permitting the insertion, deletion or repair of genetic sequences.

Regardless of their potential, genome editing technologies are highly problematic in terms of ethical and safety concerns. The unintended genetic changes (off-target effects) continue to be a serious issue and can

cause adverse results. Moreover, the ethical aspects of germline editing, a potential risk that can be passed on to the next generation have attracted controversy around the world. Problems of equitable access, technological exploitation and safety in the future need to be taken into account as well. Genome editing is therefore, a potential that is truly massive but the application of this technology in clinical practice must be highly controlled and responsibly put to use [17].

Table 1: Comparison Between Viral and Non-Viral Gene Delivery Systems

Feature	Viral-Mediated Systems	Non-Viral Systems
Transfection Efficiency	High	Low to moderate
Safety Profile	Risk of immunogenicity and toxicity	Low toxicity, minimal immune response
Gene Size Capacity	Limited	No significant limitation
Risk of Infection	Present	Absent
Cost and Production	Expensive, complex	Cost-effective, easy to prepare
Stability	Moderate	High
Target Specificity	Often tissue-specific	Broad, but less targeted
Clinical Application	Widely used, several approvals	Emerging, under development

2.3 Genome Editing Technologies

Gene therapy has undergone a revolution because to genome editing technologies, which allow precise and exact altering of living cells' genetic structure. CRISPR-Cas9, ZFNs (Zinc Finger Nucleases), and TALENs (Transcription Activator-Like Effector Nucleases) are a few of the most notable. These technologies work based on formation of site-specific double-stranded breaks within the DNA which are subsequently mended by cellular pathways enabling the insertion, deletion or repair of genetic sequences [18].

CRISPR-Cas9 is the most common system of genome editing because it is simple, efficient and versatile. It employs a guide RNA to target the Cas9 enzyme to a given sequence in DNA, allowing very precise gene editing. ZFNs and TALENs, in contrast, were based on protein-DNA interactions engineered to bind specific sites in the genome, and are more complex to design, but are also very specific. Although ZFNs were some of the first tools created, TALENs enhanced the flexibility of targeting and CRISPR-Cas9 has made the process even easier, making genome editing more accessible to research and treatment [19].

They are important technologies in precision medicine, whereby treatment is customized to the genetic profile of the person. Genome editing can be used to repair disease-causing mutations, create patient-specific therapies, and drive forward other areas, including cancer therapy, genetic diseases, and regenerative medicine. As an example, defective genes can be fixed in the edited cells and used to repair normal cell functions or targeted cancer treatment using engineered immune cells [20].

Regardless of their potential, genome editing technologies are ethically and safety problematic. The unintended genetic changes (off-target effects) continue to be a serious issue and can cause adverse results. In addition, ethical considerations of the germline editing, which could be passed on to the subsequent generation are controversial issues that have been viewed globally. Concerns of equitable access, technological maltreatment and eventual security should be likewise taken into consideration. Thus, the possibilities of this genome editing are enormous; however, the use of such technology on the clinical level has to be strictly regulated, and they must be used responsibly [21].

3. Regenerative Medicine Based on Gene Therapy

Gene therapy regenerative medicine is a rapidly growing interdisciplinary field of research that seeks to repair or replace aging, injured or diseased tissues, organs and cells. It is a combination of various techniques such as stem cell therapy, tissue engineering and targeted gene delivery to re-establish normal biological activity. They can be in vitro, ex vivo and in vivo whereby stem cells, differentiated cells or genetically engineered cells can be used as sole agents or in combination with biomaterials and therapeutic agents to stimulate tissue repair and remodeling of the host environment [22].

One of the key questions of the field is stem cell-based gene therapy and it involves different types of stem cells including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs) and mesenchymal stem cells (MSCs). They are genetically modified to improve the regenerative ability of these cells by improving their survival, proliferation, differentiation and secretion of therapeutic factors. This enables tissues to be repaired more effectively and focused [23].

Also, through gene therapy and tissue engineering, scaffold based systems have now been developed that support cell growth and also deliver genes that encode growth factors and cytokines. Such systems facilitate controlled and concentrated expression of genes which augments angiogenesis, tissue remodeling and organ repair. These combinational strategies are especially useful to recapitulate complex tissues and enhance functional outcomes [24].

Gene therapy-based regenerative medicine has clinical relevance in a broad spectrum of applications such as in neurology, cardiovascular, musculoskeletal repair, and wound healing. Within the last 20 years, some major advances have seen the acceptance of numerous biologics, biopharmaceuticals, and cell-based medical devices, which point to the translational promise of these technologies. All in all, the interplay between regenerative medicine and gene therapy is rapidly progressing to offer new therapeutic approaches, which can provide hopeful solutions to heretofore incurable diseases [25].

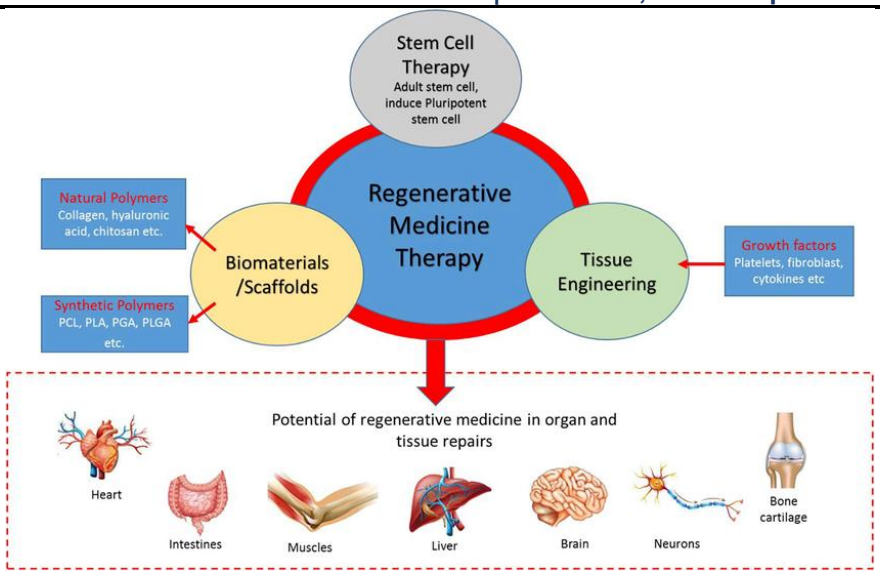

Figure 2: The regenerative medicine therapy (RMT) triad. Stem cell therapy, biomaterials/scaffolds, and tissue engineering are components of regenerative medicine in organ/tissue repairs.

3.1 Stem Cell-Based Gene Therapy

Stem cell-based gene therapy is a pioneer of regenerative medicine, which integrates the capability to renew and differentiate of stem cells with the accuracy of genetic engineering. The types of stem cells used include embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), as well as mesenchymal stem cells (MSCs). ESCs have pluripotency and have the ability to differentiate into any cell type, but iPSCs provide similar abilities without ethical issues, as they are made of somatic cells. MSCs are most commonly utilized in clinical and experimental studies because they are easy to isolate, immunomodulatory and can differentiate into bone, cartilage and adipose tissues [26].

Stem cell regenerative potential is increased through genetic modification as it improves regeneration, proliferation and targeted differentiation. Growth factors, cytokines or transcription factors can be engineered into engineered stem cells to induce tissue repair and remodeling of the local microenvironment. Ex vivo (alteration out of the organism and then transplantation) and in vivo (direct gene delivery) methods are used, based on the treatment goal. These vectors offer long-term and localized expression of therapeutic genes, which surpasses constraints of direct protein delivery like limited half-life and high cost [27].

3.2 Tissue Engineering and Gene Therapy

Gene therapy combined with tissue engineering is a potent and dynamic approach of the regenerative medicine, which tries to regenerate the structure and functionality of the damaged tissues and organs. This combined method involves the use of cells, biomaterials and genetic materials to design a supportive environment that facilitates healing and regeneration of tissues [28]. Gene therapy in the context of tissue engineering is usually obtained in two distinct methods: in vivo and ex vivo gene delivery. The delivery of therapeutic genes directly into the target tissue is a relatively simple and cost-effective approach to in vivo delivery. But it does not have specific control of gene expression and specificity of targeting. On the other hand, ex vivo gene delivery, also known as cell-mediated gene therapy is a type of gene therapy where the

isolated cells are genetically altered out of the body and reintroduced to the injury location. It is more complicated and expensive and necessitates cell expansion, validation, and safety testing, but provides better control over cellular activity, and gene expression [29].

The various methods of delivery of gene in tissue engineering can be classified under non-viral and viral vectors. Adenoviral and lentiviral vectors are virus vectors that are very effective transfection vectors and have been widely used both in experimental and clinical practice [30]. They have their use restricted, but because of safety issues, such as immunogenicity and the possibility of insertional mutagenesis. Non-viral vectors, on the other hand, are less immunogenic, safer and simpler to manufacture, but typically less efficient in gene transfer. The two systems are being optimized actively to be used in the regenerative medicine applications [31].

3.2.1 Scaffold-Based Gene Delivery

Gene delivery through the use of scaffolds is one of the most important aspects of tissue engineering. Scaffolds: Three dimensional biomaterials based on the natural extracellular matrix arrangement which support the structural mass where cells are adherent, growing and differentiating. The perfect scaffold must also be biocompatible, biodegradable and have the right mechanical strength mechanism and be able to deliver therapeutic genes to the location of interest [32].

Recent advancements have found the scaffold-mediated delivery of gene useful in stimulating tissue regeneration. One such example is the poly(ε-caprolactone) (PCL) scaffolds containing lentiviral vectors containing transforming growth factor-23 (TGF-23) which have been shown to enhance chondrogenic differentiation and cartilage-like matrix formation. Likewise, biomineral-coated scaffold of poly(L-lactic acid) (PLLA) and PCL have also been reported to exhibit enhanced bone formation when compared with gene delivery vectors expressing osteogenic factors, e.g., BMP-7. The findings of this paper demonstrate the significance of scaffold composition and surface modification in the process of regeneration effects [33].

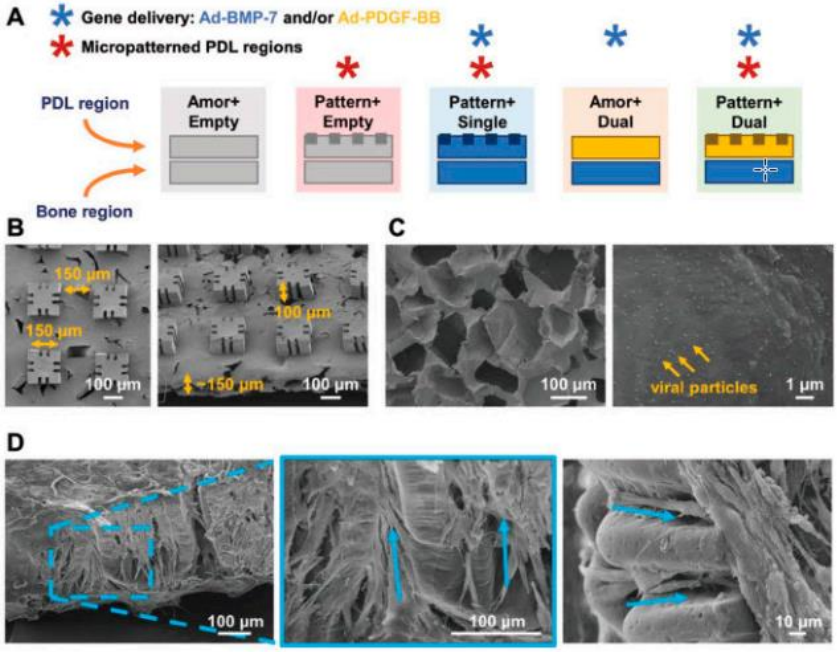

Figure 3: Scaffold design for periodontal tissue neogenesis.

3.2.2 Growth Factor Gene Expression

Gene therapy enables sustained and localized expression of growth factors, which are critical regulators of tissue regeneration. In contrast to direct protein delivery, short half-life and rapid degradation of therapeutic molecules, gene-based methods allow sustained production of therapeutic molecules at the target site. Some of the growth factors include: bone morphogenetic proteins (BMPs), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor (TGF), which are involved in the following processes: angiogenesis, cell proliferation and differentiation [34].

The new strategies are advanced, dealing with spatiotemporal regulation of genes expression to achieve optimal therapeutic effects. The methods of localizing and releasing genes where needed include chemical vapor deposition (CVD) and scaffolds with micropatterns, which enable the reduction of off-target effects and enhance tissue-specific regeneration. Viral systems and non-viral systems have been effectively implemented to express growth factor genes and show long-term gene expression and improved healing in preclinical models [35].

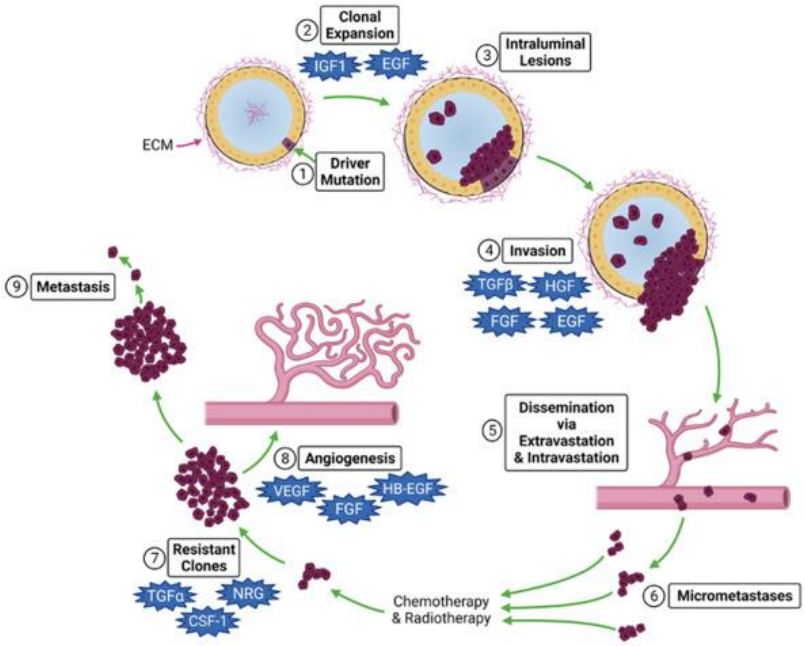

Figure 4: Growth Factor-Mediated Gene Expression in Regeneration

3.2.3 Organ Regeneration Strategies

The integration of gene therapy with tissue engineering has significantly advanced organ regeneration strategies [36]. Combination of gene delivery and biomaterials and stem cells can be applied in reproduction of complex tissue structures and in stimulating functional recovery. One such example is scaffold-based systems which have been discovered to provide over one growth factor gene to stimulate bone, ligament and periodontal tissue regeneration. The hybrid approaches involving both viral and non-viral delivery of genes enhance the effectiveness of regeneration due to safety and efficacy balance [37].

The non-viral gene-activated matrices (GAMs) such as the polyethyleneimine (PEI) and the collagen-based scaffold have been demonstrated to have promoted gene expression and tissue repair during extended periods of time. These systems enable controlled release of plasmid DNA, and also facilitate long-term regeneration. In addition, the adoption of combinational therapies based on scaffold design, gene delivery and cell therapy are increasing and proving to be effective in repairing more complex tissues and organs [38].

3.3 Clinical Applications

Gene therapy based regenerative medicine has shown enormous potential in the wide range of clinical applications through enabling targeted repair, regeneration and functional reconstruction of the damaged tissue. The therapies are supposed to cure the cause of the disease rather than to cure the symptoms through the delivery of the genes using cell-based and tissue engineering modalities. Significant applications involve neurological diseases, cardiovascular diseases, musculoskeletal regeneration and wound healing [39].

3.3.1 Neurological Disorders

Those neurological disorders that are the most challenging to treat using regenerative therapies are Parkinson disease and spinal cord injury since the central nervous system is characterized by a low regenerative potential. Gene therapy is as well a very promising therapy as it entails the transfer of genes that code neurotrophic factors, enzymes or signaling molecules to stimulate the survival and regeneration of the neurons. Gene delivery approaches in the treatment of PD seek to repair dopamine synthesis or to preserve dopaminergic neurons by expressing genes e.g., tyrosine hydroxylase or glial cell line-derived neurotrophic factor (GDNF) [40].

Gene therapy is applied in spinal cord injury to improve the regeneration of the axons, decrease inflammation, and induce functional recovery. Growth factor delivery: Experimental models of neuronal survival and synaptic plasticity have improved with delivery of neurotrophic factor brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF). Moreover, stem cell transplantation together with gene therapy has also enhanced results by providing a favorable microenvironment to repair the neural. Even though clinical translation is complicated, the approaches have high potential of restoring neurological functionality [41].

3.3.2 Cardiovascular Diseases

Cardiovascular diseases (myocardial infarction and ischemic heart disease) are one of the most frequent causes of death and are the main aim of regenerative medicine. Gene therapies in this area are primarily geared towards angiogenesis promotion, anti-cell death and repair of heart tissue. The genes that are of interest are the vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and hepatocyte growth factor (HGF) which have been extensively studied because they have potential in stimulating the growth of blood vessels and increasing blood supply to tissues under anaerobic conditions [42].

Additionally, genetically modified stem cells aimed at improving cardiac regeneration through a higher survival rate and integration into damaged myocardium are explored. In vivo and ex vivo preclinical and early clinical trials have demonstrated improved cardiac functions. Nevertheless, issues that need to be overcome include effective gene delivery, sustained expression and safety prior to widespread clinical usage [43].

3.3.3 Musculoskeletal Regeneration

Gene therapy is vital in the repair of musculoskeletal tissues such as bone, cartilage and skeletal muscle. Trauma, degenerative diseases, and aging often have an influence on these tissues. Osteogenic gene (e.g., bone morphogenetic proteins (BMPs)) and transcriptional factor (e.g., RUNX2 and osterix) deliveries enhance bone formation and repair in the bone regeneration. Likewise, genes that encode growth factors like transforming growth factor- 2 (TGF- 2) and insulin-like growth factor (IGF) stimulate chondrogenesis and extracellular matrix synthesis in cartilage regeneration [44].

The strategies of muscle regeneration include the introduction of genes that control muscle growth and repair, especially in diseases like muscular dystrophy. Defective genes can be replenished or regenerative

signaling pathways advanced through gene therapy, which can ameliorate muscle activity and decrease degeneration. There are also better therapeutic outcomes that have been achieved in musculoskeletal applications with the use of gene therapy incorporating biomaterials and stem cells [45].

3.3.4 Wound Healing and Skin Regeneration

Gene therapy has clinical uses in wound healing and skin regeneration of interest to chronic wounds, burns and diabetic ulcers. Gene delivery techniques aim at accelerating the healing procedure by increasing the rate of cell proliferation, angiogenesis, and extra-cellular matrix producing. Growth factors which are usually used to stimulate tissue repair include platelet-derived growth factor (PDGF), VEGF and epidermal growth factor (EGF) [46].

Scaffold-based systems and gene-activated matrices are becoming more popular as a source of sustained delivery of therapeutic genes at the wound site. Moreover, stem cell gene therapy has shown the possibility of improving wound healing by showing higher cell survival and inflammatory control. Such techniques are not only utilized in order to increase the healing rate, but also to improve the quality of the regenerated skin, reduce scarring and restore functionality [47].

Table 2: Regenerative Medicine Based on Gene Therapy

Category	Key Components	Role of Gene Therapy	Applications
Stem Cell-Based Therapy	ESCs, iPSCs, MSCs	Genetic modification to enhance differentiation, survival, and function	Tissue repair, neuroregeneration, bone and cartilage healing
Tissue Engineering	Scaffolds, biomaterials, engineered tissues	Gene delivery through scaffolds for controlled expression of growth factors	Organ regeneration, bone and cartilage repair
Gene Delivery Approaches	Viral (AAV, lentivirus), Non-viral (liposomes, nanoparticles)	Efficient transfer of therapeutic genes to target cells/tissues	In vivo and ex vivo therapies
Growth Factor Therapy	BMPs, VEGF, PDGF, TGF-β	Sustained production of regenerative proteins	Angiogenesis, wound healing, tissue regeneration
Clinical Applications	Multi-system diseases	Targeted gene correction and regeneration	Neurological, cardiovascular, musculoskeletal, skin repair

4. Recent Progress in Non-Viral Gene Therapy

Recent years have witnessed significant advancements in non-viral gene therapy, particularly in the development of nanoparticle-mediated delivery systems. Nanoparticles are currently regarded as one of the most successful vectors of nucleic acids which offers a superior ability to resist degradation by enzymes and uptake by cells. These involve polymeric nanoparticles and biodegradable systems which have shown promise in delivering DNA, siRNA and mRNA with improved kinetics of stability and controlled release [48].

The successful application of lipid nanoparticles (LNPs) in mRNA-based therapies has become one of the biggest breakthroughs in the given field. The safety, scalability, and effectiveness of LNP-based delivery platforms were shown by the use of mRNA vaccines around the world during the COVID-19 pandemic. These systems rely on a lipid composition, e.g., PEG-lipids and ionizable lipids to entrap and deliver mRNA into cells, which could then be translated into therapeutic proteins. Although such platforms are very effective in short-term applications like vaccination, their modification to long-term therapeutic applications is a subject of ongoing research [49].

The effort of delivering genes in a controlled and targeted manner has also advanced immensely with measures focusing on improving tissue specificity and decreasing the off-target effects. To increase precision in gene delivery, surface modifications, ligand-based targeting and stimuli-responsive systems are under development. Controlled-release, e.g. biodegradable implants can also be used to deliver therapeutic nucleic acids over the long term which is particularly useful in chronic disease and cancer therapy [50].

Reduced toxicity and better biocompatibility of non-viral systems is another important benefit over viral vectors. Such systems decrease immune reaction by preventing the utilisation of viral parts and eliminate the possibilities of insertional mutagenesis. However, there are still certain problems, including decreased transfection efficiency and intracellular delivery, which are yet to be resolved [51].

Recent experimental and clinical research is also supportive of the potential of non-viral approaches. Indicatively, sustained-release implants, such as those made of PLGA, have shown the capacity to deliver siRNA over a number of months in tumor models, indicating their potential use in cancer therapy. All these advancements indicate the evolution of non-viral delivery systems of genes to prove safe, versatile and clinically significant as an alternative to regenerative medicine and gene therapy [52].

5. Field Advances and Trends in 2024–2025

The blistering increase in human pluripotent stem cell (hPSC) based therapies into clinical trials and then the development of these into later-stage products is one of the largest recent advances. There is an increase in approved trials that have shown promising safety profiles, and the number of patients enrolling in trials is rising. The most significant models in which stem cell-based 0-cell therapies has shown an improvement in functionality have been diseases such as type 1 diabetes and; insulin productions and improved glucose control [53]. Although this has been achieved, issues pertaining to long-term engraftment, vascularization and long term functioning are some of the key areas of study.

5.1 Immune Engineering for Scalable Cell-Based Therapies

Rejection by the immune system is a major challenge in allogeneic cell therapy. In a bid to curb this, the immune engineering techniques have been devised to produce hypoimmune or immune-evasive cell products. The idea of these strategies is to prevent the necessity to use long-term immunosuppression, and to enable the development of off-the-shelf regenerative therapies. The recent preclinical studies have

demonstrated that engineered cells can be maintained in immunocompatibles over prolonged periods of time, which presupposes their scalability and their availability in general [54].

5.2 Advances in Gene Delivery and In Vivo Genome Editing

Lipid nanoparticle (LNP)-based technologies, as well as various other technologies, have significantly increased the efficacy of nucleic acid therapeutics, including mRNA-based therapeutics. In vivo CRISPR-based genome editing is becoming a powerful regenerative method, parallel. The single-dose treatments with genes have resulted in long-term, durable therapeutic effects in clinical studies, demonstrating that direct gene correction is possible in the body in the long-term treatment of the diseases [55].

5.3 Clinical Translation and Regulatory Progress

The last regulatory achievements have increased the pace of clinical translation of gene and cell therapies. The further liberalization of authorizations of gene therapies against disease such as muscular dystrophy will show the increased trust in its safety and efficacy. These breakthroughs are shaping the regulation policies and driving more innovation in the regenerative medicine [56].

5.4 Gene-Edited Xenotransplantation and Organ Replacement

Multiplex gene editing to allow xenotransplantation is another innovative technology in the field of regenerative medicine. The effectiveness of the transplantation of the gene-edited animals to humans with their organs is a grave move in resolving the organs shortage. It is hoped that further clinical trials will help in evaluating the safety, effectiveness and long term viability of these methods which would redefine the methods of organ replacement in future [57].

6. Overview of Contributions in This Special Issue

6.1 Enabling Strategies for Gene Therapy and Gene Delivery in Regenerative Contexts

This Special Issue lists some of the enabling strategies which are intended to improve the efficiency and feasibility of gene therapy. One of the strategies is to promote ex vivo growth of hematopoietic stem and progenitor cells (HSPCs) which is necessary to enhance the cell yields, functional performance and variability in the gene therapy process. Further, comparative BMP2 gene-delivery of bone regeneration provide valuable information on the usefulness of in vivo and ex vivo use, which resolve valuable translational concerns of safety and control. Furthermore, combination therapies, such as HGF and VEGF in the case of ischemic injuries, are also under investigation, and demonstrate that underlying metabolic conditions have the potential to influence the effects of therapy, and it is also crucial to implement patient-specific therapy [58].

6.2 Cell Therapies, Tissue Microenvironments, and Biomaterial Support

Some of the studies revolve around the effectiveness of cell therapies and how the tissue microenvironment affects the regenerative process. The route of administration, e.g. nasal delivery of adipose-derived stem cell, underscores the importance of administration routes as a way of enhancing therapeutic efficacy

particularly in neural and sensory regeneration. The studies of osteoarthritis indicate that the synovial fluid may enhance the viability of the stem cells, which supports the idea that success of the therapy is not only determined by the cell product, but also by the host environment. Additionally, the large-animal models provoke the information on stromal cell plasticity and tissue formation. Cell retention, survival and functional integration in the damaged tissue is also further improved by biomaterial-based strategies such as hydrogel-supported stem cell delivery [59].

6.3 Reviews: Cell Sources, Omics-Informed Differentiation, and Gene Delivery Platforms

The review articles contained in this issue offer more comprehensive views on translational regenerative medicine. Other important areas of research are the production of red blood cells using human pluripotent stem cells, where issues of scaling and maturation are of concern. The innovations in transcriptomics-based differentiation underline the importance of omics technologies in guaranteeing the identity and quality control of cells. Additionally, the papers about gene delivery systems, particularly adeno-associated viral vectors, and cell source of retinal regeneration can give a relative outlook of therapeutic design and clinical translation. All these contributions observe the importance of integrating the application of high-tech technologies to improve precision and efficiency of regenerative therapies [60].

7. Challenges and Limitations

Despite the tremendous progress that has been made, a number of challenges are linked to regenerative medicine, which involves use of gene therapy that curbs wide application of the practice in clinical work. Efficiency and targeting of delivery is one of the major concerns. There is still a challenge of accurate delivery of therapeutic genes to certain tissues or cell types especially in systemic delivery. The off-target effects that are associated with viral and non-viral vectors, lack of penetration into target tissues and efficient uptake by cells reduce the efficacy of therapeutic delivery [61].

Immune reactions and safety issues are also the greatest difficulties. Viral vectors are highly efficient but may induce immune and inflammatory responses, which may cause toxicity or decreased gene expression with time. Opposite this is the likelihood of insertional mutagenesis especially, by inserting integrating vectors that can result in interference with the normal functioning of genes and oncogenesis. Non-viral systems are less risky but may be problematic in terms of stability, and transient gene expression [62].

The other factor that is important is the ethical and regulatory issues. The use of stem cells, particularly the embryonic stem cells has been challenged on an ethical perspective, and genome editing technologies, such as the CRISPR, have been questioned because of their potential to cause germline alterations and their future impact on society. The regulatory procedures of gene therapy are complex and constantly evolving in nature, with safety, efficacy and long-term effects needing to be considered stringently before authorization [63].

Lastly, it has high cost and scalability as a major limitation. Gene therapy products, in particular those that are based on personalized or ex vivo methods, are costly and technically challenging to produce. The mass

production, quality assurance and distribution also pose other challenges making the reach to wider groups less [64].

Conclusions

The regenerative medicine based on gene therapy is a promising and rapidly developing field that aims at restoring the damaged tissues and organs using a combination of biological and engineering techniques. The combination of the gene delivery systems, stem cell therapies and tissue engineering has resulted in an immense improvement on the regenerative outcomes. Non-viral systems, despite their relative safety and versatility, are better, especially in the recent advances of nanoparticle-based and mRNA-based delivery, whereas the viral vectors are highly efficient. The emerging technologies, such as genome editing, immune engineering, and biomaterials, contribute to further development of precision and therapeutic potential." Nevertheless, safety, efficiency of delivery and massive implementation challenges are still present. In general, there is a positive trend in the field towards multi-modal, personalized regenerative approaches with high chances of clinical success in the future.

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