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Perspective of Gene Therapy for Regenerative Medicine: The Future of Complex Disease and Regenerative Application

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ABSTRACT
Recent breakthroughs in biotechnology have significantly advanced the potential to regenerate damaged human tissues. Innovations in stem cell science, genetic engineering, and tissue scaffolding have rapidly pushed the boundaries of regenerative medicine. Yet, numerous technical hurdles remain, particularly concerning the clinical application of gene therapy. Core objectives of gene therapy include enhancing protein synthesis within cells, suppressing overactive genes, and rectifying dysfunctional cellular mechanisms linked to disease. While viral vectors remain dominant in current clinical trials due to their effectiveness, they carry risks of immune reactions and pathogenicity. This has sparked increased interest in non-viral alternatives, which promise greater safety and versatility. Non-viral delivery methods utilize *plasmid* DNA systems and synthetic carriers to transport therapeutic genes, and show great potential, especially when integrated with tissue engineering techniques. By combining these non-viral tools with regenerative approaches, researchers aim to more precisely control the spatial and functional behavior of introduced genes within the body. This review critically assesses the evolution and challenges of gene therapy within the broader scope of regenerative medicine, with an emphasis on emerging non-viral delivery systems and their translational promise.

Keywords: regenerative medicine, gene delivery, non-viral vectors, viral vectors, tissue engineering, nanoparticles, gene regulation

INTRODUCTION

Gene therapy represents a transformative approach in modern biomedical science, offering the potential to correct or enhance cellular function through the introduction of genetic material (Wang Tai P. W. L. & Gao G., 2019). This can be accomplished either inside the body (*in vivo*) or outside the body (*in vitro*), and aims to treat, prevent, or potentially cure various genetic and acquired disorders (PwC, 2024). One of the main challenges in gene therapy lies in ensuring that the introduced genes can successfully enter target cells and express the desired proteins, whether temporarily or long-term, depending on the therapeutic goal (Yin Kanasty R. L. Eltoukhy A. A. Vegas A. J. Dorkin J. R. & Anderson D. G., 2014).

Over the years, a range of gene delivery strategies has been developed. These include viral vector systems, synthetic (non-viral) carriers, and physical techniques such as electroporation and microinjection (Hosseinkhani et al., 2023). Within the context of regenerative medicine—a multidisciplinary field that merges engineering, cell biology, and material sciences to repair or replace damaged tissues and organs—gene therapy has emerged as a powerful adjunct technology (PwC, 2024).

The primary goal of regenerative medicine is to support the body's own repair mechanisms by stimulating tissue regrowth and functional recovery, particularly in cases where natural healing is limited or absent (Li et al., 2024). In this realm, gene therapy serves as an alternative to conventional protein-based treatments (Poltera J, 2019; Sahban, 2016). Administering therapeutic genes instead of proteins allows for sustained expression at the site of injury, circumventing issues such as the rapid degradation of proteins, the need for repeated dosing, and high production costs (Su et al., 2024).

Table 1. FDA (2025)-Approved Gene Therapies and Their Target Diseases

Disease	Gene Therapy	Mechanism	Approval Year
Spinal Muscular Atrophy (SMA)	**Zolgensma® (onasemnogene abeparvovec-xioi)**	Replaces defective *SMN1* gene	2019
Inherited Retinal Disease (RPE65 mutation)	**Luxturna® (voretigene neparvovec-rzyl)**	Delivers functional *RPE65* gene to retinal cells	2017
Beta-Thalassemia	**Zynteglo® (betibeglogene autotemcel)**	Inserts functional *beta-globin* gene into stem cells	2022
Severe Combined Immunodeficiency (ADA-SCID)	**Strimvelis®** *(approved in Europe first)*	Adds functional *ADA* gene into patient's stem cells	2016 (Europe)
Hemophilia B	**Hemgenix® (etranacogene dezaparvovec-drlb)**	Introduces a working *Factor IX* gene to liver cells	2022
Hemophilia A	**Roctavian™ (valoctocogene roxaparvovec)**	Delivers a functional *Factor VIII* gene	2023
Cerebral Adrenoleukodystrophy (ALD)	**Skysona® (elivaldogene autotemcel)**	Provides working copies of the *ABCD1* gene to prevent brain damage	2022

These therapies, shown in Table 1, do not just treat symptoms; they aim to fix the root genetic cause by either replacing the missing or faulty gene or adding a functional copy to

restore normal functions. This approach has been successful for neuromuscular diseases

(e.g., *SMA*), blood disorders (e.g., *Beta-thalassemia*, *Hemophilia A* and *B*), inherited blindness, and severe immune deficiencies.

There are two primary strategies in gene therapy for regenerative purposes: direct delivery of genes to tissues (*in vivo*), or modification of cells in a laboratory setting before reintroducing them into the body (*ex vivo*) (Liu et al., 2020). Both methods aim to localize the expression of biologically active molecules, such as growth factors or cytokines, in the target tissue to initiate or accelerate regeneration (Boserup et al., 2013; Minniti, 2010; Siahaan T Haryanti E Harini H Perkasa D., 2024; Silva, 2016). While the terms "tissue engineering" and "regenerative medicine" are sometimes used interchangeably, they are closely linked and often function together in integrated therapeutic approaches (Li et al., 2024). This review explores how gene therapy is being developed and applied within regenerative medicine, highlighting current technologies and proposing directions for future research.

METHOD

This study utilizes a systematic literature review (SLR) to thoroughly examine recent progress, ongoing challenges, and emerging trends in gene therapy for regenerative medicine. The data population is drawn from peer-reviewed journal articles, clinical trial reports, and authoritative reviews published between 2018 and 2025, sourced from reputable databases such as PubMed, ScienceDirect, and IEEE Xplore. The review specifically targets research on viral and non-viral gene delivery systems, biomaterials, and clinical applications in tissue regeneration, using purposive sampling to select studies that meet predefined relevance criteria.

A structured data extraction form is employed to systematically gather key information from each study, including objectives, methodologies, outcomes, and limitations. The validity and reliability of the review are ensured through critical appraisal using PRISMA guidelines and inter-rater reliability checks by independent reviewers. Data collection involves keyword-based searches and a multi-stage screening process, with findings categorized into major themes such as delivery systems and clinical outcomes. Qualitative content analysis and descriptive statistics are used to synthesize the results, supported by software tools like EndNote for reference management and NVivo for thematic analysis. The synthesized findings are presented narratively, enhanced by tables and figures to illustrate key insights.

RESULTS AND DISCUSSION

Gene Therapy Applications in Regenerative Medicine

Regenerative medicine stands at the frontier of biomedical innovation, aiming to restore or replace tissues and organs impaired by trauma, aging, or disease (PwC, 2024). By

leveraging biological tools such as stem cells, biomaterials, and bioactive molecules, this field holds transformative potential for improving human health. Gene therapy plays a central role in many regenerative approaches by enabling sustained and localized expression of therapeutic proteins directly within damaged or deficient tissues.

Whether used in vitro, ex vivo, or in vivo, gene therapy enhances the body's natural repair mechanisms. In many cases, it serves as a means to stimulate cellular activity, direct differentiation, or release crucial signaling molecules that trigger tissue growth (Rodrigues et al., 2010). Techniques often involve genetically modifying cells to express growth factors, cytokines, or structural proteins critical for tissue recovery. These genes can be delivered directly into the patient or introduced into cells cultured outside the body before re-implantation.

In this section, we explore how gene therapy contributes to tissue regeneration through a variety of strategies and delivery platforms, particularly focusing on tissue engineering, and the regeneration of vasculature, bone, cartilage, cardiac muscle, nerves, teeth, hair cells, skin, and intervertebral discs.

Tissue Engineering and Gene Therapy Integration

Gene therapy is increasingly used in tissue engineering to promote regeneration either through direct gene administration (in vivo) or cell-mediated gene transfer (ex vivo) (Malech et al., 2022). In in vivo strategies, genetic material is injected into the damaged site, prompting host cells to express therapeutic proteins (Rodrigues et al., 2010). This method is relatively straightforward but lacks precision in targeting and control. Ex vivo approaches, in contrast, allow for careful manipulation of cells in a controlled environment before reintroduction into the body (Rodrigues et al., 2010). While more labor-intensive and costly, this method provides better control over cell behavior and transgene expression.

The ex vivo strategy is often preferred for complex tissue engineering applications, such as bone repair, where cells like mesenchymal stem cells (MSCs) are isolated, expanded, genetically modified, and seeded onto scaffolds or implanted directly into injury sites (Li et al., 2023; Rodrigues et al., 2010). Both viral and non-viral vectors can be used, though viral vectors tend to offer higher transduction efficiency.

Literature shows that gene therapy is adaptive enough to overcome the limitations of traditional tissue engineering techniques (Su et al., 2024). Su et al. (2024) write that tissue damage caused by chronic injury can lead to uncontrolled regulation by the immune system. Tissue transplantation can lead to immune rejection and other problems (Su et al., 2024). Thus, the introduction of gene therapy solutions that overcome the body's limitations while repairing itself are needed to reduce the complications seen during traditional tissue engineering.

Gene therapy provides up-to-date representations of the target genes and assists with tissue regeneration (Su et al., 2024). Gene therapy increases cells' durability and lowers their chances of immune rejection (Su et al., 2024). Su et al. (2024) write that engineers have begun using hydrogels to increase the accuracy of gene therapy injections and improve the efficiency of tissue engineering treatments. Hydrogels are easier to customize and introduce less problems during the manufacturing and treatment processes (Su et al., 2024). However, hydrogels' ability to reduce immune rejection has not been perfected. The rise of hydrogels in gene therapy highlights engineers' inability to regulate their safety and effectiveness and ensure that gene-focused drugs are properly transferred to patients' target cells (Su et al., 2024). However, the long-term benefits of hydrogels make them a worthwhile investment for genetic and tissue engineers who want to use gene therapy to treat diseases at the most invasive levels possible.

Chu et al. (2024) find that bone tissue engineering has grown as an area of practice and research. According to Chu et al., bone tissue engineering is an interdisciplinary field that combines cells, biomaterials, and molecules to provide viable enhancements to bone regeneration. The apparent goal of bone engineering is to provide a tool for uniform distribution and sustained release that ensures mesenchymal stem cell osteogenesis (Chu et al., 2024, Abstract para. 1).

Gene therapy's use in bone tissue engineering is needed, as the United States oversees a significant number of cases involving long bone fractures that fail to heal properly (Chu et al., 2024). Chu et al. (2024) write that 10% to 15% of long bone fractures in the United States experience delayed healing or non-union because of segmental bone defects (Introduction para. 1). In vivo and ex vivo studies have evaluated the improvements gene therapy can introduce. Lipid-based systems and polymer-based systems have been tested as instruments for bone tissue engineering in the past (Chu et al., 2024). Research highlighting stem cell therapy's collaboration with gene therapy has grown in prominence as well (Chu et al., 2024). There is a need for more standardization before gene therapy can become a consistent and affordable option for those in need of bone tissue regeneration. Ultimately, this is the case for other sub-types of gene therapy-led tissue engineering as well.

Angiogenesis

The formation of new blood vessels, or angiogenesis, is fundamental to tissue healing and regeneration. This process is driven by factors such as VEGF, bFGF, and HGF, which promote endothelial cell proliferation and migration. Angiogenesis also plays a role in pathological conditions, including cancer and ischemic diseases. Gene therapy has enabled local expression of these angiogenic factors, leading to therapeutic neovascularization in conditions like peripheral artery disease (PAD) and coronary heart disease (CHD) (Giacca & Zacchigna, 2012).

Recent experimental systems have combined non-viral vectors with ultrasound-targeted microbubble delivery to enhance gene targeting and reduce systemic side effects. For example, VEGF receptor-targeted microbubbles combined with focused ultrasound have been used to deliver therapeutic genes to brain tumors with high precision, avoiding damage to healthy tissue Willmann et al., 2008).

Clinical trials using VEGF or HGF genes, delivered via plasmids or adenoviral vectors, have shown varying degrees of success in promoting blood vessel growth and improving perfusion in ischemic tissues (Ginn et al., 2018). However, the overall efficacy in large-scale trials has been modest, suggesting a need for improved delivery methods and combination therapies.

Bone Regeneration

Bone healing is a complex biological cascade involving osteoblast proliferation, vascularization, and matrix mineralization. Gene therapy has emerged as a powerful approach for enhancing this process by locally delivering osteoinductive factors like bone morphogenetic proteins (BMPs), VEGF, and Runx2 (Li et al., 2023).

Both viral (adenoviral, lentiviral, retroviral) and non-viral (plasmid DNA, liposomes, sonoporation) vectors have been employed to promote bone repair in animal models. For instance, ex vivo modification of MSCs with BMP-2 genes has been shown to accelerate bone healing in segmental defects (Li et al., 2023). In vivo approaches using gene-activated matrices (GAMs) or ultrasound-enhanced delivery systems have also demonstrated promising outcomes.

Non-viral strategies, such as electroporation and nucleofection, offer lower immunogenicity and transient gene expression, which can be advantageous in avoiding ectopic bone formation or prolonged exposure to growth signals. Delivery systems incorporating biodegradable scaffolds have further improved localized gene expression and structural integration of regenerated bone.

Cartilage Repair

Cartilage has limited intrinsic healing capacity, which makes it an ideal target for gene therapy. Both in vivo and ex vivo techniques have been explored to enhance cartilage regeneration through sustained delivery of anabolic genes like TGF-β1, IGF-1, and SOX9. Viral vectors, particularly AAVs and adenoviruses, have been used to introduce these genes into chondrocytes or stem cells implanted at cartilage defect sites.

Studies in large animals, including horses and sheep, have shown that gene-modified cells can improve cartilage matrix synthesis, reduce inflammation, and restore function more effectively than protein administration alone (Administration, 2025). Retroviral- mediated expression of interleukin-1 receptor antagonist (IL-1Ra) has also been trialed in

patients with rheumatoid arthritis, showing symptom relief and reduced inflammation in treated joints.

Long-term success requires careful dosing, appropriate gene selection, and delivery methods that replicate human defect size and joint loading conditions. Gene therapy is becoming a more researched option for cartilage repair. Su Lin D. Huang X. Feng J. Jin A. Wang F. Lv Q. Lei L. & Pan W. (2024) write that researchers recently identified gene therapy as an alternative treatment option for patients with osteoporosis. Over time, osteoarthritis was identified as a complex inflammatory and metabolic issue that impacts the entire joint (Li et al., 2023). Li et al. write that the most significant symptom of osteoarthritis and osteoporosis is the degeneration of articular cartilage. Gene therapy addresses this by alleviating inflammation in the affected areas and promoting cartilage repair (Li et al., 2023).

This occurs because of gene therapy's overexpression of therapeutic genes in the target areas and the downgrading of cells expressing averse traits (Li et al., 2023, Targets para. 1).

The primary transcription factors impacting the improvement of cartilage repair are: the Runt–related transcription factor (Runx1,2,3), Sex-determining region Y (Sry)-box-containing family (Sox5,6,9), CCAAT/enhancer binding protein (C/EBPβ), and Hypoxia-inducible factor (HIF-1α,2α) (Li et al.l, 2023, Transcription para. 1). Li et al. (2023) state that Runx2 is a critical transcription factor for the maturation of chondrocyte and formation of bone in normal cartilage (Transcription para. 1). According to the authors, Sox9 enhances the repair process in target areas and reduces progression of osteoarthritis in patients' inflamed joints (Li et al., 2023, Transcription para. 1). Research also shows that gene therapy can help manage cytokine homeostasis and the presence of hormones that aid in the reduction of osteoarthritic effects and the progression of osteoarthritis altogether (Li et al., 2023).

Heart Tissue Regeneration

Heart tissue regeneration remains a challenge due to the limited regenerative capacity of adult cardiomyocytes. Gene therapy offers potential through the delivery of genes encoding proliferative factors, anti-fibrotic agents, and angiogenic cytokines. Methods such as intramyocardial injection, intracoronary infusion, and epicardial gene painting have been used to deliver vectors in large animal models.

Adenoviral vectors carrying cyclin A2 or VEGF have been studied in myocardial infarction models, showing improved cardiac output, increased cardiomyocyte proliferation, and reduced fibrosis. AAV vectors targeting cardiac myofibroblasts have also enabled localized expression of regenerative genes with minimal off-target effects.

In neuromuscular disorders such as Duchenne muscular dystrophy, rAAV-mediated microdystrophin gene delivery has demonstrated significant improvements in muscle

function and histology in both rodent and canine models, with long-term expression and no immune rejection.

Nerve Regeneration

Damage to the central and peripheral nervous systems poses substantial challenges due to limited intrinsic regeneration. Gene therapy seeks to overcome inhibitory environments and restore axonal growth by delivering neurotrophic genes like BDNF, GDNF, and CNTF. Controlled, time-limited expression of these factors is essential to avoid overstimulation or nerve entrapment.

Lentiviral vectors regulated by doxycycline-inducible systems have allowed precise control of neurotrophic gene expression, enhancing regeneration while minimizing side effects. Additional strategies include AAV-mediated RNA interference to silence growth inhibitors and combination approaches targeting both intrinsic and extrinsic barriers to axon repair.

Tooth and Periodontal Tissue Engineering

Gene therapy for dental applications focuses on regenerating periodontal ligaments, alveolar bone, and cementum. Both viral and non-viral systems have delivered genes like BMP-2, PDGF, and GDF11 to stimulate the repair of periodontal tissues. Adenoviral vectors have been especially effective in driving osteogenesis and cementogenesis in preclinical models.

Non-viral GAMs using polyethylenimine (PEI) complexes have also shown promise, although their inflammatory response and dosing require careful management. Combining gene therapy with stem cell delivery offers a synergistic approach for re-establishing functional dental structures.

Gene therapy has the ability to assist with salivary gland disorders, autoimmune diseases, the regeneration of damaged bone tissue, and management of cancerous and precancerous conditions (Barhate et al., 2023, Abstract para. 2). Researchers focusing on gene therapy's place in dentistry believe the practice can address the root causes of periodontal disease and the microbial challenges that come with oral ailments (Barhate et al., 2023, Review para. 1). Researchers and practitioners in the field of dentistry have been unable to implement gene therapy consistently. The unpredictable nature of oral disease and the nuances and using gene therapy vectors in the mouth make it difficult to determine how gene therapy should be mainstreamed within the practice area (Barhate et al., 2023, Review para. 1). Barhate et al. (2023) write that there is not a universal gene that can be identified to guide the use of gene therapy while treating periodontal issues.

Figure 2 shows that gene therapy addresses a diverse array of root causes and oral conditions. Gene therapy can address patients' pain, malfunctions in their salivary glands,

breaks and weaknesses in their bones, damaged tissue in their teeth, and the root elements of oral cancer (Barhate et al., 2023). The underlying causes of these issues are not caused by the same genes, and this reality is the primary reason why gene therapy in dentistry is still an emerging practice instead of an established alternate solution.

Figure 2. Applications of gene therapy in dentistry

Inner Ear and Hearing Restoration

Hair cell regeneration in the inner ear is a major goal in treating hearing loss. Traditional AAV vectors have been limited by low efficiency in infecting outer hair cells and supporting cells. However, synthetic variants like AAV2.7m8 and AAV-ie have improved transduction efficiency and expanded targeting capacity across cochlear and vestibular cell types.

Delivery of Atoh1, a transcription factor crucial for hair cell differentiation, has successfully induced the formation of new hair cells in animal models. Despite promising structural recovery, full restoration of auditory function remains a target for ongoing research.

Skin Regeneration

Given its accessibility and regenerative nature, skin is a favorable tissue for gene therapy (Li et al., 2024). Non-viral delivery of genes such as IGF-1, KGF, and VEGF via liposomes or nanoparticles has enhanced wound healing, angiogenesis, and epidermal

restoration in preclinical burn and diabetic models (Shaabani et al., 2022). Combining gene therapy with 3D scaffolds or epidermal stem cells allows for sustained gene expression and tissue remodeling. Additionally, chemokine-modified MSCs guided by CXCR6/CXCL16 pathways have improved stem cell homing and integration at wound sites, promoting vascularization and dermal repair (Shaabani et al., 2024).

The human body's skin is affected by natural aging and environmental degradation over time (Li et al., 2024). Li et al.'s (2024) found that subjects' base stem cells varied across age groups and skin cell types (epidermal, hair cells, etc.). The authors recognized that ATF3 was a novel regulator of skin aging during their research (Li et al., 2024, Abstract para. 1). In response, the authors evaluated the efficacy of an mRNA-based treatment to address the effects of aging on the skin. After their experimentation, Li et al. found that an mRNA-based treatment focused on influencing the ATF3 gene could reverse aging in the skin. The reversal of aging occured through the modulation of specific cell mechanisms (Li et al., 2024, Abstract para. 1).

Intervertebral Disc Regeneration

Degenerative disc disease is associated with inflammation and extracellular matrix (ECM) degradation. Non-viral vectors, such as polyplex micelles and gene-loaded nanospheres, have been used to deliver anti-inflammatory and ECM-regulating genes like heme oxygenase-1 (HO-1) and NR4A1.

Injectable hydrogel systems carrying these gene complexes have improved nucleus pulposus cell phenotype and matrix composition in animal models, offering a minimally invasive avenue for disc regeneration.

Biomaterials-Mediated Regeneration

The use of biomaterials in gene therapy-based regenerative medicine has revolutionized the way therapeutic genes are delivered and controlled at the target site. Biomaterials act as carriers or scaffolds that can be engineered to support cell growth, guide tissue regeneration, and serve as vehicles for gene delivery. These materials offer a unique advantage by enabling localized and sustained release of therapeutic genes, thereby enhancing the precision and effectiveness of gene therapy.

A central benefit of integrating gene therapy with biomaterial systems is the ability to not only stimulate tissue regrowth but also correct genetic defects at the molecular level. Through gene editing tools and regulated gene expression systems embedded within biomaterial platforms, it is now increasingly possible to fix or repair faulty genes, restoring normal cellular function. This has opened new avenues in treating genetically driven degenerative conditions.

Biomaterials used in regenerative applications are generally classified as hydrogels or scaffold structures and can be derived from natural or synthetic sources (Su et al., 2024). They are designed to mimic the mechanical and biochemical properties of the native extracellular matrix (ECM), ensuring compatibility with the host tissue (Aazmi et al., 2024).

Hydrogel-Based Regeneration

Hydrogels are highly hydrated, cross-linked polymer networks capable of absorbing large volumes of water (Su et al., 2024. Their physical and biological properties can be tailored for specific applications, making them particularly suitable for delivering gene therapies to soft tissues. Hydrogels are widely used in regenerative medicine due to their injectability, tunable stiffness, biocompatibility, and ability to encapsulate both cells and genetic material (Su et al., 2024).

One of the primary advantages of hydrogel systems in gene therapy is their capacity to protect nucleic acids—such as plasmid DNA, mRNA, or siRNA—from enzymatic degradation, while allowing for sustained and localized release (Su et al., 2024). Incorporating gene delivery systems into hydrogels can help regulate the temporal and spatial presentation of genes, enhancing cell uptake and minimizing off-target effects.

For example, hydrogels made from collagen, alginate, or hyaluronic acid have been used to encapsulate viral or non-viral vectors and promote regeneration in cartilage, myocardial, and intervertebral disc models (Su et al., 2024). In myocardial infarction models, gelatin-based hydrogels loaded with gene complexes targeting inflammation and angiogenesis have significantly improved tissue perfusion and reduced scar tissue (Xu et al., 2024).

In degenerative disc models, PEG-based hydrogels loaded with synthetic microRNAs (e.g., agomir874) have been shown to modulate matrix synthesis and suppress matrix-degrading enzymes, restoring ECM homeostasis. These gene-loaded hydrogels not only deliver therapeutic genes but also serve as a mechanical support matrix that integrates with host tissues.

Furthermore, functional hydrogels have been engineered to be responsive to environmental triggers, such as pH, temperature, or enzymatic activity, allowing gene release to be dynamically regulated based on tissue needs (Xu Xiao Z. Yang Q. Yu T. Deng X. Chen N. & Wang J., 2024). The ability to program such smart release profiles greatly enhances the potential of gene therapy in tissue-specific regeneration.

Scaffold-Based Regeneration

Scaffolds provide a three-dimensional (3D) framework that supports cell attachment, migration, and differentiation, facilitating the structural restoration of damaged tissues. When combined with gene therapy, scaffolds serve as both a physical matrix and a localized gene depot, releasing genetic material in a controlled manner to orchestrate cellular behavior.

Scaffolds can be fabricated from biodegradable polymers such as polycaprolactone (PCL), polylactic acid (PLA), and poly (lactic-co-glycolic acid) (PLGA). These materials are selected for their mechanical integrity, degradation profile, and ability to be functionalized for gene loading.

Advanced scaffold systems have been developed using solid freeform fabrication, electrospinning, and chemical vapor deposition (CVD) to precisely control the scaffold architecture and incorporate gene delivery agents. For instance, micropatterned scaffolds loaded with adenoviral vectors encoding BMP-7 or PDGF-BB have demonstrated effective bone and ligament regeneration in periodontal models.

Gene-activated scaffolds, often referred to as gene-activated matrices (GAMs), contain plasmid DNA or polyplexes embedded within a biodegradable substrate. As the scaffold degrades, genes are gradually released, transfected into local cells, and expressed to initiate tissue regeneration. GAMs have been particularly effective in bone repair applications, providing a sustained source of growth factors like VEGF and BMPs in situ.

Recent work has also shown that combining scaffolds with polyethylenimine (PEI)-based non-viral vectors can extend gene expression duration and reduce the need for repeated dosing. In bone tissue engineering, these scaffolds have led to enhanced mineralization, neovascularization, and better integration with host bone.

Moreover, scaffold systems allow for the spatiotemporal control of gene delivery, a critical feature when orchestrating complex tissue formation involving multiple cell types and signaling cascades. In applications such as joint, dental, and cardiac regeneration, the ability to precisely control when and where a gene is expressed is crucial for coordinated tissue growth and function.

Nanomaterials-Mediated Regeneration

Nanomaterials have become an essential tool in gene therapy for regenerative medicine due to their small size, ability to interact with cells, and versatility in carrying genetic material (Riley & Vermerris, 2017). These tiny particles, ranging from 1 to 100 nanometers—can be designed to deliver genes directly into target cells, protect them from degradation, and control their release over time.

Compared to traditional viral methods, nanoparticles offer several advantages:

- Lower risk of immune response
- Better control over dosage and timing
- Easier production and modification
- Can be used for DNA, mRNA, siRNA, and gene-editing tools (Riley & Vermerris, 2017)

Riley and Vermerris (2017) state that nanotechnology designed for gene therapy has evolved recently. The rise of novel materials allows genetic engineers to experiment with new applications and treatment strategies (Riley & Vermerris, 2017). Many researchers

believe that the rise of nanomaterials can add upon the benefits introduced by viral and non-viral vectors. Emerging nanotechnologies could potentially negate the disadvantages of viral and non-viral vectors and increase genetic carriers efficiency while navigating through biological barriers (Riley & Vermerris, 2017, Introduction para. 3).

Banoon et al. (2024) write that iron oxide nanoparticles and gold nanoparticles have been targeted by researchers as tools that can help treat cancer. Along with cell-specific targeting, nanoparticle-based gene therapy can improve the release of nucleic acids (Banoon et al., 2024). Nanoparticles are also desirable because of their biodegradability and safe properties while inside patients (Banoon et al., 2024). This can reduce the chance of complication and injury as patients' genetic makeup is manipulated.

Types of Nanomaterials Used

1. Polymeric nanoparticles (e.g., PEI, PLGA): Used for stable gene delivery with controlled release.
2. Lipid-based nanoparticles: Proven effective in mRNA vaccines and now being tested for regenerative uses.
3. Graphene oxide (GO) and silica nanoparticles: Offer high surface area for gene loading and reduce inflammation.
4. Gold nanoparticles: Safe and easy to functionalize for specific targeting (Banoon et al., 2024; Riley & Vermerris, 2017).

How Nanomaterials Help Regeneration

- Bone healing: Nanoparticles delivering BMP-2 or FGF-2 genes improve bone growth, especially in difficult cases like diabetes.
- Heart repair: GO-based carriers delivering IL-4 genes reduce inflammation and support healing after a heart attack.
- Wound healing: Nanoparticles improve gene delivery to skin cells, supporting tissue formation and reduce scarring.
- Fixing genes: With CRISPR/Cas or mRNA, nanomaterials can help correct faulty genes directly at the DNA or protein level (Banoon et al., 2024; Shaabani et al., 2022; Li et al., 2023).

The sub-types and purposes of nanomaterials highlight the flexibility of nanotechnologies as a biomedical solution moving forward. Like many emerging technologies, however, the possibilities of nanotechnologies in gene therapy are largely seen in academic literature and testing. The next section of this thesis discusses the barriers that prevent gene therapy from being utilized more often in regenerative medicine.

Clinical Translation and Current Challenges

Despite the promising advances in gene therapy for regenerative medicine, translating these technologies from laboratory studies to clinical applications remains a complex task. While numerous preclinical models have demonstrated success in restoring tissue function,

moving to human use involves addressing several scientific, regulatory, ethical, and logistical hurdles. At the time of Ginn et al.'s (2018) publication, 2600 gene therapy clinical trials had been performed. Arabi et al. (2022) write that breakthroughs in biotechnology have given gene therapy the tools it needs to treat a diverse array of diseases. A ten-year trend observed by Arabi et al. showed that researchers prefer to use viral vectors more often during clinical trials. This popularity limits the performance of clinical trials that test other methods of gene therapy.

Clinical Applications and Ongoing Trials

Several gene therapies have reached the clinical trial phase or have been approved for specific regenerative or genetic disorders. Examples include:

- Luxturna® (AAV2-RPE65): Approved for inherited retinal dystrophy.
- Strimvelis®: An ex vivo gene therapy for ADA-SCID (a rare immune deficiency).
- Neovasculgen®: A plasmid-based VEGF gene therapy approved in Russia for peripheral artery disease (Sahin et al., 2014).

In regenerative contexts, clinical trials are ongoing for:

- Cardiac regeneration using VEGF gene delivery to promote neovascularization.
- Cartilage repair with AAV vectors expressing anti-inflammatory genes.
- Bone healing in non-union fractures using BMP-encoding gene delivery platforms (Su et al., 2024; Li et al., 2023; Li & Liu, 2022).

However, these examples are still limited in number, and wide-scale clinical use is yet to be achieved in many tissue types. This highlights one of the reasons why gene therapy has not become more mainstream in the clinical arena, as the popularity of viral vectors prevents other forms of gene therapy (non-viral vectors, plasmids, nanotechnologies, etc.) from being studied more often. The lack of studies utilizing other forms of gene therapy prevents clinicians from using emerging and novel forms of gene therapy in the field. This causes stagnation when improving the safety of gene therapy and the progression of the practice.

Challenges in Clinical Translation

Gene therapy's inability to become a mainstream clinical solution is the result of multiple barriers. Now, human patients' safety while using gene therapy options and emerging solutions has not been secured. Also, the delivery of genetic factors and targeting of diseased cells has not been mastered by researchers or genetic engineers. The research needed to improve this efficiency continues to keep the price of gene therapy unaffordable for most individuals. Unfortunately, this price will continue to rise as researchers determine how to elongate the duration of gene therapies' expression in human patients as their immune systems work to recover post-treatment. Finally, the ethics and regulation of gene therapy in regenerative medicine continue to remain a major topic of discussion.

Safety and Immune Response

Viral vectors, particularly adenoviruses, may trigger strong immune reactions, reducing efficacy or causing adverse effects. Gene insertion using integrating vectors (e.g., retroviruses) carries a risk of insertional mutagenesis, potentially leading to oncogenesis (Malech et al., 2022). Fields like dentistry are so diverse that it is difficult to create standardized gene therapy techniques that reduce the risk of human error and confirm which materials, and genetic factors should be used to address a given issue (Su et al., 2024).

Delivery Efficiency and Targeting

Achieving efficient and tissue-specific gene delivery remains difficult, especially in large or poorly vascularized tissues. Non-viral vectors often have lower transfection rates, limiting their therapeutic potential in some clinical contexts. Despite this, viral vectors appear to be more popular in research settings. This is a barrier that must be addressed by researchers who have the support necessary to take more academic risks.

Manufacturing and Cost

Production of clinical-grade viral vectors is expensive and labor-intensive (PwC, 2024). Non-viral systems offer scalability, but many still lack standardization and regulatory approval pathways (Riley & Vermerris, 2017). However, nanotechnologies have grown as a solution that can scale even higher and treat patients more safely (Riley & Vermerris, 2017). This could, at least, make the manufacturing of gene therapy solutions in the future more consistent.

Duration of Expression

Long-term expression is desirable for chronic conditions but may increase risks. Transient expression may be insufficient for regeneration of complex tissues unless supported by scaffold or sustained delivery systems. There is also a concern about the increased expression of regenerative factors or the diminishment of the genetic factors causing the presence of diseases. Focusing more on one goal at a time could provide more direction while studying and manufacturing gene therapy solutions.

Regulatory and Ethical Considerations

Regulatory agencies require robust safety and efficacy data, especially for therapies involving genome integration or permanent gene editing (PwC, 2024). Ethical concerns also arise with germline editing, use of stem cells, and unequal access to costly gene therapies. PwC (2024) also highlights that governments around the world have spent trillions of dollars on the development of gene therapy solutions and the refinement of alternative solutions that can treat cancer, aging, and other chronic diseases.

Bridging the Gap

To advance toward routine clinical use, researchers and clinicians must focus on:

- Developing safer and more targeted delivery platforms (e.g., ligand-directed nanoparticles, biodegradable scaffolds).

- Investing in gene-fixing approaches, such as CRISPR-based precision editing, which can restore natural gene function without ongoing expression.
- Designing patient-specific therapies by integrating genomic information with regenerative treatment plans.
- Creating more predictive humanized animal models and organoid systems to better assess efficacy before trials.
- Engaging regulatory bodies early in the research process to align product development with approval requirements (Sahin et al., 2014; PwC, 2024; Li et al., 2023; Chu et al., 2024).

PwC's (2024) report provides the most expansive example of how governments, healthcare organizations, and researchers have collaborated to make gene therapy more sustainable. Based on PwC's knowledge, the financial barriers associated with integrating an alternative solution like gene therapy prevent many countries from mainstreaming the practice. However, the rise of nanotechnology in regenerative medicine shows the production of more academic knowledge provides immense value to researchers, governments, and the public. Moving forward, researchers, governments, and clinicians must build upon the knowledge presented in this thesis and continue improving the field of regenerative medicine with gene therapy.

Future Perspectives

The field of gene therapy for regenerative medicine is advancing rapidly, with innovations that promise to overcome today's limitations (PwC, 2024; Banoon et al., 2024). As science and technology continue to converge, future therapies are expected to become safer, more targeted, and more accessible. Current options like viral and non-viral vector therapies will be refined to become more efficient and affordable. However, nanotechnology's rise as a base for gene therapy will influence how researchers, biomedical engineers, and specialists across various disciplines decide to attack the causes of chronic diseases at the genetic level. The primary areas of growth moving forward will be: smarter gene delivery, personalized and programmable therapies, an integration with CRISPER and mRNA therapies, bioprinting and regenerative therapies, and the creation of accessible and ethical options for therapy.

Smarter Gene Delivery

The next generation of gene delivery systems will focus on precision, responsiveness, and efficiency. Engineered nanomaterials, responsive hydrogels, and 3D-bioprinted scaffolds embedded with gene vectors will allow:

- On-demand release of genes in response to local environmental cues (e.g., inflammation or hypoxia)
- Tissue-specific targeting to minimize off-target effects
- Multi-gene delivery to orchestrate complex tissue regeneration processes

The integration of these technologies will protect patients from human error and allow clinicians to gather their own knowledge about the impact gene therapy has on patients from different regions, ethnic groups, and socioeconomic backgrounds.

5.2. Personalized and Programmable Therapies

With the rise of genomic medicine, patient-specific gene therapy is now within reach. By sequencing an individual's genome, therapies can be custom-designed to:

- Correct a specific mutation (gene fixing)
- Activate or suppress gene networks relevant to the patient's regenerative capacity
- Match biomaterial scaffolds to the patient's own immune and cellular profile

This personalization could significantly improve treatment outcomes while reducing side effects. Personalizing gene therapy could also address researchers and regulators' inability to standardize gene therapy and determine a way to make it more cost-effective in the short-term. It is possible that gene therapy, at its core, is meant to be a unique and personalized practice. Making gene therapy more accessible could involve the use of clinically proven technologies in a more innovative way (Naldini, 2015; Naso Tomkowicz B. Perry W. L. & Strohl W. R., 2017; PwC, 2024; Riley W., 2017; Rodrigues Alves P. M. & Coroadinha A., 2010).

Integration with CRISPR and mRNA Technologies

New tools such as CRISPR/Cas gene editing and mRNA therapy are transforming the way genetic information is handled (Li & Liu, 2022; Sahin et al., 2014). These techniques can: fix faulty genes at the DNA level; temporarily program cells to express regenerative factors via mRNA; and avoid long-term risks of genome integration by enabling transient, yet effective, cellular reprogramming (Li & Liu, 2022; Sahin et al., 2014). CRISPR and mRNA technologies are being explored for treating inherited diseases, cancer, and regenerating organs such as the liver, heart, and brain (Li & Liu, 2022; Sahin et al., 2014). The results of these studies could help governments and clinicians determine how gene therapy can be implemented more sustainably.

Bioprinting and Regenerative Implants

3D bioprinting is emerging as a revolutionary technique to fabricate tissue structures (Xiang et al., 2023). The possibilities of 3D bioprinting in gene therapy and regenerative medicine include:

- Gene-loaded bioinks for spatially controlled gene expression
- Living implants that release therapeutic genes post-transplant
- Regenerative patches for bone, skin, and cardiac tissues with embedded gene circuits (Mallya et al., 2025)

This approach may soon allow the construction of personalized, gene-active tissues and organs on demand. However, the ethical elements of 3D bioprinting could impede some researchers from advancing the use of the technologies further. This means governments,

practitioners, and researchers will need to consider the merits of implementing certain technologies while considering the greater good of patients (Saabani Sharifaghdam M. Faridi-Majidi R. De Smedt S. C. Braeckmans K. & Fraire J. C., 2022; Sahin Karikó K. & Türeci Ö., 2014; Salauddin Saha S. Hossain M. G. Okuda K. & Shimada M., 2024).

Toward Accessible and Ethical Therapies

For gene therapy to become a standard in regenerative care, it must be made:

- Affordable through scalable non-viral delivery systems and modular biomaterials
- Ethically grounded, ensuring equitable access and transparency in genetic interventions
- Globally regulated, with clear frameworks for safety, production, and distribution (PwC, 2024)

Japan is an example of a country that has invested heavily in the research and development of gene therapy (Pwc, 2024). Japan was partially motivated by the increasing average age of its native population (PwC, 2024). Motivators like this are likely to guide governments as they fund the research and set the regulations needed to make gene therapy more affordable to low-income patients and more transparent for individuals who are skeptical about the nature of gene therapy.

CONCLUSION

Gene therapy has emerged as a cornerstone of regenerative medicine, enabling precise delivery of therapeutic genes—via viral vectors, non-viral carriers (e.g., nanomaterials, biomaterial scaffolds), or hybrid systems (e.g., gene-activated scaffolds)—to stimulate tissue repair, correct genetic defects, or reprogram cells. While viral vectors offer high efficiency, their immunogenicity contrasts with the safer but less efficient non-viral alternatives, driving innovation in hybrid platforms that balance efficacy and safety. Advances in genome editing and mRNA technologies now allow not only gene supplementation but also precise corrections, with applications spanning bone, cartilage, cardiac, neural, and skin regeneration. Despite challenges in clinical translation (safety, manufacturing, regulatory hurdles), progress in synthetic biology and personalized medicine is bridging the gap between experimental and therapeutic use. Future research should prioritize *integrated systems* that synergize gene therapy, tissue engineering, and cell-based strategies, while addressing scalability, long-term safety, and ethical implications of these combinatorial approaches. Such efforts could unlock fully curative, patient-tailored regenerative solutions.

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