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Regulatory Challenges in The Approval of Cell and Gene Therapies: A Comprehensive Review of Current Advancements and Future Directions

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Abstract

Background: The evolution of gene therapy has faced numerous regulatory challenges since its inception, particularly regarding the approval processes for cell and gene therapies. The FDA's recent authorization of Tecartus, the first cell-based gene therapy, underscores the significant advancements in this field. Despite progress, concerns about vector safety and efficacy persist, particularly with viral vectors.

Methods: This review analyzes the current landscape of gene therapy, focusing on the use of non-viral vectors, including polymers, lipids, and inorganic materials. We examine the mechanisms of action, efficiency, and toxicity of various delivery systems. The review further discusses recent clinical trials and their implications for regulatory frameworks.

Results: Non-viral vectors, such as cationic polymers and lipid nanoparticles, have shown promise due to their reduced immunogenicity and cytotoxicity compared to traditional viral vectors. However, challenges remain in optimizing gene transfer efficiency and ensuring the long-term expression of therapeutic genes. Recent advancements in formulation strategies, including the use of biodegradable polymers and lipid-based nanoparticles, have improved transfection rates and reduced adverse effects.

Conclusion: The regulatory landscape for gene therapies is evolving, necessitating a balanced approach that addresses safety and efficacy while fostering innovation. Ongoing research into non-viral delivery systems is critical for overcoming existing obstacles and enhancing the therapeutic potential of gene therapies. A collaborative effort among regulators, researchers, and industry stakeholders is essential to create a conducive environment for the successful development and approval of these novel therapies.

Keywords: gene therapy, regulatory challenges, non-viral vectors, transfection efficiency, therapeutic delivery.

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1. Introduction

Twenty-twenty signifies a further milestone in the development of gene therapy. The FDA authorized Tecartus, the first cell-based gene therapy using a white blood cell enrichment stage, in July (1). The trajectory of gene therapy evolved from the first successful clinical study in 1990 to the unfortunate fatality at the University of Pennsylvania in 1999, which led to a decline in research. However, the field had a resurgence in 2017 with three FDA approvals within a single year. Currently, there are ten gene therapy drugs available in the U.S. market, with over 100 clinical studies actively enrolling patients on clinicaltrials.gov. The tumultuous history of gene therapy over the last three decades has generated several lessons and established a robust basis for the increased enthusiasm over the potential of gene delivery methods to address some of the most catastrophic illnesses. Although several recent clinical trials have used non-viral vectors, the majority continue to employ conventional viral vector systems, which are difficult to produce cost-effectively at a commercial scale (2, 3). A vector serves as a vehicle for transporting genetic material to its intended destination. It is crucial for the product's effectiveness and safety. The use of a viral vector has always been contentious. Despite the absence of evidence indicating that viral vectors damage patients, the little danger of eliciting immunogenic responses and the possibility for transgene mis-insertion have prompted many in the field to pursue non-viral delivery systems.

In recent years, the most extensively studied non-viral vectors include polymers, lipids, inorganic particles, or their mixtures (Figure 1). In contrast to viral vectors, non-viral vectors exhibit less cytotoxicity, immunogenicity, and mutagenesis, hence generating more interest from researchers to investigate this potential delivery mechanism and advance the science of gene therapy. Nonetheless, non-viral vectors exhibit suboptimal features and encounter significant obstacles, including gene transfer efficiency, specificity, duration of gene expression, and safety. Non-viral vectors have emerged as a rapidly advancing area of study in gene delivery. The paper examines current advancements in non-viral vector research and formulation factors. The difficulties and future prospects are also examined (4-6).

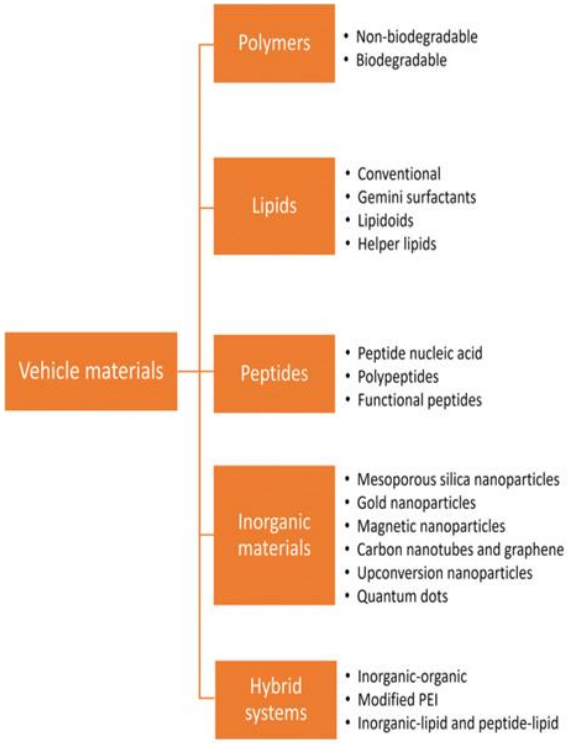

Figure 1. Vehicle substances.

2. Polymers

Gene therapy involves the introduction of genetic material into cells, transfection, and the regulation of gene expression. Cationic polymers are a crucial category of non-viral gene therapy vectors, attracting researchers for their adaptable chemical structure and promise for high loading capacity. They may neutralize the negatively charged genetic material to create a complex (polyplex) and deliver the payload to specific cells.

2.1. Non-biodegradable polymers

Polyethylenimine (PEI) was the first polycationic polymer, produced in both linear and branched configurations for gene therapy in 1995. The polymer chain has specially organized amine groups, allowing only partial protonation within the physiological pH range. In a more acidic region of the endosome, supplementary amine groups get protonated. The presence of charged PEI creates an osmotic action, known as the "proton sponge effect," which induces endosomal rupture and is thought to improve transfection efficiency. The increased buffer capacity of PEI facilitates the endosomal escape of the gene payload (7). Currently, PEI is regarded as the benchmark for assessing the transfection effectiveness of non-viral vectors (8).

Although regarded as a very effective non-viral transfection vector, PEI may nonetheless have limitations in specificity and transfection efficiency. Moreover, it is a non-biodegradable polymer that aggregates around the cell and induces cytotoxicity. In recent years, researchers have achieved considerable advancements in comprehending the mechanics behind such constraints. Clark et al. investigated the capacity of PEI to extricate itself from late endosomal vesicles during intracellular delivery, focusing on its interaction with endosomal lipids under osmotic stress, utilizing model systems comprising monolayers and vesicles derived from a blend of neutral and negatively charged lipids, specifically 1,2-dipalmitoylphosphatidylcholine (DPPC) and bis(monoacylglycerol)phosphate (BMP) (9). The findings validated the adsorption of PEI onto DPPC/BMP membranes, a crucial element for the endosomal escape of polyplexes. The model has introduced a novel instrument to examine the ensuing impacts of non-viral vectors on membrane stability and permeability.

Besides PEI, amine-terminated PAMAM constitutes another cationic dendrimer. PAMAM is one of the most used dendritic carriers in biological applications and the first employed for gene transfer. A significant drawback of these prevalent dendrimers is their toxicity, mostly linked to the chemistry of the surface amine groups. Moreover, polymethacrylates and polymethacrylamides represent two significant categories of synthetic vinyl-based cationic polymers that may replicate the pH sensitivity, proton sponge theory, and buffering characteristics of PEI (10). They have undergone continuous modifications over the last two decades to enhance gene transport efficiency and reduce toxicity (8, 11-13). Despite polymethacrylates exhibiting lower cytotoxicity than PEI, their utilization in gene therapy remains constrained owing to their diminished capacity for membrane interaction (5, 14).

Poly(vinylimidazole) (PVI) is a hydrophilic polymer produced as poly(1-vinylimidazole) and poly(4-vinylimidazole). The imidazole group becomes protonated at acidic pH levels, resulting in a conformational change of PVI chains. PVI has the attributes of biocompatibility, non-toxicity, and the capacity to evade the endosome via the activation of the proton sponge mechanism, making it a promising non-viral vector (15). Recent investigations have focused on alkylated poly(1-vinylimidazole) of varying chain lengths for the purposes of DNA complexation and transfection. Butylated PVI was identified as the most effective among them in HepG2 liver cancer cells. Additionally, a folic acid-conjugated amine-containing poly(1-vinylimidazole) was identified as an efficient agent for DNA complexation and transfection in cancer cells (16).

2.2. Biodegradable Polymers

Due to the frequent need for repeated delivery in gene therapy and the preference for reduced cytotoxicity, biodegradable polymeric vectors, whether synthetic or natural, provide a distinct advantage over non-biodegradable alternatives. Synthetic polymers have remarkable variety in chemical structure

and batch consistency; yet they may demonstrate inadequate interaction with cells (17). Conversely, natural polymers have good biocompatibility; yet they present issues of batch-to-batch variability owing to differences in origin. Therefore, to ensure product quality, it is essential to implement control measures for the critical properties of natural polymers. Excipient manufacturers may use mixing to fulfill excipient standards. Moreover, suitable tests and criteria are used to guarantee uniform quality and dependable performance. Gel permeation/size exclusion chromatography (GPC/SEC) may be used to assess the properties of polymers. A collaborative effort among pharmaceutical companies, excipient suppliers, the US Pharmacopeial Convention (USP), regulators, and the International Pharmaceutical Excipients Council (IPEC) is necessary to manage, mitigate, or minimize the potential adverse effects of excipient variability on natural excipients, including polymers (18).

Chitosan (CS) is a linear polysaccharide and one of the most prevalent natural carbohydrate polymers. It is exceptionally biodegradable, biocompatible, and non-toxic. Exhibiting an apparent pKa of 6.5, it is soluble only in acidic circumstances, whereby the majority of amino groups are protonated, facilitating the formation of a compound with genetic material. Chitosan with a high degree of polymerization (>50) was reported to significantly trigger the opening of tight junctions between cells (19). The surface of a chitosan carrier may be changed or adorned with ligands to improve cellular uptake and selectivity (20). These characteristics make chitosan an appealing non-viral vector for gene therapy. Recent studies focus on chitosan-coated nanoparticles as carriers for gene therapy in brain cancer, demonstrating increased particle uptake by human blood-brain barrier cerebral microvessel endothelial cells (hCMECs) via receptor-mediated endocytosis (21).

Poly(β-amino ester)s (PBAEs) are a category of developing non-viral vectors that have achieved considerable progress during the last two decades. The class was first designed as linear PBAEs in 2000, but switched to branching PBAEs in 2016 (22, 23). These amphiphilic polymers exhibit strong transfection capacities under difficult circumstances and possess effective endosomal escape qualities. Nonetheless, their use is constrained by the formation of self-assembled nucleic acid nanoparticles. Consequently, they are inadequate for encapsulating proteins with diverse surface charges. In 2019, Green et al. synthesized a novel hyperbranched PBAE with both cationic and anionic charges. The structural alteration has facilitated the differentiation of polymer end-group hydrophobicity, influenced protein complexation abilities, and enhanced nanoparticle internalization and endosomal escape (24). In that year, Liu et al. produced highly branched PBAE including biodegradable disulfide units within the HPAE backbone and guanidine moieties at the termini. The polymers facilitated the delivery of minicircle DNA to multipotent adipose-derived stem cells and astrocytes, resulting in elevated transfection efficiency (25).

Polylactide (PLA) is a synthetic biodegradable polymer often used in medication administration. Its carboxylic acid undergoes hydrolysis into lactic acid in vivo and swiftly transforms into glucose, which is excreted from the body without detrimental consequences. In 2013, Jones et al. developed a cationic polylactide including tertiary amines to enhance its applicability for gene therapy (26). Currently, PLA maintains sustained interest in targeted delivery by ongoing structural alterations (27, 28). The whole promise of polymer-based delivery technologies remains unfulfilled. In 2020, aminoglycosides, a category of naturally occurring and semi-synthetic antibiotics, were examined as novel cationic polymeric vectors to enhance gene transfer into cells (29).

3. Lipids

For an extended period, lipids have been used for gene delivery. Most lipids have positively charged headgroups that interact with the anionic phosphate groups of nucleic acids via electrostatic interactions to create lipoplexes. Owing to the self-assembling lipid tail structures, lipoplexes often manifest as liposomes, solid lipid nanoparticles, or lipid emulsions. In comparison to other carrier materials, lipids exhibit biodegradability, reduced toxicity, and the capacity to include both hydrophilic and hydrophobic molecules. The first FDA-approved small interfering ribonucleic acid (siRNA) therapy, Onpattro, using a lipid-based vector. Inclisiran, a potential lipid-based siRNA therapy for hyperlipidemia, received approval

in the EU in December 2020. Phase 3 clinical studies demonstrated that inclisiran reduced low-density lipoprotein cholesterol levels by 50% with subcutaneous treatment every six months (30-33).

Conventional lipids have a single head group per molecule, which may be either permanently or intermittently charged. The prevalent head groups include ammonium, imidazolium, pyridinium, lysine, and arginine, among others. Concurrently, the hydrophobic tails may consist of two saturated or unsaturated hydrocarbon chains or steroids (31). The capacity of hydrocarbon chain lipids to transport nucleic acids has been extensively investigated, particularly those including ammonium as head groups. Typical instances encompass monovalent lipids such as N-(1-(2,3-dioleyloxy)propyl)-N,N,N-trimethylammonium (DOTMA), 2,3-bis[[(Z)-octadec-9-enoyl]oxy]propyl-trimethylazanium (DOTAP), 2,3-di(tetradecoxy)propyl-(2-hydroxyethyl)-dimethylazanium (DMRIE), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), and 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), as well as multivalent lipids such as 2,5-bis(3-aminopropylamino)-N-[2-[di(heptadecyl)amino]-2-oxoethyl]pentanamide (DOGS). Although these lipids are prevalent as gene carriers owing to their positive charges, they are comparatively toxic and have suboptimal in vivo performance, such as a brief half-life.

Consequently, surface-modified ionizable lipids, including 1,2-dioleoyloxy-3-(dimethylamino)propane (DODAP) and 1,2-dilinoleyloxy-3-dimethylaminopropane (DLin-DMA), were engineered to address these deficiencies and enhance effectiveness. The materials exhibit neutrality at physiological pH, enabling systemic distribution, yet may acquire a positive charge to enhance lipoplex synthesis with DNA and aid endosomal escape. Heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (DLin-MC3-DMA) is recognized as the "gold standard" for siRNA delivery due to its exceptional gene silencing efficacy compared to alternatives and has been effectively utilized in Onpattro, the inaugural FDA-approved siRNA therapy [34]. Besides hydrocarbon chain lipids, cholesterol and its derivatives represent another class of lipids suitable for gene transfer. DC-Chol, a derivative, is currently commercially available and has been used in clinical studies for cancer gene therapy (35).

Gemini surfactants have recently emerged as a category of lipids advantageous for gene transfer. They are two surfactant monomers with head groups connected by a spacer group by covalent connections. Gemini surfactants often exhibit a lower critical micelle concentration (CMC) compared to their equivalent surfactant monomers, leading to reduced surface tension and enhanced solubilization capacity, among other effects. Consequently, the quantity of this carrier required in the delivery system is less, hence reducing its toxicity. Recent study has concentrated on elucidating the structure of gemini surfactants in relation to their bioactivity. Jin et al. examined three structurally similar gemini surfactants: 16-3-16, 16(Py)-S-2-S-16(Py), and 16-7N(G.K.)-16, all of which include an identical carbon tail length of 36. Research indicated that the glycyl-lysine dipeptide head group significantly enhanced the transfection efficacy of 16-7N(G.K.)-16 compared to both the unsubstituted 16-3-16 and the pyridinium derivative 16(Py)-S-2-S-16(Py) (36).

Lipidoids are lipid-like substances produced by the conjugation of amines with lipophilic acrylates, acrylamides, or epoxides (37). Lipidoids have gained appeal owing to their synthesis procedure, which is devoid of solvents and catalysts. This rapid and straightforward synthesis facilitates the evaluation of a vast library of lipidoids with varied architectures. In early 2008, Aknic et al. produced more than 1200 lipidoids and shown successful gene transfer and expression in mice, rats, and nonhuman primates (38). Molla et al. have synthesized 13 lipidoids with a one-pot synthetic approach based on thiolactone chemistry. The materials were engineered into liposomes for the delivery of siRNA and evaluated on HeLa-GFP cells. Five formulations exhibited greater knock-down effectiveness compared to commercial reagents, highlighting the significance of lipidoid structure for transfection efficacy and the characteristics of liposome formulations, including particle size (39). These results may provide a basis for future investigations of lipidoids in gene delivery.

Lipid-based gene delivery techniques often use "helper lipids" to augment transfection effectiveness, stabilize particles, or promote intracellular trafficking (40, 41). Unlike cationic and ionizable lipids, helper lipids are neutral substances. 1,2-Dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE) is a widely used

helper lipid, characterized by its conical molecular structure, which facilitates membrane fusion and/or bilayer rupture. Moreover, cholesterol functions as an auxiliary lipid by augmenting cell membrane fluidity and stabilizing bilayer lipids in liposome formulations, therefore enhancing effectiveness and stability (40). Sasayama et al. used cholesterol to create a nanoparticle formulation, LNPK15, derived from 1,2-distearoyl-sn-glycero-3-phosphatidylethanolamine-N-(poly-ethyleneglycol-2000). This formulation had prolonged half-lives in mice and monkeys of 15.2 hours and 27.0 hours, respectively, and also shown significant knock-down efficacy (42).

4. Peptides

Peptides are short sequences of 2 to 50 amino acid residues connected by peptide bonds. They possess biocompatibility and biodegradability, and may be systematically engineered to function as foundational components for self-assembling nanoscale architectures (43). The genetic material combines with peptides by conjugation or electrostatic interactions to produce peptiplexes, hence enhancing delivery. Peptide nucleic acid (PNA) conjugates consist of peptide and nucleic acid components connected by covalent bonds. They are stable, uncharged molecules that can withstand nuclease destruction and exhibit reduced susceptibility to acidic and basic pH levels, as well as elevated temperatures. Altrichter and Seitz have developed an antisense module using peptide nucleic acids that include a Smac mimetic molecule (SMC) (44). The SMC-PNA achieved virtually full downregulation of the cellular FLICE-like protein by the incorporation of cell-penetrating peptides.

Polypeptides constitute a significant category of peptides used for gene delivery, such as poly(L-lysine) (PLL), poly(L-arginine) (PLR), and poly(L-glutamate) (PGA). The most prevalent PLL has a high charge density in its side chains, facilitating efficient DNA condensation. The efficient internalization of PLL/plasmid DNA (pDNA) complexes via endocytosis has been shown, with an approximate size of 100 nm (45). Nonetheless, its inadequate transfection efficiency and inefficient endosomal release have limited its use. PLL has been altered with many functional groups, such PEI or palmitic acid, to enhance effectiveness. It has been amalgamated with other peptides to enhance endosomal escape efficacy. Zhang et al. synthesized the PLL/DNA polyplex using a glutamic acid–modified peptide (AR-23), facilitating endosomal escape and augmenting lytic activity (46).

Polypeptides may be engineered into dendrimers, using amino acids as fundamental components in the core, branches, surface, or any combination of these three elements. Peptide dendrimers may provide the requisite cationic groups to interact with genetic material, enhance the probability of traversing the cellular membrane, and possess the buffering capacity essential for endosomal escape. A PLL dendrimer may have a flexible branching dendrimer architecture with lysine as its core component (47). Recent research has broadened the selection of amino acids from lysine to arginine or other alternatives, enhancing the advantages of the PLL dendrimer as a gene delivery vector. These initiatives have altered the flexibility and charge distribution of the dendrimer, enhancing interactions with nucleic acids and augmenting cellular absorption (48). Dendrimer systems may potentially integrate lipids or polymers to provide enhanced effectiveness. Transfection was shown to be improved by including a polyol into the lipid/dendrimer hybrid or a polymer excipient, such as Polyvinylalcohol 18 (PVA 18) (49, 50).

Alongside polypeptides, some functional peptides have been synthesized. These peptides have specific sequences in their structure, yielding advantages such as improved cell penetration or targeting. Cell-penetrating peptides (CPP) are diminutive peptides that readily traverse cell membranes and enable the movement of genetic material. The trans-Activator of Transcription (TAT) protein, a frequently used cell-penetrating peptide (CPP), was recently assessed on solid tumors using multicellular tumor spheroids as biological models. Higher TAT doses considerably enhanced peptide absorption (51). Alongside TAT, penetratin, GALA, transportan, and their derivatives, including PepFect and NickFect, have garnered interest for their cell penetrating capabilities (52). Certain peptides may selectively target certain cells by binding to surface receptors, leading to improved efficacy and less toxicity. Numerous targeting peptides have been identified or produced, including the RGD peptide and transferrin (Tf). Supplementary Tf receptor-binding peptides, such the T7 peptide, are garnering attention to enhance targeting efficacy. Gu et

al. used T7-modified polypeptide nanoparticles, CRD-PEG-T7, to transport the plasmid DNA pPMEPA1 for the treatment of bone metastatic prostate cancer. The integration of T7 suppressed tumor proliferation and prolonged the survival duration of tumor-bearing animals (53).

5. Inorganic Substances

Inorganic materials have greater stability than organic materials and have been used as gene carriers. The first documented non-viral gene delivery used calcium phosphate in the 1960s (54). Currently, the most often cited inorganic carriers are silica-based systems, including mesoporous silica nanoparticles, gold nanoparticles, magnetic nanoparticles, carbon nanotubes, graphene, upconversion nanoparticles, and quantum dots (55). Gold nanoparticles have comparatively low toxicity and may be synthesized using polymeric and lipid carriers. Liu et al. developed a gold nanoparticle composite for the therapy of Parkinson's disease, in which pDNA was adsorbed onto the surface of positively charged gold nanoparticles and enclosed inside liposomes, then conjugated with targeted NGF and DHA. This approach demonstrated substantial neuroprotective benefits in mice by enhancing both motor and non-motor functions (56). Carbon nanotubes serve as an appealing carrier, consisting of one or more graphene sheets that vary in size from hundreds of nanometers to tens of microns. Carbon nanotubes enable gene entry through the cell membrane without relying on the endocytosis mechanism of mammalian cells. Utilizing molecular dynamics modeling, Liang et al. discovered that carbon nanotubes facilitated nucleotide penetration across a lipid membrane by reducing the free energy of the process. In 2020, a single-walled carbon nanotube conjugated with siRNA targeting Caspase3 was created for the treatment of cardiovascular disorders. This gene vector markedly enhanced transfection effectiveness, leading to increased silence of the Caspase3 gene (57).

6. Obstacles And Opportunities

Gene therapy has achieved significant advancements in recent years, focusing on particular cell populations across several therapeutic domains. The mechanistic difficulties of administering gene therapy using a non-viral vector have been thoroughly examined by Yin and Anderson et al. in 2014 (58). A non-viral vector must possess the ability to safeguard genetic material against endonuclease destruction, facilitate transport to the nucleus, ensure nuclear absorption, and enable vector unpacking, frequently necessitating a tailored system. The delivery methods must be tailored to various mechanisms of action for treatment modalities. The delivery of DNA into the nucleus is essential for its therapeutic efficiency; hence, the comparatively larger particle size presents an additional obstacle to effectiveness. RNA does not need entry into the cell nucleus for expression, yet it exhibits lower stability than DNA. Moreover, the interaction between the cell and vector differs across various modalities, significantly influencing transfection efficiency. A universal technique for selecting a non-viral vector delivery technology has not proven practical yet.

All three recently FDA-approved or emergency-use authorized gene delivery products utilizing lipid nanoparticles as vectors have developed distinct lipid systems, despite both Moderna and Pfizer/BioNTech providing mRNA vaccines aimed at COVID-19 prevention. Furthermore, the vector systems may be quite complex. The Pfizer/BioNTech vaccine utilized a combination of four lipids: an ionizable cationic lipid for encapsulating the negatively charged mRNA, a PEGylated lipid for regulating particle size, distearoylphosphatidylcholine (DSPC) as a phospholipid, and cholesterol to aid in the formation of the lipid nanoparticle structure (59). The intricate nature of vector formulations necessitates substantial effort to identify an effective vector. During the development of patsiran, a siRNA medication, over 300 ionizable lipids were required to be tested. Recently, GuidTx has created a high-throughput technique to evaluate lipid nanoparticle systems, which may enhance the efficiency of choosing non-viral vectors for gene delivery with more accuracy (60).

7. Conclusion

The landscape of gene therapy is marked by both significant advancements and formidable challenges. The transition from initial enthusiasm to cautious optimism reflects the complex interplay between

scientific innovation and regulatory oversight. As the field matures, it is imperative to refine the regulatory frameworks that govern the approval of gene therapies. This refinement must account for the unique characteristics of non-viral vectors, which offer promising alternatives to traditional viral delivery systems.

Despite the progress made, issues related to gene transfer efficiency, specificity, and safety remain pertinent. Non-viral vectors, such as cationic polymers and lipid nanoparticles, have demonstrated reduced toxicity and immunogenicity, yet their ability to achieve optimal gene expression levels is still hindered by various biological barriers. Therefore, ongoing research is crucial to enhance the performance of these delivery systems and ensure their clinical applicability.

Moreover, fostering collaboration among academic institutions, industry stakeholders, and regulatory bodies is essential to expedite the translation of research findings into clinical practice. By sharing knowledge and resources, these entities can work together to establish standardized testing protocols and guidelines that prioritize patient safety while encouraging innovation.

In conclusion, as we advance into a new era of gene therapy, there is a pressing need to strike a balance between regulatory scrutiny and the facilitation of scientific progress. The potential of gene therapies to address previously untreatable conditions is immense, but realizing this potential requires a comprehensive understanding of the underlying mechanisms, robust delivery systems, and a collaborative regulatory approach that embraces change while prioritizing safety and efficacy. Embracing these principles will be pivotal in shaping the future of gene therapy and ensuring its successful integration into mainstream medical practice.

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التحديات التنظيمية في اعتماد علاجات الخلايا والجينات: مراجعة شاملة للتطورات الحالية والتوجهات المستقبلية

الملخص

الخلفية :واجه تطور العلاج الجيني العديد من التحديات التنظيمية منذ نشأته، خاصةً فيما يتعلق بعمليات اعتماد علاجات الخلايا والجينات. يمثل ترخيص إدارة الغذاء والدواء الأمريكية (FDA) لعقار *Tecartus*، أول علاج جيني قائم على الخلايا، تقدمًا كبيرًا في هذا المجال. ومع ذلك، ما زالت هناك مخاوف مستمرة بشأن سلامة وكفاءة الناقلات، خاصةً الفيروسية منها.

الطرق :تحلل هذه المراجعة المشهد الحالي للعلاج الجيني مع التركيز على استخدام الناقلات غير الفيروسية، بما في ذلك البوليمرات والدهون والمواد غير العضوية. نستعرض آليات العمل، الكفاءة، والسمية لأنظمة التوصيل المختلفة. كما تناقش المراجعة التجارب السريرية الحديثة وآثارها على الأطر التنظيمية.

النتائج :أظهرت الناقلات غير الفيروسية، مثل البوليمرات الكاتيونية وجزيئات النانو الدهنية، وعودًا كبيرة نظرًا لانخفاض تأثيرها المناعي والسمية الخلوية مقارنةً بالناقلات الفيروسية التقليدية. ومع ذلك، ما زالت التحديات قائمة لتحسين كفاءة نقل الجينات وضمان التعبير طويل الأمد للجينات العلاجية. أسهمت التطورات الحديثة في استراتيجيات الصياغة، مثل استخدام البوليمرات القابلة للتحلل وجزيئات النانو الدهنية، في تحسين معدلات النقل وتقليل الآثار السلبية.

الخاتمة :يشهد الإطار التنظيمي للعلاجات الجينية تطورًا مستمرًا، مما يستلزم نهجًا متوازنًا يعالج قضايا السلامة والكفاءة مع تعزيز الابتكار. يعد البحث المستمر في أنظمة التوصيل غير الفيروسية أمرًا بالغ الأهمية للتغلب على العقبات الحالية وتعزيز الإمكانات العلاجية للعلاجات الجينية. يتطلب النجاح في تطوير واعتماد هذه العلاجات الحديثة تعاونًا وثيقًا بين الجهات التنظيمية والباحثين وأصحاب المصلحة في الصناعة.

الكلمات المفتاحية :العلاج الجيني، التحديات التنظيمية، الناقلات غير الفيروسية، كفاءة النقل، التوصيل العلاجي.