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Gene Transfecting Reagent using for Cancer Therapy

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Abstract: *Gene transfecting reagents have emerged as essential tools in the progress of cancer gene therapy, enabling efficient and safe transfer of therapeutic genes into target cells. Since cancer is a multifactorial genetic disorder, gene therapy provides a promising alternative to conventional chemotherapy and radiotherapy by allowing correction of defective genes, silencing of oncogenes, or reactivation of tumour-suppressor genes. The success of these therapeutic strategies depends on the choice of transfection reagents that ensure high delivery efficiency, biocompatibility, and minimal cytotoxicity. Gene delivery systems are broadly categorized into viral and non-viral vectors. Although viral vectors exhibit high transfection efficiency, their use is limited by immunogenicity, insertional mutagenesis, and complex manufacturing processes. Non-viral vectors such as cationic lipids, polymers, dendrimers, peptides, and inorganic nanoparticles have gained attention for their safety, ease of modification, and cost-effectiveness. These systems facilitate gene transfer through electrostatic interactions, endocytosis, and membrane fusion. Recent advances in nanotechnology, hybrid systems, and stimuli-responsive materials hold great promise for next-generation transfection reagents, enhancing targeting precision and therapeutic efficacy in personalized cancer therapy.*

Keywords: Gene transfection, cancer gene therapy, viral vectors, non-viral vectors, cationic lipids

I. INTRODUCTION

Cancer remains one of the leading causes of death worldwide, accounting for nearly 10 million deaths annually according to the World Health Organization (WHO, 2022). It is characterized by abnormal cell growth driven by genetic and epigenetic alterations that disrupt normal cellular signalling, proliferation, and apoptosis.[1] Although traditional treatment methods like surgery, chemotherapy, and radiation therapy have considerably improved patient outcomes, their systemic toxicity and nonspecific action frequently lead to modest effectiveness and serious adverse consequences. As a result, there has been a greater need for innovative treatment approaches that can selectively target cancer cells while minimizing damage to healthy tissues. In modern oncology, gene therapy has become a ground breaking strategy because it allows us to treat faulty genetic data and regulate gene expression at the molecular level. It entails introducing, altering, or silencing genetic material inside a patient's cells to achieve therapeutic results.[2] In cancer treatment, gene therapy can be employed to restore tumour suppressor genes, inhibit oncogenes, induce apoptosis, enhance immune recognition, or sensitize tumours to chemotherapy and radiotherapy.[3] The success of these therapeutic interventions, however, relies heavily on the efficiency, specificity, and safety of the gene delivery system employed. The process of delivering genetic material into target cells is termed transfection, and the reagents or carriers facilitating this process are known as gene transfecting reagents. These reagents ensure that nucleic acids such as DNA, RNA, siRNA, or CRISPR constructs are successfully transported across the cell membrane and released into the cytoplasm or nucleus, where they can exert their therapeutic function.[4] Broadly, gene delivery systems are classified into viral and non-viral vectors. Viral vectors, including adenoviruses, lentiviruses, and adeno-associated viruses, are highly efficient due to their natural ability to infect host cells and integrate genetic material. Nevertheless, their clinical use is limited by immunogenicity, insertional mutagenesis, and complex production processes [5] In contrast, non-viral transfection reagents have attracted growing interest owing to their improved safety, lower cost, and

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potential for large-scale synthesis. These include cationic lipids, polymers, peptides, dendrimers, and inorganic nanoparticles, which form complexes with negatively charged nucleic acids to facilitate cellular uptake [6] The mechanisms underlying non-viral gene delivery involve electrostatic interactions, endocytosis, membrane fusion, and endosomal escape. Despite continuous progress, major challenges persist, such as limited transfection efficiency, cytotoxicity, poor tissue specificity, and rapid clearance by the reticuloendothelial system [7] Recent advances in nanotechnology and biomaterials engineering have revolutionized the design of gene transfecting reagents. Novel hybrid systems combining lipids, polymers, and nanoparticles have demonstrated enhanced stability, targeted delivery, and controlled gene release [8] Moreover, the integration of stimuli- responsive carriers and ligand-modified nanocarriers has enabled tumour-specific targeting, reducing off-target effects and improving therapeutic efficacy. [9]

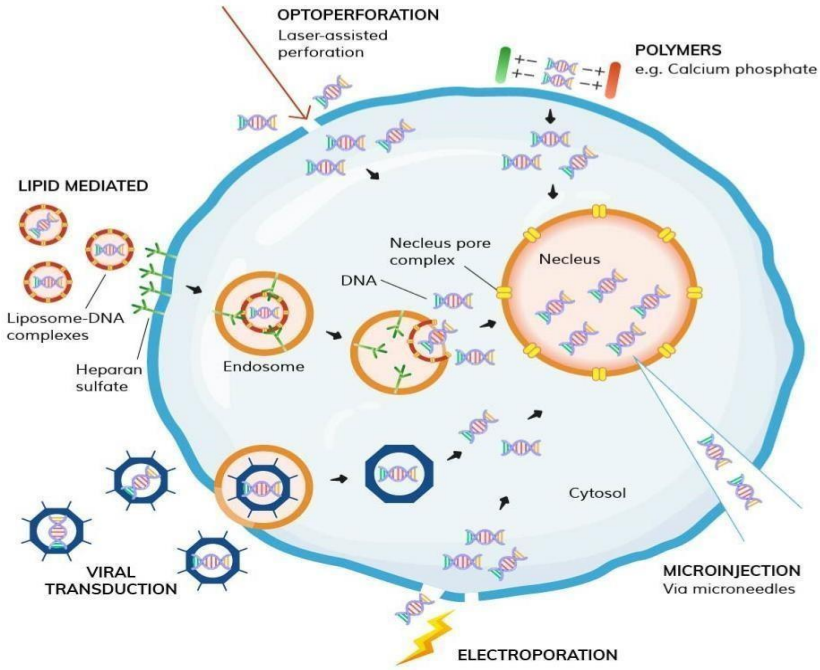

Fig. No. 1 Transfection

Types of gene transfecting reagents

The success of gene therapy relies heavily on the development of efficient and biocompatible gene transfecting reagents capable of transporting therapeutic nucleic acids across cellular membranes and delivering them to their intended intracellular targets. These reagents are broadly divided into viral and non-viral systems, each characterized by specific mechanisms, transfection efficiencies, and safety profiles. [10]

1. Viral Gene Transfecting Reagents

Viral vectors utilize the natural infection pathways of viruses to introduce exogenous genetic material into host cells. Their structural proteins are modified to remove pathogenic genes while retaining the ability to efficiently enter cells and express therapeutic sequences [11]

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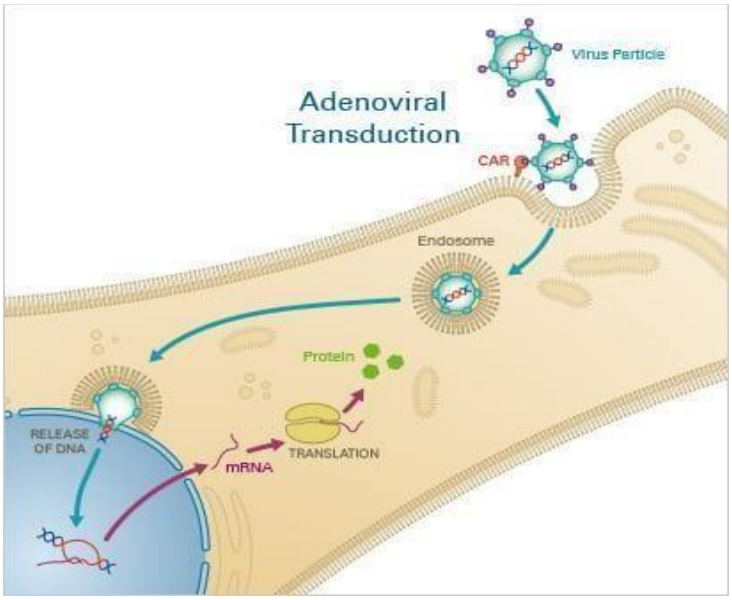

Fig. No. 2 Viral transfection

1.1 Adenoviral Vectors

Adenoviruses are double-stranded DNA viruses that do not integrate into the host genome, allowing transient but robust gene expression. Their large packaging capacity (up to 36 kb) makes them suitable for delivering larger genes. However, they often trigger strong immune responses and inflammation, limiting repeated administration. [12]

1.2 Retroviral and Lentiviral Vectors

Retroviruses integrate their genetic material into the host cell genome, resulting in stable and long-term expression. Lentiviruses, a subclass of retroviruses, can transduce both dividing and non-dividing cells, making them highly useful for cancer gene therapy and immunotherapy applications. Nevertheless, the risk of insertional mutagenesis and the difficulty of large-scale production restrict their clinical application. [13]

1.3 Adeno-Associated Virus (AAV) Vectors

AAVs are small, non-pathogenic viruses that provide long-lasting gene expression with minimal immune reactions. Their inability to replicate independently and low toxicity make them one of the safest viral vectors. However, their small packaging capacity (≈4.7 kb) limits the size of genes that can be delivered. [14]

1.4 Herpes Simplex Virus (HSV) Vectors

HSV vectors are neurotropic, enabling targeted gene transfer to the nervous system. They can accommodate large transgenes but pose safety concerns due to latent infection and reactivation risks. [15]

II. NON-VIRAL GENE TRANSFECTING REAGENTS

Non-viral systems have gained prominence as safer, more versatile options for gene delivery. They are composed of synthetic or naturally derived materials that interact electrostatically with negatively charged nucleic acids to form complexes known as lipoplexes, polyplexes, or nanoplexes, facilitating cellular entry. [16]

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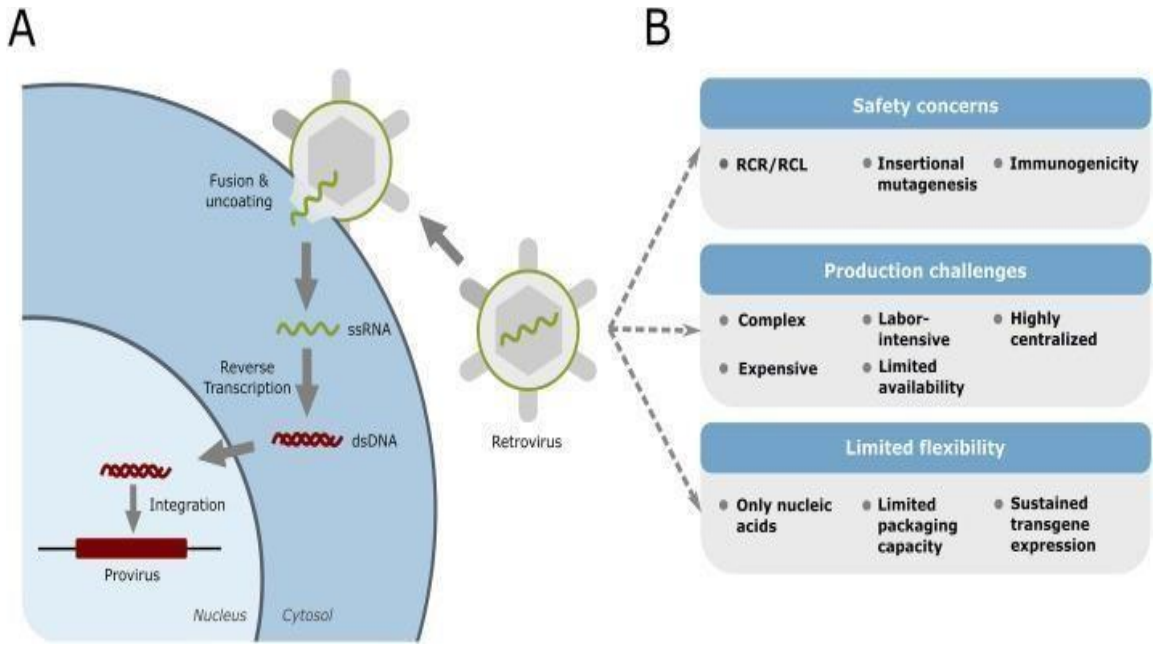

Fig. No. 3 Non-viral Gene transfection

2.1 Lipid-Based Transfection Reagents

Cationic lipids were among the first non-viral carriers developed for gene therapy. They form self-assembled vesicles, or liposomes, that encapsulate nucleic acids and fuse with cell membranes. Common examples include DOTMA, DOTAP, and DC-Chol derivatives. These systems offer relatively high transfection efficiency, low immunogenicity, and ease of production.[17]

Commercial lipid formulations such as Lipofectamine™ and Oligofectamine™ are widely used for in vitro and in vivo applications. However, lipid-based systems often suffer from instability in serum, potential aggregation, and limited endosomal escape. Recent progress in ionizable lipids and lipid nanoparticles (LNPs) has significantly enhanced mRNA and siRNA delivery for cancer therapy and vaccine development

2.2 Polymer-Based Transfection Reagents

Polymers offer structural flexibility and chemical tunability, making them a major focus of current non-viral research. Polyethyleneimine (PEI) is a widely used polymer with high transfection efficiency due to its proton-sponge effect, which facilitates endosomal escape.[19] However, its high cationic charge density can induce cytotoxicity. To mitigate this, biodegradable or low-molecular-weight PEI derivatives and natural polymers such as chitosan, poly-L-lysine (PLL), and dextran are employed. These materials exhibit improved biocompatibility and are capable of sustained gene release.

Dendrimers, another polymeric class with branched architectures, offer precise control over molecular size and surface functionality. Polyamidoamine (PAMAM) dendrimers, for instance, have shown promising gene delivery results when conjugated with targeting ligands and polyethylene glycol (PEG) to enhance solubility and reduce toxicity.[20]

2.3 Peptide-Based Delivery Systems

Short peptides known as cell-penetrating peptides (CPPs) can traverse cellular membranes without causing significant membrane disruption. Peptides such as TAT, penetratin, and transportan are often linked to nucleic acids or

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nanoparticles to improve intracellular uptake[21] . Their low immunogenicity and tunable functionality make them attractive for cancer-targeted delivery, although their stability in biological fluids remains a limitation.

2.4 Inorganic and Hybrid Nanoparticle Systems

Inorganic materials such as gold nanoparticles (AuNPs), silica nanoparticles, magnetic nanoparticles, and calcium phosphate have been extensively explored as gene carriers due to their structural stability and ability to co-deliver drugs and nucleic acids. Their surfaces can be functionalized with polymers, peptides, or antibodies to achieve active tumor targeting [22]. Recent hybrid systems that integrate lipid, polymer, and inorganic components have shown enhanced stability, gene protection, and targeted delivery efficiency. Stimuli-responsive nanocarriers that release their cargo in response to pH, enzymes, or redox gradients within the tumor microenvironment represent the forefront of modern gene delivery research [23].

III. COMPARATIVE INSIGHTS AND FUTURE PERSPECTIVES

While viral vectors remain the gold standard for gene transfer due to their efficiency, their biosafety concerns have shifted focus toward non-viral and hybrid systems. Advances in material science and nanotechnology are enabling non-viral reagents to bridge the gap in efficiency while retaining superior safety and scalability. Future trends involve combining targeting ligands, CRISPR/Cas systems, and imaging functionalities within single transfection platforms, paving the way for personalized and precision-based cancer gene therapy[24].

Mechanism of Action of Gene Transfecting Reagents

Effective gene transfection hinges on the delivery of therapeutic nucleic acids such as DNA, mRNA, siRNA or gene-editing systems into target cancer cells in a way that maintains the integrity of the cargo and enables its biological function. The transfection process can be broken down into several key stages: from cellular uptake, endosomal escape, cytoplasmic transport and degradation avoidance, to eventual nuclear localization and gene expression [25].

1. Cellular Entry and Internalization

The first critical barrier is crossing the cell membrane. Gene–carrier complexes (lipoplexes/polyplexes/nanoparticles) often bear a positive charge that promotes binding to the negatively charged surface of cells (proteoglycans, phospholipids). Once adhered, the complexes are internalized by endocytic mechanisms commonly via clathrin-mediated, caveolin-dependent pathways or micropinocytosis depending on parameters such as size, charge and surface modifications [26].

2. Endosomal Escape

Following internalization, many carriers are sequestered in endosomes, which mature into lysosomes containing degradative enzymes and acidic milieu that can destroy nucleic acids. Hence, an efficient transfecting reagent must trigger escape from the endosome before cargo degradation. Polymer-based carriers exploit the “proton sponge” effect (buffers causing osmotic swelling and membrane rupture), while certain lipids undergo pH-induced destabilization of the endosomal membrane to release their load [27].

3. Cytoplasmic Trafficking & Protection

Once freed into the cytosol, the nucleic acid cargo faces a crowded and hostile environment (nucleases, proteases, cytoskeletal barriers). To counter this, carriers often incorporate stealth features (e.g., PEGylation, shielding groups) or targeting ligands to guide the complexes and prolong their residence time in the cytoplasm [28]. For mRNA and siRNA payloads, cytoplasmic localization suffices for translation or silencing; for plasmid DNA, further transport is required.

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4. Nuclear Translocation (for DNA Vectors)

If therapeutic DNA is to be transcribed, it must reach the nucleus. In dividing cells, this can occur during mitosis when the nuclear envelope briefly disappears; in non-dividing cells, nuclear localization requires carriers fitted with nuclear targeting signals or peptides that mimic cellular transport motifs [29]. Without this nuclear entry, gene expression remains inefficient.

5. Degradation, Clearance & Release

In systemic in vivo administration, gene–carrier complexes are subject to clearance (renal filtration, reticuloendothelial uptake), immune recognition, or premature release of the cargo. To avoid this, carriers are surface-modified (e.g., with PEG, albumin, or hyaluronic acid) or made stimuli-responsive so that release occurs selectively in the tumor microenvironment (e.g., low pH, redox imbalance) [23].

6. Gene Expression & Therapeutic Outcome

Finally, once internalized and localized appropriately, the nucleic acids perform their intended function:
Plasmid DNA is transcribed into mRNA, which is then translated into therapeutic proteins. mRNA can bypass the transcription step and directly engage translation. siRNA/shRNA trigger RNA interference, knocking down specific gene expression. CRISPR/Cas systems edit genomic sequences to inactivate oncogenes or restore tumor- suppressor genes. These interventions ultimately aim to induce apoptosis, inhibit proliferation, or modulate immune response in tumors [22].

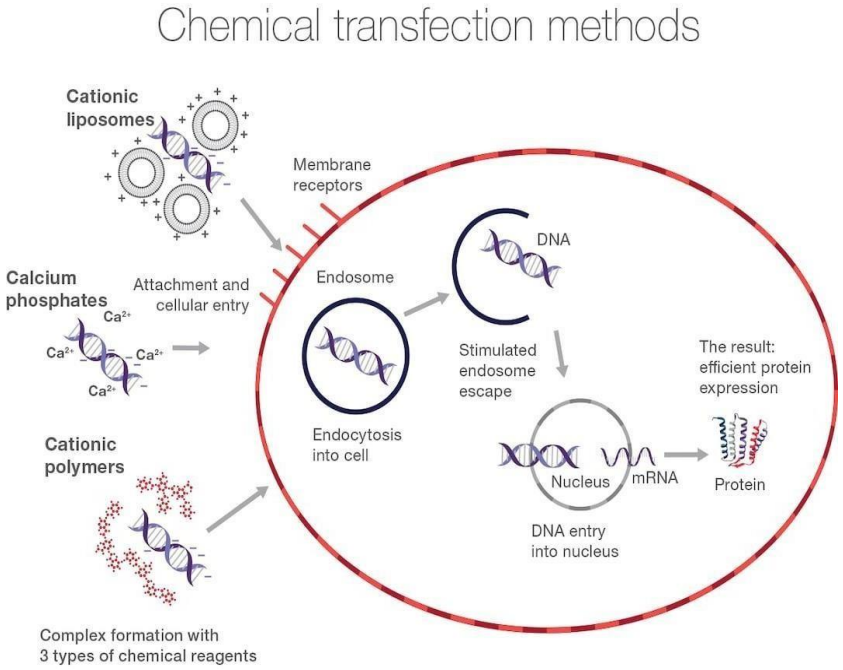

Fig. No. 4 Mechanism of Action of Gene Transfecting Reagents Applications of Gene Transfecting Reagents in Cancer Therapy

Gene transfection technology has transformed cancer research and therapeutic strategies by enabling targeted genetic modification of tumor cells. Through precise delivery of therapeutic genes, gene transfecting reagents have made it possible to regulate oncogenic signaling, stimulate immune responses, and restore normal cellular functions. These applications can be broadly categorized into tumor suppressor gene replacement, oncogene silencing, suicide gene therapy, immunomodulation, and gene-directed enzyme prodrug therapy [30].

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1. Tumor Suppressor Gene Replacement

Loss or inactivation of tumor suppressor genes such as p53, RB1, and PTEN is a hallmark of many cancers. Gene transfecting reagents facilitate the reintroduction of these genes into malignant cells, reinstating apoptosis and cell-cycle control. Lipid-based and polymeric vectors have been successfully used to deliver p53 DNA constructs in breast and lung cancer models, significantly reducing tumor growth [31]. Recent developments in nanoparticlemediated gene transfer have improved nuclear localization and enhanced transgene stability, contributing to superior therapeutic outcomes [32].

2. Oncogene Silencing and RNA Interference

Another promising approach involves silencing overexpressed oncogenes using RNA interference (RNAi). Transfecting reagents capable of delivering small interfering RNA (siRNA) or short hairpin RNA (shRNA) can suppress oncogenic drivers such as KRAS, BCL-2, or MYC, leading to inhibited tumor proliferation [33]. Polymer-based systems such as polyethyleneimine (PEI) and dendrimers have shown remarkable efficiency in siRNA delivery. Their structural flexibility allows conjugation with ligands like folate or transferrin to achieve tumor-specific targeting, thereby minimizing off-target gene silencing [34].

3. Suicide Gene Therapy

In this therapeutic strategy, transfecting reagents are used to deliver genes that encode enzymes capable of converting non-toxic prodrugs into cytotoxic metabolites selectively within tumor tissues. A classical example is the Herpes Simplex Virus Thymidine Kinase (HSV-TK) gene, which converts ganciclovir into a toxic nucleotide analog that kills dividing cancer cells [35]. Both viral and non-viral vectors have been employed in clinical studies targeting gliomas, pancreatic cancer, and hepatocellular carcinoma. The combination of suicide gene therapy with chemotherapeutic agents enhances tumor cell death while reducing systemic toxicity [36].

4. Immunomodulatory Gene Therapy

Gene transfecting reagents are also applied to modulate the immune system against tumors.

Delivery of cytokine genes such as IL-2, IL-12, GM-CSF, or IFN-γ can potentiate immune cell activation and infiltration into tumors [37]. Lipid nanoparticles (LNPs) and polymeric nanocarriers have been widely used to deliver mRNA vaccines that encode tumor-associated antigens, effectively promoting antigen-specific T-cell responses. This approach has gained significant attention following the success of mRNA-based immunotherapies in melanoma and lung cancer [38].

5. Gene-Directed Enzyme Prodrug Therapy (GDEPT)

GDEPT involves introducing genes that encode enzymes capable of activating a subsequently administered prodrug at the tumor site. Commonly used systems include cytosine deaminase (CD)/5-fluorocytosine and nitroreductase/CB1954, which have been delivered using polymeric nanoparticles and cationic liposomes [38]. These systems offer localized cytotoxicity, sparing normal tissues while enhancing tumor regression. Recent designs integrate tumor-targeting ligands and stimuli-responsive components to maximize selectivity [39]

6. Combination Therapy and Co-Delivery Systems

Modern gene transfection research emphasizes combination strategies, where gene reagents co-deliver nucleic acids along with chemotherapeutic or immunotherapeutic drugs. For instance, lipid–polymer hybrid nanoparticles co-delivering p53 plasmid DNA and doxorubicin have demonstrated synergistic effects in breast and colon cancers [41]. Similarly, CRISPR/Cas9 systems integrated with non-viral carriers have enabled precise genome editing in oncogenic pathways while concurrently improving sensitivity to radiotherapy [42]. Such hybrid systems not only enhance efficacy but also help overcome multidrug resistance.

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VII. FUTURE PROSPECTS AND CLINICAL IMPLICATIONS

Despite remarkable preclinical progress, clinical translation of gene transfection-based cancer therapies still faces challenges such as low in vivo stability, limited biodistribution, and potential immune activation. However, continuous advancements in biomaterial engineering, tumor microenvironment-responsive nanocarriers, and personalized gene therapy are expected to redefine cancer treatment paradigms. Emerging trends focus on integrating artificial intelligence and bioinformatics for designing tailored gene delivery systems that optimize dose, vector type, and targeting precision [43].

Challenges and Future Perspectives of Gene Transfection in Cancer Therapy

Despite the tremendous progress achieved in the field of gene therapy, several critical challenges continue to impede its full translation into clinical success. The efficiency of gene transfecting reagents largely depends on achieving a delicate balance between transfection efficacy, biocompatibility, and target specificity. Addressing the limitations associated with safety, delivery, and gene expression remains essential for the advancement of cancer gene therapy [44].

1. Biological and Physiological Barriers

The human body presents several biological hurdles that restrict the success of gene transfection. After systemic administration, gene–carrier complexes are often neutralized by serum proteins, cleared by the reticuloendothelial system, or filtered by the kidneys, which drastically reduce their bioavailability [45]. Furthermore, the tumor microenvironment (TME), characterized by abnormal vasculature, hypoxia, and dense extracellular matrices, limits nanoparticle penetration and gene diffusion. Therefore, designing transfecting reagents that can navigate these barriers and achieve tumor-specific accumulation is a primary focus in ongoing research [46]

2. Cytotoxicity and Immunogenicity

Most cationic lipids and polymers, though efficient, exhibit dose-dependent cytotoxicity due to their positive charge, which disrupts cellular membranes and induces oxidative stress [37]. Additionally, repeated administration of viral or non-viral vectors may trigger immune responses, leading to inflammation or clearance of the therapeutic gene. To mitigate these issues, researchers are developing biodegradable carriers and ionizable lipids that maintain transfection efficiency while minimizing toxicity and immunogenicity [47]. Surface modification using hydrophilic polymers such as polyethylene glycol (PEG) also enhances circulation time and reduces immune detection.

3. Limited Targeting and Transfection Efficiency

Achieving precise tumor targeting remains another challenge. Conventional delivery systems often exhibit non-specific uptake, causing off-target effects and low therapeutic gene expression at the tumor site. The incorporation of ligand-based targeting moieties, such as antibodies, peptides, aptamers, and folate receptors, has emerged as a promising approach to enhance cell-specific recognition [48]. Moreover, advanced stimuli-responsive nanocarriers, which release genes in response to pH, temperature, redox potential, or enzymatic activity, have been developed to achieve controlled intracellular delivery [49].

4. Gene Stability and Controlled Expression

The stability of genetic material during delivery is another major concern. Nucleic acids are prone to degradation by nucleases and hydrolysis in physiological conditions. Although encapsulation within liposomes or polymers provides protection, maintaining long-term and regulated expression of the therapeutic gene remains difficult [50]. Integrating self-amplifying mRNA, promoter engineering, or epigenetic control mechanisms into transfecting systems could provide sustained and tunable gene expression, especially for chronic cancer conditions.

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5. Manufacturing and scale-up limitations

The clinical application of gene transfecting reagents also faces production challenges. Many complex nanocarriers require multi-step synthesis, specialized purification, and strict quality control to ensure reproducibility and stability. These factors significantly increase manufacturing costs and hinder large-scale commercialization [51]. Simplifying the synthesis process and adopting green nanotechnology or microfluidic-based manufacturing platforms could accelerate clinical translation.

6. Ethical and Regulatory Concerns

The emergence of genome-editing technologies such as CRISPR/Cas9 and TALENs has raised ethical debates surrounding the alteration of human DNA. Concerns regarding germline editing, off-target effects, and long-term genetic consequences remain under regulatory scrutiny [52]. International guidelines are being updated to ensure that gene therapy remains safe, ethical, and strictly therapeutic, particularly when dealing with hereditary cancer syndromes.

7. Future Perspectives

Future advances in gene transfection will rely on multidisciplinary integration of nanotechnology, molecular biology, and computational modeling. Innovations such as AI- assisted vector design, machine learning-based optimization, and 3D tumor modeling are being used to predict optimal carrier properties and therapeutic outcomes [53]. Combining gene therapy with immunotherapy, radiation, and chemotherapy is also anticipated to yield synergistic effects, enhancing overall cancer treatment efficacy.

VIII. CONCLUSION

Recent advancements in gene-transfecting reagents for cancer therapy have led to the development of highly efficient, biocompatible, and targeted delivery systems that overcome many limitations of conventional methods. Modern non-viral carriers, particularly polymeric and lipid-based systems, offer enhanced transfection efficiency with reduced toxicity and improved tumor specificity. By integrating targeting ligands and stimuli-responsive components, these reagents ensure selective gene delivery to cancer cells while minimizing off-target effects. Such innovations not only enable precise modulation of oncogenic pathways but also open new possibilities for personalized and effective cancer treatments. Continued research and optimization of these systems will be vital for translating laboratory success into reliable clinical outcomes.

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