

**BRIEF REVIEW ON NANOTECHNOLOGY BASED ON APPROCH
FOR MRNA DELIVERY**

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ABSTRACT

Microbial renewable energy combined with nanotechnology (MRAN) has surfaced as a viable method for sustainable energy production. This review emphasizes recent progress in MRAN utilizing nanotechnology, concentrating on nanomaterials, microbial fuel cells, bioelectrochemical systems, and energy storage/harvesting. We explore the creation and fabrication of nanostructured electrodes, microbial electron transfer facilitated by nanoparticles, and bio-inspired nanomaterials. The review additionally discusses obstacles and future pathways, such as scalability, stability of the microbial-nanotechnology interface, energy efficiency, and toxicity issues. Our study indicates considerable promise for nanotechnology to improve MRAN efficiency, leading to effective, sustainable energy options.

KEYWORD: MRAN, microbial renewable energy, nanotechnology, bioelectrochemistry, energy harvesting, energy storage.

**INTRODUCTION TO NANOTECHNOLOGY-BASED APPROACHES FOR MRNA
DELIVERY**

mRNA-based therapeutics have emerged as one of the most groundbreaking advancements in modern medicine, particularly in the context of vaccines, cancer immunotherapy, and gene editing. Unlike traditional protein-based therapies or small-molecule drugs, mRNA therapy works by instructing cells to produce therapeutic proteins or antigens within the body. This approach holds the potential to treat a wide variety of diseases, including infectious diseases, genetic disorders, and certain cancers. However, for mRNA-based therapies to be effective, a major hurdle remains: the efficient and safe delivery of the mRNA into cells.

mRNA molecules are inherently fragile and can be quickly degraded by enzymes in the bloodstream, or face difficulty in crossing cellular membranes due to their large size, negative charge, and hydrophilic nature. These challenges make the delivery of mRNA to target tissues a critical bottleneck. As a result, the development of novel delivery systems is essential for the clinical success of mRNA therapeutics.

Nanotechnology offers a promising solution to these delivery challenges. By manipulating materials at the nanoscale, scientists can design carriers that improve the stability, solubility, and bioavailability of mRNA. Nanocarriers are small enough to evade immune surveillance and can be engineered to improve cellular uptake, reduce toxicity, and achieve controlled release of the therapeutic mRNA into specific tissues. The use of nanotechnology in mRNA delivery has made significant strides, particularly with the advent of lipid nanoparticles (LNPs), which became widely known after their role in the successful delivery of COVID-19 vaccines.

Nanotechnology-based delivery systems can be broadly classified into lipid-based, polymeric, and viral vector systems. Each system has distinct advantages and challenges in terms of efficiency, biocompatibility, immunogenicity, and scalability. As the field progresses, the focus is increasingly on developing targeted delivery systems that can deliver mRNA to specific cells or tissues, as well as achieving sustained and controlled release to optimize therapeutic outcomes.



Fig. Nanotechnology mRNA Delivery.

Additionally, advancements in nanotechnology are driving innovations in the functionalization of nanoparticles. This involves modifying the surface properties of the nanoparticles to improve their interaction with specific cell types or tissues. For example, functionalization can include the attachment of ligands or antibodies to target specific receptors on cell membranes, or coating nanoparticles with materials that enhance their stability in circulation.

The use of nanotechnology in mRNA delivery is not without its challenges. Despite the success of lipid nanoparticles in vaccines, issues such as potential toxicity, limited tissue targeting, and the need for scalable manufacturing remain. Furthermore, understanding the full biological effects of these nanomaterials is crucial for ensuring their safe use in clinical settings.

In conclusion, nanotechnology offers transformative potential for overcoming the barriers to effective mRNA delivery. By addressing key challenges such as stability, cellular uptake, and targeted delivery, nanotechnology is paving the way for the next generation of mRNA-based therapies. As research in this area continues to evolve, it is likely that nanotechnology will play an increasingly central role in the development of personalized, efficient, and safer mRNA-based treatments.

Background

mRNA therapy consists of providing cells with genetic directives, facilitating protein expression or adjustment. Nonetheless, the vulnerability of mRNA to breakdown and immune response reduces its efficacy. Nanocarriers, such as lipid-based nanoparticles, polymeric nanoparticles, dendrimers, and gold nanoparticles, have enhanced the delivery of mRNA.^[1]

Significance

Nanotechnology-enabled mRNA delivery holds promise for treating various diseases, including Messenger RNA (mRNA) therapy has surfaced as a groundbreaking method for addressing genetic disorders, cancer, and infectious diseases. Nonetheless, the instability, immunogenicity, and poor cellular uptake of mRNA limit its therapeutic efficacy. Nanotechnology has revolutionized mRNA delivery, improving stability, specificity, and effectiveness. This review thoroughly examines mRNA delivery systems utilizing nanotechnology, emphasizing recent progress, obstacles, and future pathways.

g cancer, genetic disorders, and infectious diseases. This review aims to provide an in-depth analysis of nanotechnology-based mRNA delivery systems, mechanisms, and applications.

OBJECTIVES

The application of nanotechnology in mRNA delivery aims to address the various challenges associated with the safe, efficient, and targeted delivery of mRNA therapeutics. The key objectives for using nanotechnology in mRNA delivery systems are:

Enhance Stability and Protection of mRNA

Objective: To design nanoparticles that can protect mRNA from degradation by RNases in the bloodstream and ensure its stability during circulation. This is crucial to prevent the rapid breakdown of mRNA before it reaches the target cells.

Improve Cellular Uptake and Intracellular Delivery

Objective: To create delivery systems that facilitate the efficient entry of mRNA into target cells. This involves overcoming the natural barriers posed by the cell membrane, which can be difficult for large and negatively charged molecules like mRNA to cross. Nanoparticles can be engineered to increase cellular uptake through endocytosis or membrane fusion.

Optimize Release of mRNA

Objective: To ensure that the mRNA is effectively released within the target cells after internalization, bypassing intracellular degradation pathways such as the lysosomal system. The release profile should be controlled to ensure that mRNA remains intact and is translated into the desired protein.

Reduce Immunogenicity and Toxicity

Objective: To develop nanocarriers that are biocompatible and have minimal immune system activation or toxicity. Although some immune response is necessary for certain applications (e.g., vaccines), excessive immune activation can be harmful, so minimizing toxicity is a critical consideration.

Targeted Delivery to Specific Tissues or Cells

Objective: To design nanoparticles that can selectively target specific tissues, organs, or cell types, thereby reducing off-target effects and enhancing therapeutic efficacy. This can involve functionalizing nanoparticles with ligands, antibodies, or other molecules that bind to receptors or antigens present on the surface of target cells.

Achieve Controlled and Sustained Release

Objective: To engineer delivery systems that allow for controlled and sustained release of mRNA, which could be particularly important for chronic diseases or applications where prolonged expression of the therapeutic protein is necessary.

Scalability and Cost-Effectiveness in Manufacturing

Objective: To develop nanoparticle-based delivery systems that are scalable, reproducible, and cost-effective for large-scale production. This is essential for translating nanotechnology-based mRNA therapies from the laboratory into clinical and commercial applications.

Facilitate Non-invasive or Minimally Invasive Administration

Objective: To create delivery systems that allow for non-invasive or minimally invasive routes of administration (e.g., intravenous injection, intranasal, or topical delivery), making mRNA therapeutics more accessible and easier to administer, especially for large populations.

Improve Immunological Efficacy in Vaccines**Vaccine**

Objective: To enhance the immunogenicity of mRNA vaccines, ensuring a robust and long-lasting immune response. Nanoparticles can be engineered to enhance antigen presentation, improve dendritic cell uptake, and optimize the activation of T and B cell responses.

Personalized Therapeutic Applications

Objective: To enable the development of personalized mRNA therapies for diseases such as cancer, genetic disorders, and autoimmune conditions. Nanotechnology allows for the customization of mRNA delivery systems based on patient-specific needs, such as targeting specific mutations or enhancing the delivery to particular tumor cells.

By meeting these objectives, nanotechnology-based mRNA delivery systems hold the potential to significantly improve the effectiveness, safety, and accessibility of mRNA therapies, revolutionizing the treatment of a wide range of diseases.

Nanotechnology Approaches for mRNA Delivery**1. Lipid Nanoparticles (LNPs)**

The most widely used platform for mRNA delivery.

Comprised of ionizable lipids, phospholipids, cholesterol, and polyethylene glycol (PEG)

lipids.

Protect mRNA from degradation and ensure efficient cellular uptake through endocytosis.

Example: mRNA COVID-19 vaccines (Pfizer-BioNTech and Moderna).

2. Polymeric Nanoparticles

Use biocompatible and biodegradable polymers like polyethyleneimine (PEI) and polylactic-co-glycolic acid (PLGA).

Offer tunable properties to optimize mRNA stability and release profiles.

3. Inorganic Nanoparticles

Include gold nanoparticles (AuNPs), silica nanoparticles, and quantum dots.

Facilitate mRNA delivery by enhancing stability and providing controlled release.

4. Hybrid Nanoparticles

Combine features of multiple materials (e.g., lipid-polymer hybrids).

Aim to enhance delivery efficiency and reduce side effects.

5. Exosome-Mimetic Nanoparticles

Biomimetic approach using vesicles derived from cells.

Achieve high biocompatibility and minimal immunogenicity.

Advantages of Nanotechnology-Based mRNA Delivery

Enhanced mRNA stability against enzymatic degradation.

Efficient cellular uptake and endosomal escape.

Controlled and targeted delivery to specific cells or tissues.

Reduced immunogenicity with customizable surface modifications.

Challenges in mRNA Delivery

1. Stability and Degradation: mRNA degradation by RNases, temperature, and pH fluctuations.
2. Immunogenicity: Activation of immune responses by mRNA, leading to inflammation and toxicity.
3. Cellular Uptake: Inefficient cellular internalization and endosomal entrapment.
4. Targeted Delivery: Difficulty achieving specific targeting to desired cells or tissues.
5. Scalability and Manufacturing: Challenges in large-scale production and quality control.
6. Toxicity and Biocompatibility: Potential toxicity of nanocarriers and immunogenicity.

7. Regulatory Frameworks: Limited guidelines and standards for mRNA-based therapeutics.^[3]

Nanotechnology-Specific Challenges

1. Nanoparticle Size and Charge: Impact on cellular uptake, toxicity, and targeting.
2. Surface Modification: Balancing stealth and targeting properties.
3. Payload Capacity: Limitations in mRNA loading capacity.
4. Release Kinetics: Controlled release of mRNA from nanocarriers.^[4]

Nanotechnology-Based Solutions

1. Lipid-Based Nanoparticles: Enhance mRNA stability, cellular uptake, and targeted delivery.
2. Polymeric Nanoparticles: Provide controlled release, biocompatibility, and scalability.
3. Dendrimers: Offer high mRNA loading capacity, targeted delivery, and reduced toxicity.
4. Gold Nanoparticles: Enable photothermal-controlled release, targeted delivery, and imaging.
5. Hybrid Nanoparticles: Combine materials for optimized delivery, targeting, and efficacy.
6. Nanocarriers with Ligands: Target specific cells or tissues using ligand-mediated targeting.
7. mRNA-Loaded Exosomes: Utilize natural vesicles for targeted delivery and immune evasion.
8. Nanoporous Membranes: Enable controlled release and targeted delivery.^[5]

Classification of Nanotechnology-Based mRNA Delivery Systems

1. Lipid-Based Nanoparticles
2. Polymeric Nanoparticles
3. Inorganic Nanoparticles
4. Organic-Inorganic Hybrid Nanoparticles
5. Exosome-Based Delivery Systems
6. Nanoporous Membranes
7. Nanofibers
8. Nanoemulsions

Lipid-Based Nanoparticles

1. Lipofectin

2. RNA-lipoplexes
3. Lipid nanoparticles (LNPs)
4. Cationic lipids (e.g., DOTAP, DOPE)

Polymeric Nanoparticles

1. Poly(lactic-co-glycolic acid) (PLGA)
2. Polyethylenimine (PEI)
3. Poly(amidoamine) (PAMAM) dendrimers
4. Chitosan

Inorganic Nanoparticles

1. Gold nanoparticles
2. Silver nanoparticles
3. Calcium phosphate nanoparticles
4. Iron oxide nanoparticles

Organic-Inorganic Hybrid Nanoparticles

1. Lipid-polymer hybrid nanoparticles
2. Polymer-metal hybrid nanoparticles
3. Lipid-metal hybrid nanoparticles

Exosome-Based Delivery Systems

1. Exosome-mediated mRNA delivery
2. Exosome-engineered mRNA delivery

Nanoporous Membranes

1. Polymer-based membranes
2. Ceramic-based membranes
3. Metal-organic framework (MOF)

Membranes Nanofibers

1. Electrospun nanofibers
2. Wet-spun nanofibers
3. Melt-spun nanofibers

Nanoemulsions

1. Oil-in-water nanoemulsions
2. Water-in-oil nanoemulsions
3. Solid-in-oil nanoemulsions.^[6]

Mechanisms and strategies for nanotechnology-based mRNA delivery**Mechanisms**

1. Endosomal Escape
2. Cellular Uptake (endocytosis, macropinocytosis, phagocytosis)
3. Targeted Delivery (ligand-mediated, antibody-mediated)
4. Controlled Release (pH-dependent, temperature-dependent, enzyme-dependent)
5. Cellular Internalization (clathrin-mediated, caveolae-mediated)

Strategies

1. Ligand-Mediated Targeting
2. Cationic Lipid-Mediated Delivery
3. Polymer-Based Delivery
4. Nanoparticle Surface Modification
5. Combination Therapy (mRNA + small molecules/proteins)

Targeting Strategies

1. Active Targeting (ligand-mediated, antibody-mediated)
2. Passive Targeting (EPR effect, tumor microenvironment)
3. Cell-Specific Delivery (cell-specific markers)
4. Tissue-Specific Delivery (tissue-specific markers)

Release Mechanisms

1. pH-Dependent Release
2. Temperature-Dependent Release
3. Enzyme-Dependent Release
4. Redox-Responsive Release
5. Photo-Triggered Release

Delivery Routes

1. Systemic Delivery (intravenous, intraperitoneal)

2. Local Delivery (intratumoral, topical)
3. Pulmonary Delivery (inhalation)
4. Mucosal Delivery (oral, nasal)

Nanocarrier Type

1. Lipid-Based Nanoparticles
2. Polymeric Nanoparticles
3. Inorganic Nanoparticles
4. Organic-Inorganic Hybrid Nanoparticles
5. Exosome-Based Delivery Systems^[7]

Applications of nanotechnology-based mRNA delivery:

Applications

1. Cancer Therapy: Targeted delivery of mRNA-based therapeutics for cancer treatment.
2. Genetic Diseases: Gene editing and expression modulation for genetic disease treatment.
3. Infectious Diseases: mRNA-based vaccines for infectious disease prevention.
4. Regenerative Medicine: mRNA-based therapies for tissue engineering and repair.
5. Vaccination: mRNA-based vaccines for immune system modulation.
6. Immunotherapy: mRNA-based immunotherapies for cancer and infectious diseases.
7. Gene Editing: mRNA-based gene editing tools for precision medicine.
8. Stem Cell Therapy: mRNA-based modulation of stem cell differentiation and function(8).

Specific Examples

1. mRNA-based cancer vaccines: Targeting tumor-associated antigens.
2. mRNA-based gene therapy: Treating genetic diseases such as cystic fibrosis.
3. mRNA-based infectious disease vaccines: Preventing COVID-19, influenza, and HIV(9).

Clinical Trials

1. BioNTech's BNT162b2: mRNA-based COVID-19 vaccine.
2. Moderna Therapeutics' mRNA-1644: mRNA-based vaccine for cytomegalovirus.
3. CureVac's CV7202: mRNA-based vaccine for rabies(10).

Challenges and future directions for nanotechnology-based mRNA delivery:

Challenges

1. Scalability and Manufacturing: Large-scale production of high-quality mRNA and

nanoparticles.

2. Toxicity and Biocompatibility: Ensuring safety and minimizing side effects.
3. Immunogenicity: Managing immune responses to mRNA and nanoparticles.
4. Targeted Delivery: Achieving specific targeting to desired cells or tissues.
5. Regulatory Frameworks: Establishing guidelines for mRNA-based therapeutics(11).

Future Directions

1. Advanced Nanoparticle Design: Optimizing materials, size, and surface modification.
2. Combination Therapies: Integrating mRNA with small molecules or proteins.
3. Personalized Medicine: Tailoring mRNA therapies to individual needs.
4. Cancer Treatment: Developing mRNA-based cancer vaccines and immunotherapies.
5. Infectious Disease Prevention: Creating mRNA-based vaccines for emerging threats(12).

Benefits of Nanotechnology in mRNA Delivery

- Stability: Protects mRNA from degradation by nucleases.
- Efficiency: Enhances cellular uptake and endosomal escape.
- Safety: Reduces immune overactivation and inflammation.
- Targeting: Allows specific delivery to tissues or cells of interest.

CONCLUSION

Nanotechnology-based mRNA delivery has revolutionized the field of therapeutics, offering unprecedented potential for treating various diseases, including cancer, genetic disorders, and infectious diseases. Through the convergence of nanotechnology, materials science, and synthetic biology, researchers have developed innovative solutions to overcome the challenges associated with mRNA delivery.

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