Advances in Immune Engineering Biomaterials for Precision Immunotherapy

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***Abstract*—Immune engineering biomaterials, based on immunology and materials science, have enhanced the efficacy of immunotherapy by precisely regulating the immune microenvironment and targeted delivery of immunotherapy drugs. In recent years, research on immune engineering biomaterials has been increasing sharply to develop more effective immunotherapy tools. This article provides a critical review of previous literature, with a particular focus on the roles of nanoparticles, hydrogels, and organic polymer biomaterials in therapeutic cancer vaccines, Chimeric Antigen Receptor (CAR)-T cell therapy, and other immunotherapies. Furthermore, it analyzes the current challenges in clinical translation and prospects the future development directions of this field, aiming to provide critical insights for the advancement of precise immunotherapy. This review clarifies the basic natures, delivery mechanisms, and translational advantages of immune engineering biomaterials, and identifies essential breakthroughs in improving targeting efficiency.**

***Keywords*—immune engineering, biology material, nanoparticle, hydrogel, organic polymer**

I. Introduction

Immunological engineering represents a rapidly evolving interdisciplinary field that combines immunology, biomaterials science, and nanotechnology to manipulate immune responses for disease treatment, vaccination, and tissue repair. Clinical applications of cancer immunotherapy, Chimeric Antigen Receptor (CAR)-T cell treatment, and mRNA therapies have shown great promise in recent years. However, their translation is severely hindered by critical challenges, including insufficient cargo stability, poor targeted delivery, off-target accumulation, uncontrolled release, and limited biocompatibility. Conventional delivery systems fail to overcome biological barriers and achieve precise immune regulation, creating an urgent demand for advanced biomaterial-based platforms.

Nanoscale delivery systems have become ideal candidates to address these limitations. Lipid Nanoparticles (LNPs), as the most clinically successful carriers for mRNA vaccines, still face bottlenecks like liver tropism and insufficient stability. New methods like thermostable LNPs and bispecific antibody-mediated pre-targeting make it possible to deliver nanoparticles to specific cells without changing their properties. This opens up new therapeutic uses beyond the liver. Peptide nanoparticles and gold nanoparticles offer excellent biocompatibility, high loading efficiency, and precise targeting ability, making them powerful tools for immune modulation and antigen delivery. Besides, functional hydrogels, biodegradable polymers and nanocomposites integrated with 3D printing and stimuli-responsive design provide personalized release systems for cancer therapy, bone regeneration and immune microenvironment remodeling. The materials enhance CAR-T therapy by improving tumor infiltration, reducing T-cell exhaustion, and reducing off-target toxicity.

This review summarizes recent advances in biomaterials and nano delivery systems for immunological engineering, emphasizing their design principles, working mechanisms, and translational potential. It aims to accelerate the development of next-generation vaccines, cancer immunotherapies, and precision medicine.

II. Biomaterial

Nanoparticles are versatile vectors in immunological engineering, enabling precise regulation of cargo release and immune cell interactions.

A. Nanoparticle

LNPs have become the most critical delivery system for mRNA vaccines and gene therapies, revolutionizing infectious disease prevention and genetic medicine. LNPs typically consist of four core components: Ionizable lipids, 1,2-Distearoyl-Sn-glycero-3-Phosphocholine (DSPC), cholesterol, and PEGylated lipids, which collectively enable nucleic acid encapsulation, cellular uptake, and endosomal escape [1]. The LNP can encapsulate many nucleic acid cargo types, including but not limited to DNA, Antisense Oligonucleotide (ASO), siRNA, microRNA, and mRNA, as shown in Fig. 1.

In conventional LNPs, Ionizable lipids with an optimal apparent pKa of 6.2–6.5 which enables efficient nucleic acid encapsulation at acidic pH and mediate endosomal escape via charge reversal. This represents the core of

Manuscript received July 13, 2026; accepted August 7, 2026; published August 17, 2026.

LNP potency. PEG-lipids control particle size, prevent aggregation, and extend circulation, while fast-dissociating PEG-lipids support liver targeting through apoE adsorption. DSPC and cholesterol enhance structural stability, membrane rigidity, and formulation integrity.

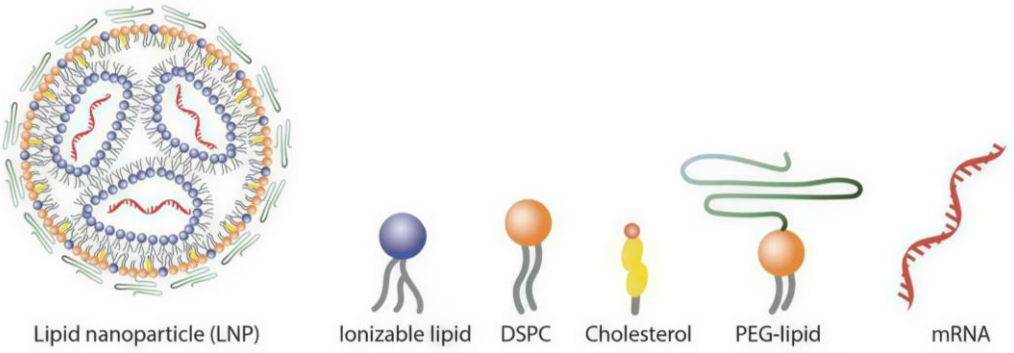

Fig. 1. Simplistic illustration of LNP and its individual components [1].

A novel cationic lipid nanoparticle, DMKD-PS, offers a breakthrough solution to the stability limitations of conventional mRNA vaccines. Unlike commercial LNPs (e.g., ALC-0315, SM-102) that require −80°C storage, DMKD-PS maintains structural integrity and protects mRNA from RNase degradation for up to 16 weeks at 4°C. The optimized formulation (DMKD:Cholesterol:DSPE-PEG2000-amine:PS = 48:40:4:2 mol%, N/P = 3:1) forms uniform 100–200 nm bilayer vesicles with high mRNA binding efficiency. In vitro studies demonstrate superior GFP mRNA expression in both RAW 264.7 macrophages and CT26 cancer cells compared to commercial LNPs. DMKD-PS addresses these issues by integrating Phosphatidylserine (PS), which acts as a signal to boost uptake by APCs such as macrophages, strengthening immune activation. This design combines exceptional storage stability, high transfection efficiency, and favorable biosafety. DMKD-PS represents a promising next-generation LNP platform for mRNA vaccines, particularly for cancer immunotherapies and infectious disease vaccines [2].

Peptide nanoparticles emerge as highly biocompatible and target-specific carriers in immunological engineering, owing to their structural versatility, low immunogenicity, and precise molecular recognition. Peptide-based nanocarriers can be constructed via physical encapsulation, chemical conjugation, or self-assembly, forming micelles, nanofibers, hydrogels, or hybrid nanoparticles that protect immunomodulatory peptides, antigens, and nucleic acids from rapid degradation. Peptide sequences can be rationally designed to target immune cell receptors or tumor-associated antigens, enabling active targeting to immune tissues and enhancing uptake by dendritic cells, T cells, or macrophages. They also support stimuli-responsive release under pathological microenvironments, including acidic pH, allowing spatiotemporally controlled cargo delivery to regulate immune activation or suppression. With excellent biodegradability and low toxicity, peptide nanoparticles are ideal for fine-tuning immune cell interactions, making them promising for cancer immunotherapy, infectious disease vaccines, and inflammatory disorder treatment [3].

Gold Nanoparticles (AuNPs) represent a class of robust inorganic metal nanocarriers with exceptional potential in immunological engineering, distinguished by high biocompatibility, large surface area, and facile surface functionalization. AuNPs can be stably modified with PEG, thiol, or amino groups to electrostatically bind or covalently conjugate immunogenic peptides, miRNAs, antigens, and immunomodulators, forming uniform nanocomplexes with high loading efficiency. Their tunable size (10–50 nm) supports efficient cellular uptake and passive accumulation in target tissues via the Enhanced Permeability and Retention (EPR) effect, while surface functionalization enables precise interaction with immune cells. In immunomodulation, AuNPs act as safe and efficient delivery vehicles for tumor-suppressive miRNAs to regulate immune-related gene expression, enhance apoptosis of cancer cells, and inhibit abnormal proliferation, indirectly reshaping the tumor immune microenvironment. Gold nanoparticles are effective tools for controlling immune cell behavior, enhancing antigen presentation, and creating precision immunotherapies because they have low intrinsic cytotoxicity, strong stability in biological fluids, and sustained cargo release [4].

B. Hydrogel

Hydrogels are widely used in biomedicine due to their excellent biocompatibility and biodegradability, yet conventional hydrogel systems face critical limitations, including burst release, poor encapsulation of hydrophobic drugs, proteins, and nucleic acids, and limited tunability for controlled drug release. Integrating nanocarriers, 3D printing, and immune-modulating design has become a promising strategy to overcome these challenges and achieve precision therapy and effective tissue regeneration.

Nanocarrier-hydrogel composites greatly improve drug loading versatility and release controllability. Liposomes, micelles, dendrimers, polymeric nanoparticles, and nanotubes enable stable encapsulation of diverse

therapeutics and sustained release profiles. These nanocomposites also exhibit stimuli-responsive behaviors (temperature, pH, redox, glucose) and enhanced mechanical strength. Combined with 3D printing—including extrusion and vat-polymerization techniques—these hydrogels can be fabricated into patient-specific geometries with precisely controlled drug release kinetics, showing great potential in cancer therapy, wound healing, and tissue engineering [5]. Fig. 2 shows the construction approach and superiority of the hydrogel-nanocarrier composite 3D printed drug delivery system.

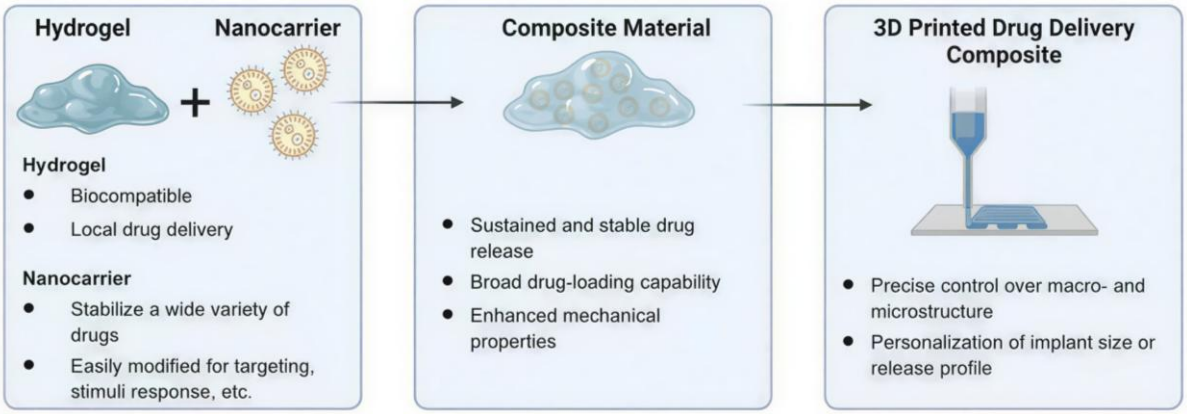

Fig. 2. Graphical abstract of nanocarrier-hydrogel composite materials [5].

In bone regeneration, immune-responsive hierarchical hydrogels address inflammation-induced mitochondrial dysfunction in Bone Marrow Mesenchymal Stem Cells (BMSCs). A Schiff-base crosslinked hydrogel based on chitosan and oxidized hyaluronate integrates dimethyl itaconate and macrophage-targeting zwitterionic nanogels. By promoting M2 macrophage polarization and enhancing intercellular mitochondrial transfer via Miro1 overexpression, this system reshapes the immune microenvironment and restores BMSC energy metabolism and osteogenic differentiation. Such injectable, self-healing hydrogels significantly accelerate critical-size bone defect repair in vivo [6].

C. Organic Polymer

Polymers offer modular design for immunological engineering, with customizable chemistry to optimize biocompatibility, cargo binding, and immune modulation. Cationic polymers including Poly (ethyleneimine) (PEI) and Poly (β-amino esters) (PBAEs) condense anionic nucleic acids via electrostatic interactions and facilitate endosomal escape through the proton sponge effect. However, PEI cytotoxicity has driven modifications including PEGylation, disulfide crosslinking, and hydrophobic conjugation to improve safety. PBAEs, with biodegradable ester linkages, enable effective systemic mRNA delivery to the spleen and lungs for cancer immunotherapy.

Natural polymers such as chitosan, protamine, and poly (amino acids) provide inherent biocompatibility and biodegradability. Chitosan forms polyplexes with nucleic acids and can be modified for enhanced stability and targeting. Protamine condenses mRNA into stable complexes and stimulates immune responses, supporting thermostable vaccine formulations. Synthetic Poly(lactic-co-glycolic acid) (PLGA) is widely used due to its FDA—approved status, tunable degradation, and sustained release of antigens and adjuvants. Block copolymers such as PEG-poly(l-lysine) self-assemble into micelles that protect cargo and enable targeted delivery via surface functionalization [7].

III. Application

A. Vaccine

The success of mRNA vaccines in combating the epidemic has significantly increased their popularity, making them a developmental platform for the application of biomaterials in immunological engineering. Most mRNA vaccines are LNP-mRNA vaccines.

LNPs typically consist of ionizable lipids, phospholipids, cholesterol, and PEG lipids. Ionizable lipids improve endosomal escape and reduce toxicity; helper lipids such as DOPE enhance membrane fusion; cholesterol stabilizes particles; and PEG lipids extend circulation but may trigger anti-PEG IgM and accelerated blood clearance. LNP size, charge, and surface functionalization strongly influence immunogenicity, biodistribution, and cellular uptake.

LNP-mRNA interacts extensively with the innate and adaptive immune systems. They activate neutrophils, macrophages, and dendritic cells via pattern recognition receptors (TLR3/7/8, RLRs, NLRs), inducing cytokine secretion and adaptive immune responses. Meanwhile, complement activation may cause pseudoallergy. Nucleoside- modified mRNA reduces innate immune recognition and improves protein expression.

Pharmacologically, LNPs protect mRNA from degradation and improve cellular delivery. Administration routes strongly affect biodistribution, with intramuscular and subcutaneous injection being most common for

vaccines. LNP-mRNA vaccines have shown promise in preclinical and clinical studies against infectious diseases such as HIV, influenza, Zika, and RSV [8].

B. CAR-T Cell Therapy

Biomaterials address key limitations in CAR-T therapy, including poor tumor infiltration, T cell exhaustion, and off-target toxicity. Hydrogel carriers provide a protective microenvironment for in situ CAR-T delivery, enhancing persistence and proliferation. GelMA hydrogels incorporating IL-2, IL-7, and IL-15 improve antitumor activity in melanoma models, while chitosan-PEG hydrogels deliver GD2-specific CAR-T cells for retinoblastoma.

Nanoparticles modulate the immunosuppressive TME and improve targeting. LNPs carrying PI3K inhibitors and α-GalCer redirect CAR-T cells to tumors and reverse immune suppression. Antibody-conjugated gold nanoparticles enhance CAR-T homing to tumor vasculature, increasing infiltration and reducing off-target effects. Biomaterial‐based artificial APCs, such as PLGA microparticles presenting anti-CD3/CD28 and IL-2, stimulate ex vivo CAR-T expansion. Tumor organoids and microfluidic tumor-on-chip systems recapitulate TME complexity, enabling efficient evaluation of CAR-T infiltration, cytotoxicity, and antigen recognition [9].

C. Other Applications

Saponin, cholesterol, phospholipids, and the TLR4 agonist Monophosphoryl Lipid A (MPLA) were combined to create Saponin/MPLA Nanoparticles (SMNP), a novel particulate adjuvant.

Mechanistically, SMNP strongly enhances lymph flow, improves antigen drainage to draining lymph nodes, and transiently reduces CD169+ subcapsular sinus macrophages, thereby increasing antigen uptake and rapid activation of cognate B cells. SMNP also promotes robust differentiation of Follicular Helper T (TFH) cells with high IL-21 and IFN-γ secretion, supporting potent Germinal Center (GC) responses. This highlights SMNP as a safe, potent adjuvant for vaccines against HIV, SARS-CoV-2, and other challenging pathogens [10].

The research team of Dietmair has developed a type of Bispecific Antibody (BsAbs) as molecular bridges between PEGylated LNPs and cell-surface markers, enabling cell-specific delivery without permanent LNP modification. Pre-targeting preserves LNP integrity, enhances tumor uptake, and reduces off-target accumulation in the liver and spleen compared to pre-mixing. This modular approach simplifies production, allows rapid adaptation to new targets by swapping BsAb binding domains, and supports the development of new tissue-specific mRNA vaccines [11].

IV. Conclusions

In conclusion, advanced biomaterials and nanoscale delivery systems have emerged as transformative and indispensable driving forces accelerating the development of modern immunological engineering, mRNA therapeutics, and cellular immunotherapy. Lipid nanoparticles, peptide nanoparticles, gold nanoparticles, engineered hydrogels, and functional polymers collectively address long-standing obstacles in biotherapeutic delivery, including insufficient cargo stability, inefficient targeted transport, uncontrolled release, off-target accumulation, and limited biocompatibility. Breakthrough innovations such as thermostable lipid nanoparticles and bispecific antibody-mediated pre-targeting enable precise, tissue-specific delivery without compromising nanoparticle integrity, effectively expanding the clinical application of mRNA therapeutics beyond hepatic tissues and creating new possibilities for treating extrahepatic diseases. Nanocomposite hydrogels integrated with 3D-printing technologies support personalized, stimuli-responsive, and sustained drug release, showing outstanding potential in cancer therapy, tissue regeneration, bone repair, and immune microenvironment remodeling.

These advanced systems significantly enhance the efficacy of mRNA vaccines, promote efficient antigen presentation, and stimulate robust adaptive immune responses. They also improve CAR-T therapeutic outcomes by enhancing tumor infiltration, relieving T-cell exhaustion, and reducing off-target toxicity. Moreover, novel nano-adjuvants boost lymph node drainage, B-cell activation, and germinal center reactions, strengthening durable protective immunity. With continuous advances in material design, biosafety, and scalable production, these delivery platforms will greatly speed up clinical translation. In the future, biomaterial-based strategies will continue to lead innovations in infectious disease prevention, cancer immunotherapy, regenerative medicine, and precision therapy, providing safe, efficient, and versatile solutions for next-generation biopharmaceuticals and personalized healthcare.

Conflict of Interest

The author declares no conflict of interest.

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