REVIEW ARTICLE

Nanotechnology-Enabled Drug Delivery for Cancer Immunotherapy: Current Progress and Future Prospects

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ABSTRACT
Cancer immunotherapy has revolutionized cancer treatment by harnessing the immune system to recognize and eliminate malignant cells through approaches such as immune checkpoint inhibitors, cancer vaccines, cytokine therapy, and adoptive cell therapies. Despite significant clinical success, its broader application is limited by poor pharmacokinetics, inadequate tumor-specific delivery, immune-related adverse events, and the immunosuppressive tumor microenvironment. Drug delivery systems (DDS) have emerged as an effective strategy to overcome these limitations by enhancing drug stability, improving biodistribution, enabling controlled and targeted release, and reducing systemic toxicity. Nanoparticles, liposomes, hydrogels, extracellular vesicles, antibody-drug conjugates, peptide-drug conjugates, and stimuli-responsive delivery platforms facilitate efficient delivery of immunotherapeutic agents to tumors and immune cells while supporting combination therapies. Recent advances in biomaterials, nanotechnology, molecular engineering, and theranostic systems have further expanded the potential of precision immunotherapy. However, challenges related to large-scale manufacturing, regulatory approval, clinical translation, cost, and patient heterogeneity remain significant. This review summarizes recent advances in immunotherapeutic drug delivery systems, highlights emerging technologies, discusses current challenges, and explores future directions for improving the efficacy, safety, and clinical application of cancer immunotherapy.

Keywords: Cancer immunotherapy, Drug delivery system, Nanoparticles, Immunomodulation, Antibody-drug conjugates, Extracellular vesicles, Targeted therapy
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KEY HIGHLIGHTS

- Enhancing the immune system's combat against cancer, autoimmune disorders, and infections.
- Key developments include cancer vaccines, CAR T-cell therapies, and immune checkpoint inhibitors.
- Challenges include immune-related adverse effects, limited efficacy, and tumor microenvironment resistance.
- Innovative immunotherapeutic drug delivery methods include microneedles, nanoparticles, liposomes, and hydrogels.
- Nanoparticle platforms deliver both antigens and adjuvants simultaneously.
- Research on tailored neoantigen vaccines, gene editing, and RNA-based therapeutics.
- Challenges include high treatment costs, regulatory approvals, and large-scale manufacturing.

INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide, creating an urgent need for more effective and targeted therapeutic strategies.[1] Unlike conventional treatments such as chemotherapy and radiotherapy, cancer immunotherapy enhances the body's immune system to recognize and eliminate tumor cells. Major immunotherapeutic approaches include immune checkpoint inhibitors, cancer vaccines, cytokine therapy, adoptive cell therapies such as chimeric antigen receptor (CAR)-T cells, and monoclonal antibodies, many of which have significantly improved survival outcomes in several malignancies.[2]

Despite these advances, immunotherapy faces important challenges. Systemically administered immunotherapeutic agents often exhibit limited tumor accumulation, rapid clearance, poor pharmacokinetic profiles, inadequate penetration into solid tumors, and immune-related adverse events caused by off-target immune activation. Furthermore, the immunosuppressive tumor microenvironment and tumor heterogeneity frequently

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reduce therapeutic efficacy and contribute to treatment resistance.[3]

Drug delivery systems (DDS) have emerged as an essential strategy for overcoming these limitations. By improving drug stability, solubility, circulation time, controlled release, and tumor-specific targeting, DDS enhance therapeutic efficacy while minimizing systemic toxicity. Modern delivery platforms—including lipid- and polymer-based nanoparticles, inorganic nanocarriers, extracellular vesicles, hydrogels, virus-like particles, and antibody- or peptide-based conjugates—enable precise delivery of proteins, nucleic acids, antibodies, cytokines, and other immunomodulatory agents to tumors and immune cells. These platforms also facilitate combination therapies by enabling the co-delivery of multiple therapeutic agents and supporting sustained or stimuli-responsive drug release.[4,5]

Recent advances in nanotechnology, biomaterials, molecular engineering, and targeted delivery have accelerated the development of multifunctional DDS capable of integrating therapeutic and diagnostic functions[6,7,8]. Such systems not only improve drug localization but also allow real-time monitoring of treatment responses, thereby advancing the concept of precision oncology.

This review provides a comprehensive overview of current drug delivery strategies for cancer immunotherapy, including nanoparticle-based systems, coupling technologies such as antibody-drug conjugates and peptide-drug conjugates, targeted protein degradation platforms, and emerging cell- and virus-based delivery approaches. It also discusses current challenges, translational barriers, and future opportunities for developing safer, more effective, and personalized immunotherapeutic delivery systems.

NANOPARTICLE BASED DRUG DELIVERY SYSTEM (DDS) FOR CANCER IMMUNOTHERAPY

Nanoparticle-based drug delivery systems (DDS) have emerged as one of the most promising strategies for improving the efficacy and safety of cancer immunotherapy.[9] Conventional immunotherapeutic agents often suffer from poor pharmacokinetics, rapid degradation, limited tumor penetration, and systemic toxicity, which reduce their therapeutic effectiveness. Nanocarriers overcome these limitations by enhancing drug stability, prolonging circulation time, improving tumor-specific accumulation, and enabling controlled drug release. Lipid-based, polymeric, inorganic nanoparticles, and extracellular vesicles (EVs) are the most extensively investigated delivery platforms.[10] Typically measuring less than 200 nm in diameter, these nanoparticles encapsulate therapeutic agents through physical entrapment, electrostatic interactions, or chemical conjugation and deliver them into target cells primarily via receptor-mediated endocytosis. Once internalized, they release their cargo in a controlled manner, thereby increasing intracellular drug concentration while minimizing off-target effects.

Extracellular vesicles, including exosomes, microvesicles, and apoptotic bodies, represent naturally occurring nanocarriers with excellent biocompatibility and low immunogenicity. Unlike synthetic nanoparticles, EVs transport therapeutic molecules through membrane fusion or endocytosis and can be engineered to carry proteins, nucleic acids, or immune modulators by genetic modification, electroporation, or chemical loading.[11,12] Their intrinsic biological origin enables efficient immune evasion and targeted delivery, making them particularly attractive for cancer immunotherapy. Advances in nanotechnology have significantly expanded the clinical potential of nanoparticle-based DDS beyond conventional chemotherapy to include immune checkpoint inhibitors, cytokines, nucleic acids, vaccines, and other immunotherapeutic agents. These systems improve drug solubility, overcome physiological barriers, and provide multifunctional platforms capable of simultaneous therapeutic and diagnostic applications.[13]

Dendritic cells (DCs) are the most effective antigen-presenting cells responsible for initiating adaptive immune responses. They process tumor antigens, activate cytotoxic $CD8^+$ T lymphocytes, and orchestrate long-term antitumor immunity. Impaired antigen presentation and defective DC maturation contribute significantly to tumor immune evasion; therefore, strategies that enhance DC activation have become central to modern immunotherapy. Nanoparticle-based DDS provide an efficient platform for delivering tumor antigens, adjuvants, and immunostimulatory molecules directly to DCs, resulting in improved antigen presentation and stronger T-cell responses [14,15].

Among the various immunostimulatory pathways, the cyclic GMP–AMP synthase–stimulator of interferon genes (cGAS–STING) signaling pathway has attracted considerable attention. Cytoplasmic DNA released from tumor cells activates cGAS, leading to the production of cyclic GMP–AMP (cGAMP), which subsequently activates STING.[16-19] This signaling cascade induces type I interferons and pro-inflammatory cytokines, promotes dendritic cell maturation, and stimulates tumor-specific $CD8^+$ T-cell responses. Consequently, STING agonists have emerged as promising immunotherapeutic agents capable of converting immunologically inactive tumors into immune-responsive lesions.

Despite their therapeutic potential, naturally occurring cyclic dinucleotides (CDNs), the principal STING agonists, possess poor membrane permeability, rapid enzymatic degradation, and limited systemic bioavailability. Intratumoral administration produces robust local immune activation but has limited efficacy against metastatic disease.[20-22] To overcome these challenges, researchers have developed liposomal and polymeric nanoparticle formulations capable of systemic delivery. These nanocarriers prolong circulation time,

improve tumor accumulation, and enhance STING activation within the tumor microenvironment. Nevertheless, limited penetration through the dense extracellular matrix of solid tumors remains a major obstacle, prompting further optimization of nanoparticle design.

The biological behavior of nanoparticles is influenced not only by their composition but also by their size, surface characteristics, and geometry. While spherical liposomes remain the most widely used nanocarriers, recent evidence suggests that non-spherical nanoparticles demonstrate superior pharmacokinetic properties.[23] Rod-shaped or disc-shaped nanoparticles exhibit prolonged circulation, reduced clearance, and improved tumor penetration compared with conventional spherical formulations. Lipid nanodiscs (LNDs), for example, effectively transport STING agonists into deep tumor tissues because of their deformable structure, enabling enhanced cellular uptake and sustained activation of antitumor immunity. Experimental studies have demonstrated increased dendritic cell activation, greater interferon production, enhanced tumor cell death, and improved therapeutic efficacy compared with traditional liposomes, highlighting the importance of nanoparticle architecture in optimizing drug delivery.[24-27]

Active targeting strategies further improve delivery efficiency by modifying nanoparticle surfaces with ligands that selectively recognize immune cells. Clec9a, a receptor highly expressed on $CD103^+$ dendritic cells, has emerged as an attractive targeting molecule.[28] Liposomes functionalized with Clec9a peptides demonstrate enhanced uptake by dendritic cells, stronger activation of type I interferon signaling, increased infiltration of cytotoxic $CD8^+$ T cells, and superior antitumor responses compared with non-targeted formulations. Moreover, combining targeted STING agonist nanoparticles with immune checkpoint inhibitors such as anti-PD-L1 antibodies produces synergistic antitumor effects, even in poorly immunogenic tumors characterized by limited T-cell infiltration.[29]

Virus-like particles (VLPs) constitute another innovative nanocarrier platform for immunotherapy. These self-assembled structures mimic the morphology of viruses but lack viral genetic material, making them non-infectious while retaining excellent immunogenicity. VLPs have long been utilized in vaccine development and are increasingly being explored for delivering immunostimulatory molecules.[30-32] Encapsulation of the STING agonist 2′3′-cGAMP within VLPs markedly improves intracellular delivery compared with conventional liposomes. Preclinical studies have demonstrated that VLP-mediated delivery enhances dendritic cell activation, increases $CD4^+$ and $CD8^+$ T-cell responses, suppresses both primary and distant tumors, and acts synergistically with PD-1 blockade.[33-36] These findings suggest that VLPs may overcome several limitations associated with free STING agonists and represent a promising platform for future cancer immunotherapy.

Therapeutic cancer vaccines aim to induce long-lasting tumor-specific immune responses by delivering tumor-associated antigens to antigen-presenting cells. Nanoparticle-based vaccine platforms enhance antigen stability, facilitate efficient delivery to lymphoid tissues, and improve dendritic cell maturation[37]. Liposomes, polymeric nanoparticles, inorganic nanomaterials, and extracellular vesicles have all been investigated as vaccine carriers, with several liposomal formulations progressing to clinical evaluation.

Among these, extracellular vesicles—particularly tumor-derived exosomes (Tex)—have gained considerable attention because they naturally contain tumor-associated antigens, co-stimulatory molecules, and adhesion proteins capable of stimulating immune responses.[38] However, native tumor exosomes may also promote tumor progression or exhibit limited immunogenicity. Consequently, engineered exosomes have been developed to improve their therapeutic efficacy. Incorporation of immunogenic cell death (ICD) inducers together with immune adjuvants enhances antigen presentation, promotes dendritic cell maturation, and stimulates robust cytotoxic T-cell responses.

For example, engineered exosomes carrying α-lactalbumin together with human neutrophil elastase and the Toll-like receptor-3 agonist Hiltonol have demonstrated potent antitumor activity in preclinical breast cancer models. These multifunctional exosomes induce immunogenic cell death, enhance dendritic cell activation, and significantly increase $CD8^+$ T-cell-mediated tumor destruction. Similar approaches have been successfully applied in pancreatic ductal adenocarcinoma, where exosome-based vaccines loaded with immunostimulatory molecules and tumor-specific peptides promote dendritic cell maturation, suppress regulatory T-cell recruitment, and inhibit tumor progression despite the highly fibrotic and immunosuppressive tumor microenvironment.

Another promising strategy involves oral nanoparticle vaccines based on genetically engineered outer membrane vesicles (OMVs) derived from *Escherichia coli*. Unlike injectable vaccines, oral OMV-based formulations stimulate both systemic and mucosal immunity while improving patient compliance. Engineered OMVs expressing tumor antigens effectively cross the intestinal epithelial barrier, interact with dendritic cells within gut-associated lymphoid tissue, and induce durable antitumor immune responses. Animal studies have demonstrated reduced regulatory T-cell populations, increased infiltration of $CD4^+$ and $CD8^+$ T lymphocytes, enhanced dendritic cell activation, and long-lasting immunological memory, indicating their potential as next-generation oral cancer vaccines.[39-42]

Tumor-Associated Macrophage Targeting and Nanoparticle-Mediated Immune Modulation

Tumor-associated macrophages (TAMs) are among the most abundant immune cells within the tumor microenvironment (TME), constituting nearly 50% of the

cellular population in certain solid tumors. Owing to their remarkable plasticity, TAMs can adopt either the pro-inflammatory M1 phenotype, which promotes antitumor immunity, or the immunosuppressive M2 phenotype, which supports tumor growth, angiogenesis, metastasis, and immune evasion. Consequently, reprogramming M2 macrophages into the M1 phenotype has become an attractive strategy for improving cancer immunotherapy. Nanoparticle-based drug delivery systems (DDS) enable selective targeting of TAMs, thereby minimizing systemic toxicity while enhancing local immune activation[43,44].

Several nanoplatforms have demonstrated the ability to remodel the immunosuppressive TME. Hypoxia-responsive iron–salicylic acid coordination polymer nanoparticles release anti-inflammatory metabolites specifically within hypoxic tumors, promoting macrophage polarization toward the M1 phenotype. This shift enhances dendritic cell maturation, increases $CD8^+$ T-cell infiltration, suppresses M2 macrophages, and significantly inhibits tumor growth in preclinical models. Similarly, metformin-loaded mannose-modified macrophage-derived microparticles selectively target mannose receptors expressed on M2 macrophages. Besides altering macrophage polarization, these biomimetic carriers reduce regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), improve cytotoxic T-cell recruitment, and enhance the efficacy of immune checkpoint blockade. These findings illustrate how nanoparticle-mediated macrophage reprogramming can convert an immunosuppressive TME into an immunologically active environment that supports durable antitumor immunity.[45-47]

The effectiveness of immunotherapy is strongly influenced by the immune status of the tumor microenvironment. Tumors are broadly classified into **"hot"** and **"cold"** phenotypes based on immune cell infiltration. Hot tumors contain abundant cytotoxic T lymphocytes, exhibit high interferon signaling and PD-L1 expression, and generally respond well to immune checkpoint inhibitors. In contrast, cold tumors are characterized by poor T-cell infiltration, low antigenicity, and extensive immune suppression, resulting in limited responsiveness to immunotherapy.

Nanotechnology provides several approaches to convert cold tumors into hot tumors by inducing **immunogenic cell death (ICD).** ICD promotes the release of tumor-associated antigens and danger-associated molecular patterns, thereby enhancing dendritic cell activation and subsequent T-cell priming. Carrier-free fluorinated polymer nanoparticles co-delivering doxorubicin, TOX-targeting siRNA, and melittin represent one such strategy. These multifunctional nanoparticles simultaneously induce ICD, suppress T-cell exhaustion, and increase production of perforin, interferon-γ, and granzyme B by cytotoxic T cells. In experimental models, this approach significantly inhibited primary tumor growth, reduced metastasis, and prolonged survival, demonstrating the potential of combination nanomedicine to enhance immune responsiveness.[48]

Photothermal therapy (PTT) and photodynamic therapy (PDT) have emerged as valuable adjuncts to immunotherapy because both induce ICD while simultaneously enhancing tumor immunogenicity. Nanoparticle-based DDS improve the delivery of photosensitizers and photothermal agents by increasing tumor accumulation, minimizing systemic toxicity, and enabling controlled local activation.

Hydrogel-based nanoparticle formulations incorporating human serum albumin nanoparticles loaded with photothermal agents and ribonuclease A provide sustained local drug release after intratumoral injection. Mild photothermal treatment induces ICD, allowing cytotoxic proteins to enter damaged tumor cells before membrane repair occurs. This process activates apoptotic pathways, enhances $CD8^+$ T-cell infiltration, and stimulates robust antitumor immune responses. Importantly, combining these formulations with PD-L1 blockade further improves therapeutic efficacy by overcoming adaptive immune resistance induced during photothermal treatment[49].

Similarly, nanoparticle-mediated PDT has demonstrated considerable promise in enhancing cancer immunotherapy. Conventional photosensitizers often suffer from aggregation, poor solubility, and reduced reactive oxygen species (ROS) generation. To address these limitations, aggregation-induced emission (AIE)-based photosensitizers encapsulated within dendritic cell-derived extracellular vesicles have been developed. These biomimetic carriers selectively target tumor mitochondria, generate abundant ROS upon irradiation, and effectively induce ICD. In addition, dendritic cell membrane proteins present on extracellular vesicles directly stimulate T-cell activation, producing synergistic antitumor immunity. These multifunctional systems integrate targeted drug delivery with immune activation, making them promising candidates for combination immunotherapy.

Challenges in Clinical Translation

Despite encouraging preclinical outcomes, relatively few nanoparticle-based DDS have successfully entered routine clinical practice. Translation from laboratory research to human application remains challenging due to biological, technical, and regulatory limitations. One major obstacle is the discrepancy between animal models and human tumors. Many nanomedicines rely on the enhanced permeability and retention (EPR) effect for tumor accumulation; however, this phenomenon is highly variable among patients and often less pronounced in human cancers than in experimental models.

Manufacturing also presents significant challenges. Large-scale production requires highly reproducible synthesis methods, rigorous quality control, and consistent physicochemical properties. Even minor variations in nanoparticle size, morphology, or surface chemistry may substantially alter biodistribution and therapeutic efficacy. Tumor heterogeneity further complicates clinical translation because different tumor types—and even different regions within the same tumor—exhibit distinct

vascular architecture, extracellular matrix composition, and immune landscapes, limiting universal applicability.

Drug Delivery Systems Based on Coupling Technology

Drug delivery systems (DDS) based on coupling technology have emerged as an important strategy for improving the precision and safety of cancer immunotherapy. Unlike nanoparticle-based DDS, coupling technologies do not require carrier materials; instead, they directly link therapeutic agents to targeting molecules such as monoclonal antibodies or peptides. This approach enhances selective drug accumulation within tumors, minimizes systemic toxicity, and improves therapeutic efficacy. The principal coupling technologies include **antibody-drug conjugates (ADCs), peptide-drug conjugates (PDCs),** and the recently developed **targeted protein degradation (TPD)** platforms. Together, these technologies represent a major advancement in targeted cancer therapy by integrating selective tumor recognition with potent therapeutic payloads.[50]

Antibody–Drug Conjugates (ADCs)

The concept of antibody-mediated targeted therapy originated from Paul Ehrlich's "magic bullet" hypothesis, which proposed selective destruction of diseased cells while sparing healthy tissues. Advances in hybridoma technology enabled large-scale production of monoclonal antibodies (mAbs), leading to the development of ADCs that combine the specificity of antibodies with the cytotoxic activity of chemotherapeutic agents. ADCs consist of three essential components: a monoclonal antibody directed against a tumor-associated antigen, a highly potent cytotoxic payload, and a chemical linker connecting the two. The linker plays a critical role in maintaining stability during circulation while ensuring drug release within the tumor. Cleavable linkers release drugs in response to intracellular conditions such as acidic pH, lysosomal enzymes, or elevated glutathione concentrations, whereas non-cleavable linkers provide greater plasma stability and lower off-target toxicity.[51]

Beyond targeted drug delivery, many ADCs retain the immune functions of the antibody Fc region, enabling antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC). These mechanisms recruit natural killer cells, macrophages, and complement proteins to enhance tumor destruction. Several cytotoxic payloads used in ADCs, including anthracyclines and platinum compounds, also induce **immunogenic cell death (ICD)**, promoting dendritic cell activation and cytotoxic T-cell responses. Consequently, ADCs not only kill tumor cells directly but also stimulate adaptive antitumor immunity. Furthermore, many ADCs increase PD-L1 expression on tumor cells, creating opportunities for synergistic treatment with immune checkpoint inhibitors.[52,53]

Recent research has expanded ADC technology beyond conventional cytotoxic drugs by incorporating immune stimulators such as Toll-like receptor (TLR) agonists and STING agonists, generating **immunostimulatory antibody conjugates (ISACs)**. Clinical candidates such as **BDC-1001**, **SBT6050**, and **SBT6290** deliver TLR agonists specifically to HER2- or Nectin-4-expressing tumors, thereby combining targeted drug delivery with immune activation. Improvements in linker chemistry, antibody engineering, and Fc receptor interactions have further enhanced ADC stability and therapeutic efficacy.[54]

Despite these advances, several challenges remain. Internalizing ADCs require high expression of target antigens and efficient cellular uptake, conditions that are not consistently present in solid tumors. Their large molecular size also limits penetration into poorly vascularized tumor tissue. To address these limitations, **non-internalizing ADCs** have been developed. These conjugates release their payload extracellularly within the tumor microenvironment through tumor-specific enzymatic or chemical triggers, allowing cytotoxic agents to diffuse into neighboring tumor cells without requiring cellular internalization. This strategy broadens the spectrum of targetable tumors while reducing systemic toxicity. Another innovative approach involves **Fc-masked antibodies**, in which the Fc domain remains inactive during circulation but regains immune effector function after enzymatic activation within tumors, thereby minimizing off-target immune reactions while preserving therapeutic activity.[55,56]

Peptide-drug conjugates represent a complementary carrier-free DDS that employs peptides rather than antibodies for tumor targeting. Structurally, PDCs consist of three components: a therapeutic payload, a linker, and a targeting peptide. Targeting peptides are classified as **cell-targeting peptides (CTPs)**, which selectively bind tumor-associated receptors, and **cell-penetrating peptides (CPPs)**, which facilitate intracellular drug delivery.

Compared with ADCs, PDCs possess several advantages, including lower molecular weight, superior tissue penetration, reduced immunogenicity, simpler synthesis, lower production costs, and easier chemical modification. These characteristics make PDCs particularly attractive for treating solid tumors, where antibody penetration is often limited. Numerous PDCs are currently undergoing clinical evaluation, while approved peptide-based therapies have demonstrated the feasibility of this strategy.[51,52,56]

Recent developments have extended PDC applications beyond drug delivery to immune modulation. Bicycle Therapeutics has developed **BicycleTICA™**, a synthetic bicyclic peptide platform that simultaneously targets tumor antigens and immune co-stimulatory receptors such as CD137. Agents including **BT7480** and **BCY12491** promote direct interaction between tumor cells and activated T lymphocytes, enhancing cytotoxic immune responses while minimizing systemic immune activation. Preclinical studies have shown significant tumor regression, increased $CD8^+$ T-cell infiltration, and favorable safety profiles.

The principal limitation of PDCs remains the short biological half-life of peptides, resulting in rapid clearance and reduced tumor exposure. Current strategies to overcome this limitation include albumin binding, Fc fusion technology, and chemical modification to improve stability and prolong systemic circulation. Continued optimization of peptide engineering is expected to enhance the clinical potential of PDCs as highly selective immunotherapeutic delivery systems.

Targeted Protein Degradation (PROTACs and LYTACs)

Targeted protein degradation (TPD) represents one of the most rapidly evolving therapeutic approaches in cancer treatment. Unlike conventional drugs that merely inhibit protein activity, TPD eliminates disease-causing proteins entirely, thereby overcoming several mechanisms of therapeutic resistance. The most advanced TPD platform is **proteolysis-targeting chimeras (PROTACs)**. These bifunctional molecules simultaneously bind a protein of interest and an E3 ubiquitin ligase, promoting ubiquitination and subsequent degradation through the ubiquitin–proteasome pathway. By removing rather than inhibiting target proteins, PROTACs can effectively target proteins previously considered "undruggable."[57,58]

Several PROTACs have entered clinical trials, including **ARV-110** for metastatic prostate cancer and **ARV-471** for estrogen receptor-positive breast cancer, both demonstrating encouraging safety and preliminary efficacy. Within cancer immunotherapy, PROTAC technology has been successfully applied to degrade immune checkpoint proteins such as **IDO1** and **PD-L1**, resulting in enhanced $CD8^+$ T-cell activity and significant tumor suppression in experimental models.[59]

However, conventional PROTACs primarily target intracellular proteins and are limited by their dependence on the ubiquitin–proteasome system. To overcome these limitations, **lysosome-targeting chimeras (LYTACs)** have been developed. LYTACs direct extracellular and membrane proteins toward lysosomal degradation by exploiting lysosome-targeting receptors such as mannose-6-phosphate/IGF-II receptors. This technology considerably expands the range of therapeutic targets, including membrane-bound immune checkpoint proteins. Despite their promise, challenges including high molecular weight, limited cell permeability, potential immunogenicity, and off-target effects continue to restrict widespread clinical application. [60]

Beyond coupling technologies, several innovative DDS are reshaping cancer immunotherapy. **Cell-based delivery systems** employ erythrocytes, platelets, stem cells, macrophages, and immune cells as natural carriers for therapeutic agents. Among these, **CAR-T**, **CAR-NK**, and **TCR-T** therapies represent landmark advances in personalized medicine, particularly for hematological malignancies. Similarly, **bispecific T-cell engagers (BiTEs)** redirect cytotoxic T cells toward tumor cells by simultaneously binding CD3 on T lymphocytes and tumor-associated antigens.

Although highly effective in hematologic cancers, both CAR-T cells and BiTEs demonstrate limited activity against solid tumors because of poor tumor infiltration and the immunosuppressive microenvironment. Recent studies combining nanotechnology with these cellular therapies have shown promising results by improving tumor homing, enhancing persistence, and increasing therapeutic specificity.[61-63]

Another rapidly advancing strategy is **oncolytic viral therapy (OVT)**. Oncolytic viruses selectively infect and lyse tumor cells while simultaneously stimulating systemic antitumor immunity. Genetic engineering enables these viruses to deliver cytokines, chemokines, immune checkpoint inhibitors, and co-stimulatory molecules directly into tumors. **Talimogene laherparepvec (T-VEC)**, the first FDA-approved oncolytic virus, has demonstrated durable clinical responses in advanced melanoma and has shown enhanced efficacy when combined with immune checkpoint inhibitors and adoptive cell therapies. Ongoing clinical trials continue to evaluate these combination strategies across multiple solid tumors. [64,65]

Future Perspectives

Future DDS research is expected to focus on multifunctional systems capable of simultaneously delivering immunomodulators, nucleic acids, vaccines, and conventional therapeutics while enabling imaging and real-time treatment monitoring. Rational selection of delivery platforms based on tumor biology, intracellular target localization, and microenvironmental characteristics will become increasingly important for precision oncology.

Emerging technologies, including laser-assisted drug penetration, photothermal therapy, photodynamic therapy, and hybrid nanotechnology–TPD platforms such as **GlueTACs**, further expand the therapeutic landscape by enhancing intracellular delivery and immune activation. Novel bacterial contractile injection systems (CISs), which function as nanoscale molecular syringes capable of delivering therapeutic proteins directly into target cells, represent another promising frontier.

Despite these advances, several challenges remain before widespread clinical translation can be achieved. Complex carrier synthesis, manufacturing scalability, co-delivery of multiple therapeutic agents, PEG-associated immunogenicity, tumor heterogeneity, and individualized treatment design continue to limit clinical implementation. Future DDS should therefore emphasize simplified design, high biocompatibility, efficient targeting, scalable manufacturing, and personalized therapeutic strategies. Continued integration of molecular engineering, biomaterials science, nanotechnology, and immunology is expected to accelerate the development of safer, more effective, and clinically translatable DDS for cancer immunotherapy.

CONCLUSION

In conclusion, the present approach of combining DDS with immunotherapy has great promise for use and can greatly increase the effectiveness of tumor treatment while lowering systemic harmful side effects. Researchers have investigated many kinds of delivery carriers by utilizing the benefits of different kinds of materials. Our goal is to inspire doctors who are interested in a certain drug carrier by giving them as complete a picture of the available DDS as feasible. It is anticipated that safe and effective immunological drug delivery techniques will soon be used in clinical settings, despite the fact that several problems remain unresolved. This is due to the advancement of DDS research, growing knowledge of materials, and material development. Immunotherapy will assist more people with cancer.

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