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REVIEW

Glucan-Based Nanoparticles Empower Precision Cancer Immunotherapy: Design Strategies, Immune Reprogramming Mechanisms, and Clinical Translation Prospects

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Abstract: Tumor immunotherapy presents new opportunities for sustained tumor control by reinstating immune surveillance. However, its clinical efficacy is significantly limited by the immunosuppressive nature of the tumor microenvironment, considerable variability in patient responses, and the delicate balance required between immune activation and systemic toxicity. Recently, glucan-based nanoparticles have gained prominence as engineered platforms in precision tumor immunotherapy due to their favorable biocompatibility, programmable structural design, and inherent immune recognition capabilities. Comprehensive research has shown that these nanosystems not only facilitate the precise delivery of tumor antigens, immunoadjuvants, and immunomodulatory agents but also modulate the tumor immune microenvironment at various levels. These nanoparticles specifically target antigen-presenting cells, reprogram tumor-associated macrophages' phenotypes, reduce the function of immunosuppressive cells, and synergistically activate both innate and adaptive immune responses, significantly boosting antitumor immunity. This review methodically examines the principal strategies in the structural design and surface functionalization of glucan-based nanoparticles, with a focus on the molecular and cellular mechanisms of immune remodeling. It further highlights recent progress in their combined use with various immunotherapeutic modalities, such as immune checkpoint inhibitors, photodynamic or photothermal therapies, and cell-based treatments. Moreover, drawing on current preclinical studies and early clinical data, this article offers a comprehensive evaluation of the translational challenges these systems face, including long-term safety, scalable production, and regulatory issues. Overall, glucan-based nanoparticles are transitioning from traditional delivery systems to versatile therapeutic platforms that play a crucial role in immune regulation. They offer significant potential for novel theoretical frameworks and technological advances in the development of more precise, effective, and sustainable tumor immunotherapy strategies.

Keywords: glucan-based nanoparticles, tumors, immunotherapy, drug design, tumor immune microenvironment

Introduction

Cancer remains one of the leading causes of mortality worldwide and continues to pose significant challenges in clinical management.[1] Current therapeutic strategies, including conventional chemotherapy, radiotherapy, targeted agents, and endocrine therapies, have somewhat improved patient survival. However, their overall efficacy is limited by several fundamental constraints. These constraints include insufficient tumor specificity,[2] complex and heterogeneous mechanisms of drug resistance,[1,3–6] the immunosuppressive nature of the tumor microenvironment (TME),[7] and challenges in

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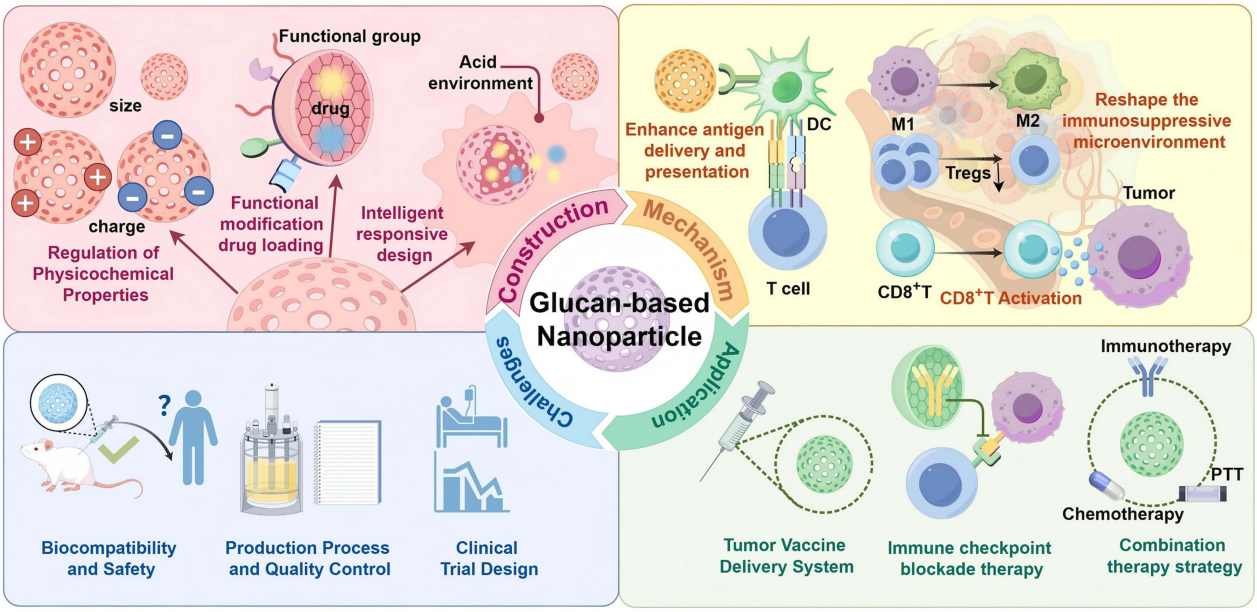
Graphical Abstract



managing toxicity during treatment.[8] Consequently, cancer-associated mortality rates are still unacceptably high. In recent years, cancer immunotherapy has emerged as a transformative therapeutic approach.[9] Instead of directly targeting tumor cells, immunotherapy engages the host immune system to recognize and destroy malignant cells, thereby facilitating durable tumor control and, in some cases, achieving long-term remission. Unlike traditional cytotoxic methods, immunotherapy aims to disrupt the immunosuppressive networks that tumors establish to evade immune surveillance.[10] Immune checkpoint inhibitors (ICIs), which block inhibitory receptors such as PD-1/PD-L1 and CTLA-4, are pivotal in modern immunotherapy. They reactivate T cell function and foster the development of sustained immunological memory, thus countering tumor immune evasion. Despite these advancements, clinical response rates in most cancer types are modest, generally ranging from 10% to 40%.[11] Both primary and acquired resistance are commonly observed,[12,13] the efficacy is limited in immunologically "cold" tumors,[14] and immune-related adverse events raise additional safety concerns.[15] Chimeric antigen receptor T (CAR-T) cell therapy has broadened the scope of immunotherapeutic options by genetically modifying patient-derived T cells to target cancer cells specifically. While CAR-T therapy has shown remarkable success in hematological malignancies, its effectiveness in solid tumors is still limited.[16] Additionally, severe toxicities, such as cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, limit its wider use.[17] These challenges highlight the critical need for precision drug delivery systems that can be controlled spatially and temporally. Such platforms have the potential to increase therapeutic efficacy, reduce systemic toxicity, and address the inherent limitations of current cancer immunotherapies.

Nanoparticles have emerged as sophisticated drug delivery platforms with significant potential to enhance cancer immunotherapy. These platforms operate through diverse and programmable mechanisms that not only enable targeted delivery of immunomodulators but also remodel the TME, augment antigen presentation, and serve as essential components of cancer vaccines.[18] Among the various nanomaterials explored, glucans, naturally derived polysaccharides, have garnered considerable interest due to their outstanding biocompatibility, and inherently low immunogenicity, which establish them as promising immunoregulatory nanocarriers (Figure 1).[19–29] The abundance of hydroxyl groups in glucan structures provides versatile chemical sites for functional modifications,[30] facilitating the attachment of various bioactive groups. Dextrans are a class of natural polysaccharides formed by glucose units linked together via various glycosidic bonds. Glucans are broadly classified into two main types based on the stereochemical configuration of their glycosidic

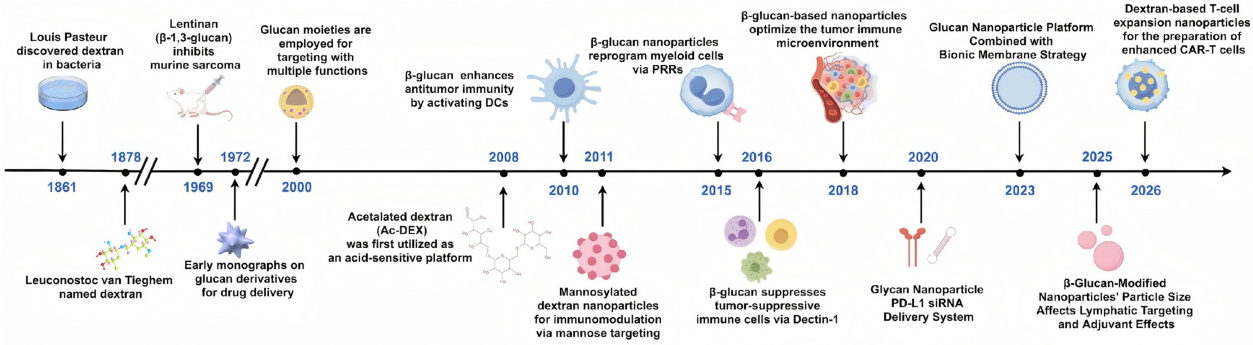


Figure 1 This timeline provides an overview of research progress on dextran and its derivatives in the fields of drug delivery and tumour immunotherapy from 1861 to 2026, comprehensively illustrating their development from discovery to clinical application.

linkages. The first type, β-glucans, are primarily derived from fungi (eg, yeast and mushrooms) and cereals.[31] Their β-1,3-D-glucan backbone forms a distinctive triple-helical structure that is specifically recognized by C-type lectin receptors, such as Dectin-1 and complement receptor 3, which are expressed on innate immune cells.[32–34] Critically, this targeting ability significantly enhances the uptake of nanoparticles by antigen-presenting cells (APCs), including dendritic cells (DCs) and macrophages, thereby facilitating precise delivery of immunomodulatory agents to the TME and promoting effective immune reprogramming. The second type, α-glucans, with dextran being the most notable example, are primarily derived from bacteria and predominantly feature α-1,6 linkages.[35] Unlike β-glucans, native dextran is relatively immunologically inert and does not contain Dectin-1 binding motifs, thus providing a "clean" and modular carrier scaffold. Through rational chemical modifications (eg, conjugation of mannose to target $CD206^{+}$ macrophages) or structural changes (eg, incorporation of pH-sensitive acetal linkages), dextran-based nanocarriers can be designed with specific immunological functions, enabling highly customizable and precision-oriented designs.

To date, there have been reviews summarizing advances in dextran biomaterials and various glycan delivery carriers.[19,30] However, most of these focus on material preparation, basic drug delivery, and general applications, with few reviews highlighting the structural and functional differences among various dextran subtypes and their unique roles in immune recognition and the regulation of the tumor microenvironment. Therefore, this paper focuses on the development of glucan nanoparticle systems from the perspective of cancer immunotherapy. It provides a comprehensive discussion and summary covering several key aspects: the rational design and engineering strategies of glucan-based nanoparticles, surface functionalization strategies, immunomodulatory mechanisms, combined immunotherapy strategies, and clinical applications and challenges. By integrating the latest therapeutic approaches and preclinical research, this paper aims to provide new insights for the development of highly effective and safe immunotherapy strategies.

Rational Design and Engineering Strategies of Glucan-Based Nanoparticles

There are two primary methods for obtaining glucans: natural extraction and biosynthesis. β-glucans are typically obtained from fungi, yeast, or grains through hot water extraction, alkali solubilization followed by acid precipitation, or enzyme-assisted extraction,[36] α-glucans, on the other hand, are primarily synthesized via microbial fermentation.[37] Glucans are predominantly linear polymeric polysaccharides. Stable nanoparticles can only be formed through molecular modification and self-assembly.[30]

Accumulating evidence demonstrates that glucan-based nanoparticles have transitioned from initial passive delivery vehicles to engineered therapeutic platforms characterized by precise structural tunability and intrinsic immunomodulatory capabilities.[30,38] Through systematic chemical modification, stimuli-responsive structural engineering, and controlled surface functionalization, it is possible to finely tailor their physicochemical properties, in vivo behavior, and immunological outcomes at both molecular and nanoscale levels. This bottom-up rational design paradigm facilitates the programmable integration of structural precision and biological functionality, offering distinct advantages in enhancing

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targeting specificity, biosafety, and therapeutic efficacy. Collectively, these advances provide a robust engineering foundation for employing glucan-based nanoplatforms in precision cancer immunotherapy.

Chemical Modification Strategies of Glucan-Based Nanoparticles

From a materials engineering perspective, chemical modification is the central strategy for endowing glucans with structural versatility and functional diversity (Table 1). As depicted in Figure 2, oxidation, crosslinking, and grafting are the three most representative and foundational approaches. These methodologies not only expand the structural dimensionality of glucan macromolecules but also establish highly controllable reaction platforms to regulate subsequent self-assembly behavior, stimuli-responsive properties, and biological functionality.

Oxidative Modification: Aldehyde Installation and Structural Programmability

Among various modification strategies, sodium periodate ($NaIO_4$)-mediated selective oxidation is regarded as one of the most established and frequently utilized methods. This technique selectively oxidizes vicinal diol structures in glucan chains, transforming a portion of hydroxyl groups into highly reactive aldehyde functionalities. Consequently, this introduces programmable chemical sites for subsequent structural construction.[60] The advantages of this reaction include its compatibility with aqueous environments and mild reaction conditions,[61] which largely preserve the

Table 1 Major Chemical Modification Strategies of Dextran-Based Nanoplatforms and Their Applications

Modification Type	Specific Modification Method	Representative Nanosystem	Purpose and Function	References
Oxidation Modification	Sodium periodate oxidation	Oxidized dextran-doxorubicin prodrug nanomicelles	Introduced highly reactive aldehyde groups for Schiff base conjugation	[39,40]
	Hydrogen peroxide (H_2O_2) oxidation	Multifunctional oxidized dextran nanosystems	Green and catalyst-free process; served as nanostabilizer, cellular delivery carrier, and modular building block for functional materials	[41,42]
Crosslinking Modification	Chemical crosslinking	Oxidized dextran-based hydrogel nanoparticles dynamically crosslinked via Schiff base (CH=N) bonds	Formation of dynamic and reversible Schiff base networks with acid-sensitive degradation; suitable for drug-controlled release and tissue engineering	[43,44]
		Epichlorohydrin crosslinking (Dextran-coated superparamagnetic iron oxide nanoparticles)	Reduced immune recognition of large nanoparticles; improved safety and bioinertness of MRI contrast agents	[45]
		Divinyl sulfone crosslinking (Dextran-polystyrene block copolymer micelles)	Stabilized micelles formed by hydrophobic dextran end groups	[46,47]
		Click chemistry crosslinking (Injectable dextran-based hydrogels)	Preparation of injectable hydrogels for cartilage tissue engineering; construction of controllably, degradable microcapsules and microgels	[48,49]
		Enzyme-catalyzed crosslinking (Hydrogel network systems)	Introduced crosslinkable sites; enabled mild and controllable nano-/gel formation; constructed stable 3D networks	[50]
	Physical crosslinking (Hofmeister effect)	Gelatin/oxidized dextran hydrogels	Improved mechanical properties and biocompatibility; suitable for wound healing	[51]
		Hydrogen-bond-induced triple-crosslinked hydrogel	Enhanced polymer network stability, structural strength, and drug-loading stability	[52]
Grafting Modification	Amino acid covalent grafting	L-arginine-modified dextran magnetic nanoparticles	Improved biocompatibility; enhanced cellular uptake and immunological activity	[53,54]
	Improved biocompatibility; enhanced cellular uptake and immunological activity	Dextran-polycaprolactone amphiphilic graft copolymers	Enhanced mechanical properties; formed core-shell self-assembled structures for efficient loading of hydrophobic drugs	[55,56]
	Cationic peptide grafting	Spermine-dextran composite nanosystem	Provided positive charge to enhance nucleic acid/drug loading and targeting capability	[57]
Acetalation Modification	Condensation between hydroxyl groups and aldehyde compounds	Magnetic-optical dual-responsive core-shell microspheres	Constructed acid-sensitive acetal bonds for pH-triggered drug release	[58,59]

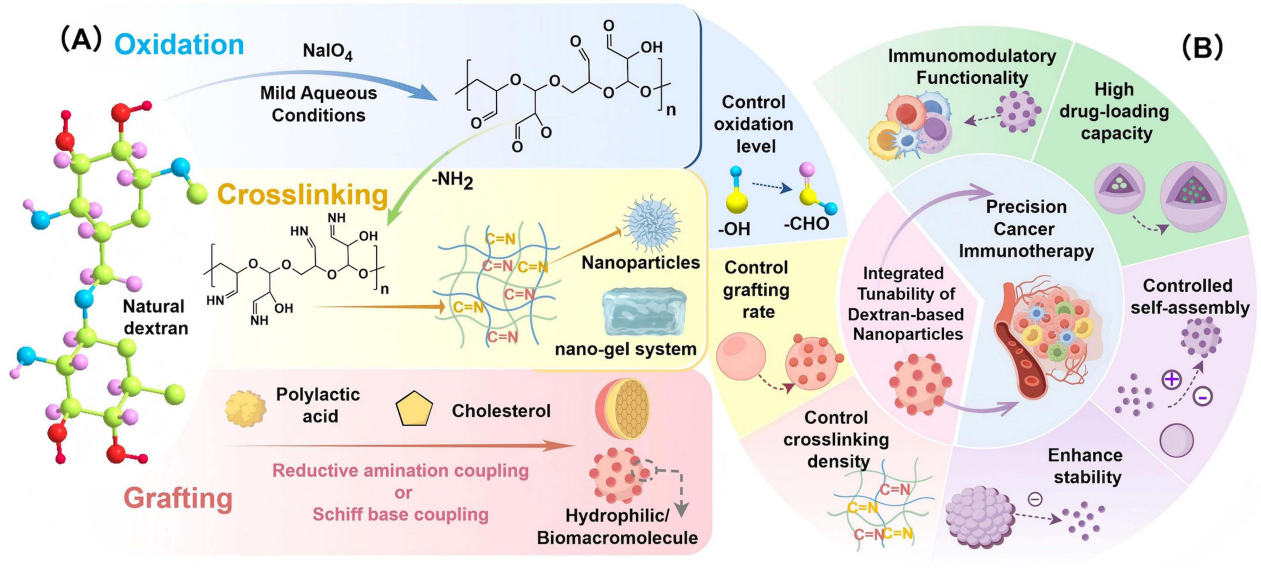

Figure 2 Chemical modification strategies of glucan-based nanoparticles. (**A**) Through three core chemical approaches, oxidation, crosslinking, and grafting, native glucan is endowed with aldehyde-reactive sites, crosslinked network structures, and amphiphilic self-assembly capability. (**B**) By fine-tuning the degree of oxidation, crosslinking density, and grafting ratio, this platform achieves integration of high drug-loading capacity, structural stability, and immunomodulatory functionality, thereby providing a programmable nanocarrier for precise tumor immunotherapy.

biological activity of the polysaccharide. Oxidized dextran (ODEX) is commonly used as an efficient crosslinking agent. It can react with natural polymers such as chitosan and gelatin to form injectable hydrogels in situ or serve as a shell-forming component in nanocapsule construction.[62,63] Compared to conventional industrial chemical crosslinkers, such as glutaraldehyde,[64] the in situ oxidation strategy utilizes the native polysaccharide backbone for network formation, significantly reducing potential cytotoxicity risks. As a result, the biocompatibility and safety of the material are substantially enhanced at the design stage.[65–67] Taking the oxidized dextran-doxorubicin/CD147 monoclonal antibody-conjugated oxidized dextran-doxorubicin, (ODEX-DOX/CD147-ODEX-DOX) nanoscale system, blank ODEX at a concentration of 250 mg/L still maintained the survival rate of human umbilical vein endothelial cells and HepG2 cells at over 80%, suggesting that the ODEX carrier itself exhibits low cytotoxicity. Furthermore, after coupling the aldehyde groups with doxorubicin (DOX) and the CD147 antibody, CD147-ODEX-DOX exhibited a tumor DOX enrichment of approximately 20% ID/g in the HepG2 tumor model, which was higher than the approximately 15% ID/g for non-targeted ODEX-DOX and the approximately 7% ID/g for free DOX. Additionally, body weight in the nanoprotec group remained more stable than in the free DOX group, indicating that the oxidation modification not only provides reactive sites for conjugation but also helps improve the therapeutic safety margin through targeted delivery and reduced exposure to off-target tissues.[39] However, oxidation with sodium periodate or hydrogen peroxide may disrupt the sugar ring structure of the dextran, leading to a decrease in molecular weight and a reduction in mechanical strength, thereby affecting the material's stability and processability.[39,40] Notably, the degree of oxidation can be precisely regulated by adjusting reaction conditions, enabling predictable control over the quantity and distribution of aldehyde groups. Related studies have shown that when the ratio of the aldehyde-containing monomer 4-(2-thiiranylmethoxy)benzaldehyde to the copolymer monomer 2-(phenoxymethyl)thiirane was adjusted from 4:6 to 1:9, the final conversion rates of both monomers approached or reached 99%, and the polymer composition was essentially consistent with the initial feed ratio, indicating that the aldehyde content is well-controlled in terms of proportion. At the same time, when the aldehyde content exceeded 40%, the system cured rapidly upon addition of a crosslinking agent and exhibited uneven crosslinking. However, keeping the aldehyde content below 30% resulted in a stably crosslinked polymer. Fourier transform infrared spectroscopy further revealed that the aldehyde C=O peak at 1685.33 cm^{-1} disappeared after crosslinking, and a C=N peak at 1642.98 cm^{-1} appeared, suggesting that the aldehyde

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groups were efficiently converted into imine bonds.[68] This controllability can lay a stable and reproducible chemical basis for subsequent network construction and the incorporation of functional modules.[61,68]

Crosslinking Strategies: Stabilized Network Formation and Functional Integration

The aldehyde groups introduced through oxidation offer highly controllable reactive sites for structural construction and functional modification. Previous studies have shown that these aldehyde functionalities can engage in Schiff base reactions with polyamine-containing molecules to form reversible imine bonds (-C=N-).[69–71] This dynamic covalent interaction facilitates the development of reversible and biocompatible covalent adaptive networks.[63,72,73] Such networks significantly enhance the structural stability of nanostructures during systemic circulation and provide opportunities for integrating multifunctional modules. By harmonizing structural integrity with functional tunability, this crosslinking strategy equips glucan-based nanoparticles with robust stability and a flexible capacity for functional expansion.[74] Taking the triple-crosslinked dynamic-responsive hydrogel of ODEX-phenylboronic acid grafted polylysine@selenium nanoparticles as an example, the SeNPs had a particle size of 57.44 ± 2.34 nm and a polydispersity index of 0.206 ± 0.051, indicating a relatively uniform nanoparticle distribution. Following the incorporation of SeNPs, the hydrogel pore size decreased from 209.11 ± 14.07 μm to 27.37 ± 3.78 μm, while the tensile strain at break increased from 83.33 ± 3.06% to 142.33 ± 4.51%, indicating that triple cross-linking enhances network density and mechanical stability. Furthermore, after treating various cell types with SeNPs at concentrations ranging from 10 to 1000 μM, cell viability remained above 80% and the hemolysis rate was below 2%, supporting the conclusion that this cross-linking system possesses both structural stability and preliminary biocompatibility.[75]

It is important to note that commonly used crosslinking agents, such as epichlorohydrin and divinylsulfone, have potential cytotoxicity, and their residues may reduce the biocompatibility of the material.[45,46] Furthermore, excessive cross-linking can hinder glucan hydrolysis, prolong the in vivo degradation cycle, and increase the risk of foreign body reactions or chronic inflammation.[50] Therefore, when designing cross-linking strategies, a balance must be struck between material stability, functional scalability, and biosafety to ensure the controllability and applicability of glucan nanomaterials.

Grafting Approaches: Self-Assembly Induction and Functional Diversification

Hydroxyl-mediated graft modification serves as an efficient strategy for constructing self-assembled nanosystems. Grafting hydrophobic entities, such as cholesterol or polylactic acid, onto the glucan backbone via hydroxyl groups,[76–78] enables the glucan derivatives to spontaneously self-assemble in aqueous environments, forming amphiphilic core-shell nanostructures.[55,79] These structures not only enhance the thermodynamic stability of the system but also significantly improve the loading capacity and in vivo delivery efficiency of hydrophobic drugs. For example, Azadpour et al further demonstrated that ODEX can form covalent bonds with amino sites on the surface of L-arginine-modified magnetic nanoparticles via aldehyde groups. After modification, the material retains its spherical morphology, magnetite crystal phase, and superparamagnetic properties, while simultaneously enhancing its surface functionalization potential and colloidal stability.[53] Research by Chung et al also demonstrated that L-arginine-modified dextran nanogels can promote the uptake, storage, and sustained release of antigenic proteins within antigen-presenting cells, as well as enhance cellular and humoral immune responses, suggesting that graft modification can further expand the immunological delivery capabilities of dextran-based nanosystems.[54] Furthermore, aldehyde groups produced through oxidation can be conjugated with hydrophilic or biomacromolecular components via reductive amination or Schiff base coupling on the particle surface.[39,80] Precise control over oxidation conditions and grafting ratios allows for the simultaneous regulation of particle size, crosslinking density, and surface properties, facilitating the fine-tuned design of the nanosystem's physicochemical behavior.[81] This tunability is crucial for developing personalized delivery platforms tailored to specific tumor types and therapeutic requirements.

Stimuli-Responsive Engineering of Glucan-Based Nanoparticles

These intelligently engineered stimuli-responsive nanoparticles are designed to maintain structural stability during systemic circulation while generating targeted responses to endogenous or exogenous stimuli. These carriers are capable of undergoing chemical bond cleavage or conformational transitions within specific pathological microenvironments, thereby enabling spatiotemporally controlled drug release. This capability significantly enhances therapeutic precision and safety.[82,83] Based on the unique biochemical characteristics of the TME, pH, reactive oxygen species (ROS), and enzyme-responsive strategies have become the three most mature and widely implemented approaches in designing dextran-based nanoparticles (Figure 3).

pH-Responsive Design: Tumor Microenvironment-Triggered Precision Release

Tumor tissues and intracellular lysosomes typically exhibit mildly to moderately acidic conditions, a consistent physicochemical characteristic that underpins the development of pH-responsive delivery systems.[84–86] This approach usually involves incorporating acid-labile linkages, such as hydrazone and acetal bonds, into the structure of glucan-based carriers. By exploiting the mildly acidic TME (pH 6.5–7.0) and the more pronounced acidity within lysosomes (pH 4.5–5.0), these linkages are cleaved, which triggers the disassembly of the carrier or the release of the drug, thereby facilitating targeted delivery. Previous studies have shown that nanoparticles made from cinnamaldehyde-modified dextran can efficiently release the antibacterial agent glabridin in acidic conditions, achieving precise eradication of intracellular methicillin-resistant *Staphylococcus aureus*.[87] Furthermore, Sun et al have developed a nanoplatform that integrates pH responsiveness with a reversible shielding feature, which becomes active in the acidic TME, significantly enhancing cellular uptake efficiency.[88] Additionally, a dextran-based nanocomposite hydrogel designed for in situ injection has been reported, it initiates drug release through the acid-responsive cleavage of crosslinking bonds within the TME for combined tumor therapy.[89] However, practical applications must carefully address the potential for nonspecific drug release in physiologically acidic environments, such as the stomach, which could compromise selectivity and diminish the therapeutic safety margin.

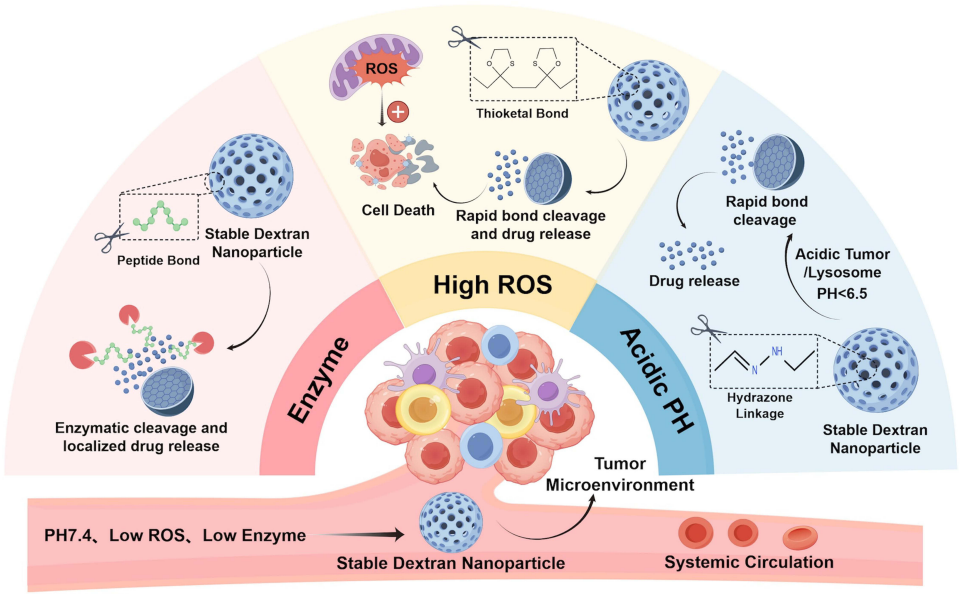

Figure 3 Endogenous stimulus-responsive behavior and precise drug release mechanisms of glucan-based nanoparticles. This schematic illustrates that glucan-based nanoparticles remain structurally stable during systemic circulation, while undergoing site-specific degradation within the TME in response to acidic pH (hydrazone bond cleavage), elevated reactive oxygen species (ROS; thioketal bond cleavage), and specific enzymes (peptide bond cleavage). These stimuli-triggered bond cleavages enable controlled degradation of the nanostructure and precise drug release at the tumor site.

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ROS-Responsive Design: Oxidative Stress-Driven Therapeutic Amplification

ROS-responsive design is aimed specifically at the high levels of oxidative stress often found in tumor cells and inflamed tissues. This strategy incorporates oxidation-sensitive chemical groups into glucan-based carriers to enable stimulus-triggered drug release. Common ROS-responsive linkages include thioketal and disulfide bonds,[90–92] which cleave under elevated ROS conditions, resulting in the disintegration of nanoparticles and the rapid release of encapsulated therapeutics within cells.[88]

Accumulating evidence has consistently demonstrated the therapeutic benefits of ROS-responsive systems across various disease models. For example, a dextran-thioketal conjugate has been developed that reacts to both elevated endogenous ROS levels and exogenous light irradiation, enabling the synergistic co-delivery of the chemotherapeutic agent doxorubicin and a photosensitizer, thus enhancing the efficacy of combination therapy.[90] Another study reported a dextran-based nano-self-assembly system that incorporates diallyl disulfide, which enhances the outcomes of photodynamic therapy (PDT) by depleting intracellular glutathione and inducing in situ ROS generation, thereby strengthening antitumor effects.[91] Moreover, nanoparticles made from ODEX and selenocystamine show dual responsiveness to ROS and GSH, enabling precise release of vancomycin at sites of bacterial infection and demonstrating favorable lesion-specific targeting capabilities.[92] Therefore, ROS-responsive glucan-based nanoparticles are particularly advantageous for tumor or inflammatory microenvironments characterized by pronounced oxidative stress,[83,90] significantly improving therapeutic selectivity and local drug concentration. However, during clinical translation, it is crucial to systematically assess the risk of nonspecific drug release triggered by basal ROS levels in normal tissues, in order to minimize off-target effects and enhance overall safety.

Enzyme-Responsive Design: Lesion-Specific Catalytic Release Mechanisms

Enzyme-responsive design exploits the aberrant overexpression of specific proteases or glycosidases during tumor initiation, invasion, and metastasis. This approach facilitates precise drug release through biomolecule-specific recognition and catalytic reactions. The fundamental principle of this strategy involves incorporating substrate motifs into glucan-based nanoparticle systems. These motifs are designed to be selectively recognized and cleaved by target enzymes, thereby providing high responsiveness and selectivity to the pathological microenvironment. For example, Dosta et al developed a dual-sensitive nanoparticle system by integrating matrix metalloproteinase-cleavable peptide substrate sequences (eg, GPLGVRG) into dextran-based nanoparticles.[93] When exposed to tumor-associated proteases, these peptide linkers are specifically cleaved, which triggers structural disassembly and subsequent drug release, significantly enhancing the spatial precision of delivery. Additionally, Meng et al successfully engineered a glycosidase-responsive β-glucan self-assembled nanotube carrier for doxorubicin delivery. In colorectal cancer models, this system demonstrated reduced systemic toxicity and increased antitumor efficacy, while also modulating the gut microbiota, indicating promising potential for integrated therapeutic applications.[94]

Overall, enzyme-responsive glucan-based nanoparticles facilitate targeted drug release through highly specific biocatalytic mechanisms and offer significant advantages in enhancing therapeutic selectivity. However, their efficacy may be limited by variability in the expression levels of target enzymes across different tumor types and among individual patients. Such biological heterogeneity must be carefully considered during system design and clinical translation.

Recent studies suggest that glucan-based stimuli-responsive nanoparticles are evolving from single-trigger systems to multi-stimuli synergistic responsiveness and multifunctional integration.[54,90–92] This trend not only enhances the spatiotemporal precision of drug release but also introduces a novel design paradigm for achieving more effective therapeutic interventions within the complex TME. However, despite these advances, most current preparation methods remain limited to small-scale laboratory production, and it is difficult to maintain batch-to-batch consistency during large-scale manufacturing.[95,96] Furthermore, single-stimulus-responsive designs may result in nonspecific release in healthy tissue, leading to potential off-target effects and compromising treatment safety.[83,93] Meanwhile, multi-stimulus systems are still in their early stages, and little is known about their synergistic or antagonistic effects. Future investigations should systematically evaluate the synergistic and potentially antagonistic interactions among different responsive mechanisms. While improving responsiveness and sensitivity, maintaining structural stability during

systemic circulation and ensuring overall biosafety are equally critical. Such efforts will facilitate the advancement of stimuli-responsive glucan-based nanoparticles towards more controllable and clinically translatable therapeutic platforms.

Surface Functionalization Strategies for Cancer Immunotherapy

Surface functionalization represents a critical engineering strategy for modulating the in vivo behavior and immunological effects of nanoparticles. Through precise chemical modification of the particle surface, it is possible to optimize both biodistribution and pharmacokinetic profiles, as well as to confer active targeting capabilities and immunomodulatory functions. These enhancements collectively improve the efficacy and safety of antitumor immunotherapy. Current approaches to nanoparticle surface functionalization fall into three major categories: grafting of targeting ligands, covalent conjugation of immunoadjuvants, and stealth modifications designed to evade immune clearance.

Engineering of Active Targeting Ligands

In tumor immunotherapy, actively targeted delivery is a critical prerequisite for enhancing therapeutic precision. Grafting specific targeting ligands onto the surface of nanocarriers facilitates selective recognition and internalization by tumor cells or lesion-associated cells. This strategy significantly increases localized drug accumulation at the target site while minimizing nonspecific toxicity to normal tissues. Extensive studies have demonstrated that the folate receptor (FR) is overexpressed on the surface of various tumor cells, whereas its expression remains relatively low in most normal tissues.[97] Leveraging this differential expression profile, folic acid-modified nanocarriers have demonstrated promising targeting capabilities and therapeutic advantages in FR-positive tumor models, including ovarian, breast, lung, and colorectal cancers.[98] Additionally, the RGD (arginine-glycine-aspartic acid) peptide sequence specifically recognizes αvβ3 integrin, which is highly expressed on tumor vascular endothelial cells and on multiple cancer cell types.[99] As a result, RGD has been widely employed in nanocarrier surface modification to enable dual targeting of both tumor cells and tumor-associated vasculature, thereby enhancing delivery efficiency and therapeutic efficacy.[100] Beyond these classical ligands, immunoregulatory targeting strategies have also garnered increasing attention. CD47, which is overexpressed on the surface of various tumor cells,[101] interacts with signal regulatory protein α (SIRPα) on macrophages. This interaction transmits a "don't eat me" inhibitory signal to the immune system, thereby suppressing phagocytosis. The conjugation of anti-CD47 antibodies onto the surface of nanocarriers can effectively block the CD47-SIRPα signaling axis, thus restoring macrophage-mediated phagocytic activity against tumor cells and enhancing the innate immune-driven antitumor responses.[102] Within glucan-based systems, the engineering of active targeting has also been extensively explored,[103] including surface modifications with ligands such as RGD peptides,[104] folic acid,[105] and mannose,[24] among others.

Overall, the engineered incorporation of targeting ligands is critical in enhancing the specificity of interactions between nanoparticles and target cells. By promoting selective binding and internalization, this strategy substantially improves the tumor accumulation and delivery efficiency of therapeutic agents. Thus, ligand-mediated surface functionalization can lay a critical engineering foundation for the development of precise tumor immunotherapy.

Covalent Conjugation of Immunoadjuvants for Signal Amplification

Covalent conjugation of immunoadjuvants to the surface of nanocarriers has been extensively explored as a strategy in the realm of nano-immunotherapy in recent years. This method not only improves the in vivo stability of immunostimulatory molecules but also facilitates their targeted accumulation at tumor sites or within APCs. Consequently, this enhances and prolongs the activation of immune signals.

The most commonly used immunoadjuvants for covalent conjugation are agonists of various pattern recognition receptors. Among these, the Toll-like receptor 9 (TLR9) agonist, CpG oligodeoxynucleotide, is particularly effective. It activates plasmacytoid DCs and B cells, triggers the secretion of multiple pro-inflammatory cytokines, and promotes DC maturation and enhanced antigen presentation capacity.[106] Similarly, the TLR3 agonist, polyinosinic-polycytidylic acid [poly(I:C)], mimics viral double-stranded RNA structures and activates both innate and adaptive immune responses, leading to the production of interferons and related cytokines.[107] Additionally, agonists of the stimulator of interferon

genes (STING) pathway, when specifically delivered to tumor-associated immune cells, activate the STING signaling pathway and induce type I interferon (IFN-1) responses, offering considerable promise in antitumor immunotherapy.[108]

In summary, the covalent conjugation of immunoadjuvants significantly enhances antitumor immunity. It activates APCs, amplifies pro-inflammatory signaling, and reshapes the tumor immune microenvironment. Through these mechanisms, it robustly enhances antigen-specific T cell-mediated antitumor immune responses. This strategy provides a precise and controllable engineering framework for the development of nanovaccines and combined immunotherapy platforms.

Stealth Surface Modification of Nanocarriers and in vivo Behavior Modulation

Under systemic administration, nanoparticles often face rapid clearance by the mononuclear phagocyte system, which compromises their therapeutic efficacy. To extend circulation time and minimize the risk of nonspecific elimination, modifying the surface physicochemical properties of nanoparticles has become crucial.[109] This "stealth" modification is primarily achieved through polyethylene glycol (PEG) coating, which is among the most prevalent techniques. The PEG coating forms a hydrophilic polymeric barrier on the nanoparticle surface, reducing opsonin adsorption through steric hindrance and thus diminishing nonspecific immune recognition and phagocytic uptake.[109,110] However, excessive PEG modification can extend circulation time at the expense of the binding efficiency of targeting ligands and weaken the biological activity of conjugated immunoadjuvants, adversely affecting the therapeutic performance.[111] Consequently, maintaining a dynamic balance between in vivo stability and functional molecule activity is a significant challenge in designing nano-immunotherapeutic systems.

In summary, the surface functionalization of nanocarriers offers multi-level engineering strategies to enhance tumor immunotherapy. Modifications that target specific ligands improve the spatial precision of delivery, while the covalent conjugation of immunoadjuvants amplifies immune activation signals. Furthermore, stealth modification is crucial for optimizing in vivo behavior. Nevertheless, integrating multiple functional modules often increases structural complexity and may lead to potential functional interference.[112] In glucan-based systems, active targeting strategies have become relatively advanced, yet the covalent surface immobilization of immunoadjuvants remains underdeveloped and largely relies on physical encapsulation. Although stealth modification can accommodate targeting modules, overall progress is fragmented and lacks the systematic development seen in mainstream platforms such as poly(lactic acid-co-glycolic acid) or liposomal systems. This gap highlights both the distinctive adaptability of glucan-based materials and the critical challenges that must be addressed. Achieving precise synergy among immune activation potency, spatial targeting accuracy, and prolonged circulation stability is essential for transitioning these nanoplatforms from laboratory research to clinical immunotherapy applications.

To further elucidate the relative advantages and limitations of these design strategies, we provide a comparative overview of their applicability across major cancer types and physiological environments (Table 2).

As summarized in Table 1, enzyme-responsive and immunostimulatory designs demonstrate the broadest applicability across different cancer types, while pH- and ROS-responsive systems show strong performance in specific tumor microenvironments but face notable challenges in oral delivery scenarios. This comparison underscores the importance of tailoring design strategies to the intended biological setting.

Table 2 Applicability of Different Design Approaches in Various Cancers or Physiological Conditions

Design Strategy	Solid Tumors	Hematological Malignancies	Immunosuppressive TME	Oral Delivery	References
pH-responsive	High	Moderate	Moderate	Low	[28,93]
ROS-responsive	Moderate	Moderate	High	Low	[113,114]
Enzyme-responsive	High	High	Moderate	Moderate	[19,115]
Multi-stimuli-responsive	High	Moderate	High	Moderate	[30,116]
Immunostimulatory β-glucan-based	High	High	High	Moderate	[83,117]

Immunomodulatory Mechanisms Mediated by Glucan-Based Nanoparticles

The success of tumor immunotherapy is heavily reliant on the effective activation and sustained maintenance of antitumor immune responses, particularly those involving antigen-specific adaptive immunity. However, the immunosuppressive mechanisms prevalent within TME often hinder the full activation of immune effector functions. To address this challenge, recent studies have increasingly combined nanotechnology with immunotherapy, employing glucan-based nanoparticles to modulate the immune microenvironment. These nanoparticles selectively regulate APC functions, reprogram myeloid cell phenotypes, activate innate immune signaling pathways, and target immunosuppressive cell populations. Consequently, dextran-based nanoparticles have emerged as versatile tools for remodeling the tumor immune microenvironment and enhancing the therapeutic efficacy of immunotherapy.

Precision Targeting and Functional Activation of Antigen-Presenting Cells

APCs, especially DCs, are pivotal in initiating adaptive anti-tumor immune responses. The effective targeting and functional activation of these cells are considered critical to the success of tumor immunotherapy.[118] In this regard, glucan-based nanoparticles, recognized for their favorable biocompatibility and innate immune recognition capabilities, have shown significant advantages in targeting APCs and co-delivering tumor antigens along with immunoadjuvants (Figure 4).

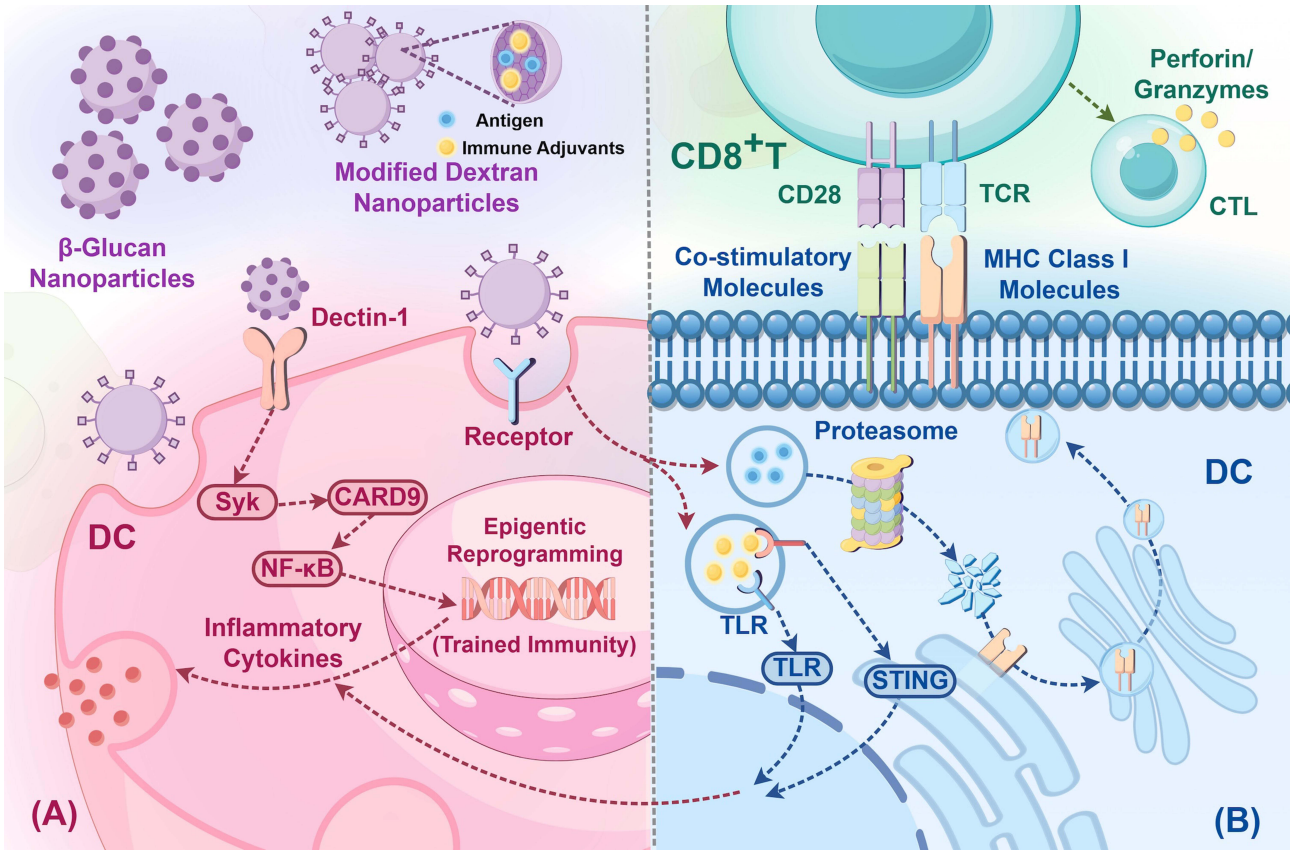

Figure 4 DC priming and antitumor T-cell immune responses mediated by glucan-based nanoparticles. (**A**) As a pattern recognition receptor ligand, β-glucan specifically binds to the Dectin-1 receptor on the surface of dendritic cells (DCs), initiating intracellular signaling pathways, inducing DC polarization toward a pro-inflammatory/antigen-presenting phenotype, and participating in the training effect of the innate immune system. Concurrently, β-glucan-based nanoparticles, acting as highly efficient delivery carriers, can encapsulate tumor antigens and immunostimulants, enter DCs via endocytosis, and facilitate the intracellular co-delivery of antigens and immunostimulants. (**B**) Tumor antigens entering DCs undergo cross-presentation via the MHC class I pathway, forming antigen-peptide–MHC class I complexes that are expressed on the DC surface. This complex binds to the TCR on $CD8^+$ T cells, while co-stimulatory molecules on the DC surface (such as CD80/CD86) bind to the CD28 receptor on the surface of $CD8^+$ T cells, providing critical co-stimulatory signals that synergistically activate $CD8^+$ T cells. The activated $CD8^+$ T cells proliferate and differentiate into cytotoxic T lymphocytes (CTLs), which release effector molecules such as perforin and granzyme to specifically recognize and kill tumor cells expressing the corresponding tumor antigens, effectively inhibiting tumor growth and metastasis.

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Natural Receptor Targeting by β-Glucan: Dectin-1-Mediated Trained Immunity

A substantial body of evidence demonstrates that β-glucan can rapidly activate the Dectin-1/Syk/CARD9/NF-κB signaling pathway by binding to the Dectin-1 receptor on macrophages and DCs. This interaction promotes the secretion of pro-inflammatory cytokines.[119–122] Remarkably, it also induces epigenetic reprogramming in monocytes and their differentiated macrophage progeny.[123] Mechanistically, the engagement of β-glucan with receptors such as Dectin-1 enhances the expression of long noncoding RNAs, for example, UMLILO,[124] which then recruits the WDR5-MLL1 complex to the promoter regions of crucial immune-related genes, thereby augmenting H3K4me3 histone modification.[125] This chromatin-level reprogramming endows innate immune cells with a memory-like functional state known as "trained immunity." During this process, the chromatin topology of immune-associated genes, including chemokines such as CXCL9 and CXCL10, undergoes remodeling,[113] and the expression of pro-inflammatory cytokines, such as IL-1β, displays enhanced and prolonged kinetics.[126] These alterations significantly increase nonspecific host responsiveness to tumor antigens and bolster antitumor immune surveillance.[127–130] However, it is important to note that studies have shown that the ability of dextran particles of different sizes to activate Dectin-1 varies. Dextran microparticles (approximately 3 μm in size) and dextran nanoparticles measuring 355 nm can interact significantly with Dectin-1 on the surface of monocytes, whereas 130-nm dextran nanoparticles have a weaker activating effect on this receptor.[131]

Engineered Targeting of Dextran: Receptor-Mediated Selective Delivery

Unlike the intrinsic bioactivity of β-glucan, native dextran does not bind to the Dectin-1 receptor and is predominantly internalized by APCs through macropinocytosis. However, this relatively inert characteristic provides a high degree of structural plasticity, facilitating a shift from passive uptake to active targeting through thoughtful chemical modification. One of the most notable strategies is the covalent attachment of mannose moieties to the dextran backbone, resulting in mannosylated dextran. This modified construct demonstrates high-affinity binding to the CD206 (mannose receptor) on M2-type DC subsets, thus enabling precise delivery of antigens or adjuvants.[132,133] An example of a clinically validated application of this targeting mechanism is the FDA-approved lymphatic tracer, Tc-99m Tilmanocept.[134]

Co-Delivery Strategies to Enhance Cross-Presentation and $CD8^+$ T Cell Activation

Building upon their targeting capabilities, glucan-based nanodelivery systems have been demonstrated to serve as efficient co-delivery platforms,[54,135,136] enabling the simultaneous intracellular delivery of tumor antigens and immunoadjuvants to APCs.[137–140] This co-delivery strategy facilitates the spatiotemporal coordination of antigen and adjuvant signals, thereby promoting the cross-presentation of antigens via the major histocompatibility complex class I pathway and effectively activating $CD8^+$ T cells.[141] Previous studies have employed dextran-based constructs to develop artificial antigen-presenting systems capable of inducing the activation and expansion of antigen-specific cytotoxic T lymphocytes (CTLs), resulting in significantly enhanced antitumor immune responses.[142]

Furthermore, co-delivered immunoadjuvants activate key signaling pathways, such as TLRs and STING, leading to the upregulation of costimulatory molecules and pro-inflammatory cytokines on APCs. This process establishes a supportive immunological microenvironment necessary for the complete activation of T cells. For instance, co-delivery systems incorporating STING agonists have effectively enhanced innate immune activation and amplified antitumor efficacy.[143,144]

Overall, glucan-based nanoparticles simultaneously enhance efficient tumor antigen presentation and adjuvant-mediated signal amplification, thereby providing both the "first signal" (antigen-specific recognition) and the "second signal" (costimulatory and inflammatory cues) required for complete $CD8^+$ T cell activation. This dual-signal synergistic mechanism contributes to overcoming immune tolerance within the TME and induces potent and durable antigen-specific CTL responses.

Remodeling the Tumor Immune Microenvironment: Tumor-Associated Macrophages Reprogramming and Treg Suppression

The immunosuppressive state within the TME constitutes a significant obstacle to effective antitumor immune responses. Specifically, the immunosuppressive network centered on M2-polarized TAMs and regulatory T cells (Tregs) plays

a crucial role in facilitating tumor immune evasion.[145,146] Consequently, strategies that involve reprogramming TAM phenotypes and suppressing Treg functions are widely acknowledged as essential for enhancing the efficacy of tumor immunotherapy.

The repolarization of TAMs from an immunosuppressive M2 phenotype to a pro-inflammatory M1 phenotype is a critical step in altering the immunological landscape of the TME. M1 macrophages secrete pro-inflammatory cytokines, such as IL-12 and TNF-α, which promote the activation of effector T cells and strengthen antitumor immune responses.[147] Simultaneously, phenotypic reprogramming of TAMs indirectly suppresses the recruitment and functional maintenance of Tregs. M2-polarized TAMs have been shown to recruit Tregs through the secretion of chemokines such as CCL22 and to sustain their immunosuppressive phenotype through cytokines including IL-10 and TGF-β.[145] Upon repolarization to the M1 phenotype, these immunosuppressive signals are significantly reduced, while the resulting pro-inflammatory environment becomes unfavorable for Treg survival and functional persistence. This alteration effectively disrupts the positive feedback loop of immune suppression mediated by the TAM-Treg interaction within the TME.

At the mechanistic level, various molecular targeting strategies have been deployed to induce TAM reprogramming. For instance, the delivery of small interfering RNA (siRNA) targeting the signal transducer and activator of transcription 6 can inhibit IL-4/IL-13-mediated M2 polarization signaling pathways.[146,148] Furthermore, small-molecule inhibitors such as BLZ-945 can disrupt colony-stimulating factor 1 receptor signaling, thus impeding survival signals essential for M2-type TAMs and diminishing their immunosuppressive functions.[149] Additionally, nanoregulatory strategies that modulate local tumor conditions such as pH, hypoxia, or ROS levels present novel approaches for TAM phenotypic reprogramming.[150–152]

In this context, glucan-based nanoparticles, due to their inherent immune recognition properties and multifunctional delivery capabilities, demonstrate significant advantages in modulating the TME. Emerging evidence suggests that these systems can modulate TAM function through multiple mechanisms. These strategies include exploiting surface charge differences to facilitate selective uptake, inhibiting immunosuppressive signaling pathways mediated by macrophage scavenger receptor A (SR-A/CD204), and delivering cytokines (eg, IL-15) or immunostimulatory agents (eg, R848). Consequently, these approaches effectively drive the phenotypic transition of TAMs from an immunosuppressive M2 state to a pro-inflammatory M1 phenotype.[153–155] Specifically, positively charged dextran nanogels have shown superior TAM-targeting efficiency compared to their negatively charged counterparts in breast cancer models, indicating that charge modulation is a critical engineering parameter for optimizing myeloid cell targeting.[156] Sulfated dextran-coated iron oxide nanoparticles selectively target scavenger SR-A/CD204 on macrophages, enabling precise labeling of M2-polarized macrophages and serving as probes for in vivo magnetic resonance imaging (MRI).[157] Moreover, low-molecular-weight dextran derivatives, such as those used in D-TAC technology, specifically target CD206-expressing M2 macrophages and activate their antitumor functions through the delivery of the TLR7 agonist DSP-0509.[158] Similarly, yeast-derived β-glucan particles activate the Syk-Card9-Erk signaling pathway through Dectin-1 engagement, directly inducing the repolarization of M2-type TAMs toward the M1 phenotype.[159]

Overall, current research on the regulation of the tumor immune microenvironment by glucan-based systems has largely focused on the phenotypic reprogramming of TAMs. The suppression of Treg function primarily relies on indirect effects resulting from this reprogramming. In contrast, there has been limited research on direct intervention strategies that specifically target Tregs to inhibit their immunosuppressive functions.

Activation and Amplification of Innate Immune Signaling Pathways

Activation of innate immune signaling pathways serves as a crucial bridge connecting innate and adaptive immune responses, playing both initiating and amplifying roles in antitumor immunity. As illustrated in Figure 5, nanodelivery systems enable the precise delivery of immunostimulatory agents to immune cells or within the TME, thereby achieving spatially and temporally controlled activation of innate immune pathways. This targeted modulation provides essential support for the induction of robust and effective antitumor immune responses.

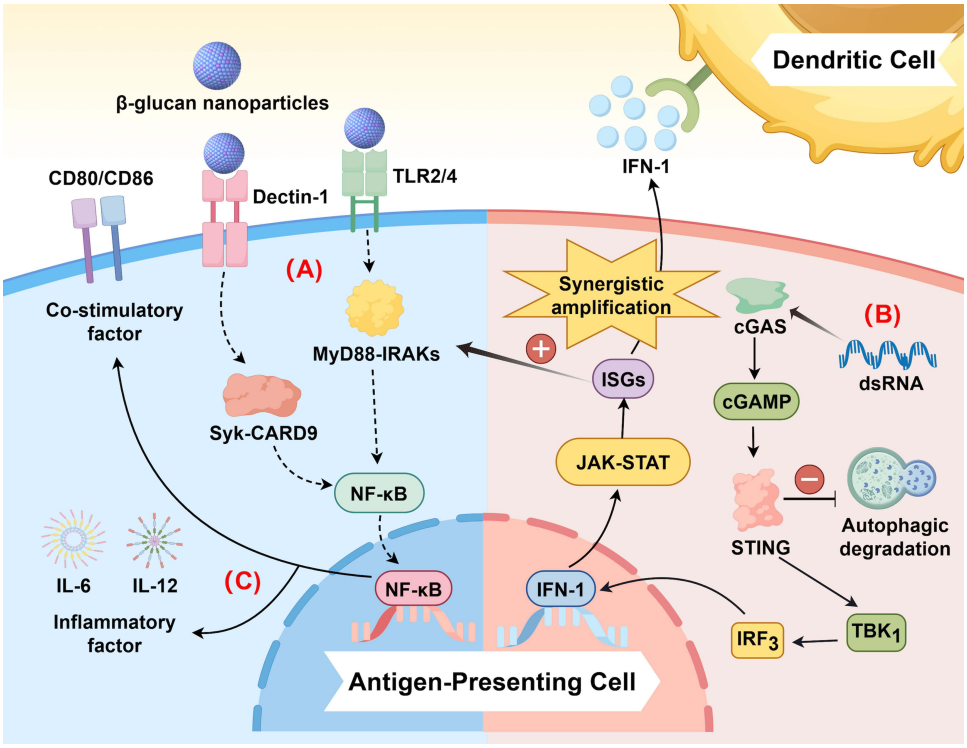

Figure 5 Multidimensional signaling cascade activation in APCs mediated by β-glucan-based nanoparticles. (**A**) Multireceptor Recognition and NF-κB Pathway Activation: β-Glucan nanoparticles serve as multivalent ligands that simultaneously engage the C-type lectin receptor Dectin-1 and Toll-like receptors TLR2 and TLR4 on the APC membrane. This dual engagement initiates the recruitment and activation of the Syk-CARD9 and MyD88-IRAK signaling axes, respectively. The convergence of these pathways robustly activates the transcription factor NF-κB, initiating the transcription of pro-inflammatory genes. (**B**) Cytosolic Nucleic Acid Sensing and Amplification of Signaling Cascades: Internalized dsRNA or cytosolic DNA induced by nanoparticles further stimulates the cGAS-STING pathway. Activation of STING promotes TBK1-mediated phosphorylation of IRF3, leading to the production of type I interferons (IFN-I). Secreted IFN-I functions in both autocrine and paracrine fashions through interferon receptors, engaging the JAK-STAT pathway and inducing the expression of interferon-stimulated genes. This pathway synergizes with Toll-like receptor signaling to amplify the signal effectively. (**C**) APC Maturation and Bridging to Adaptive Immunity: The integrated signaling cascades drive comprehensive APC maturation, characterized by the secretion of pro-inflammatory cytokines (IL-6, IL-12, TNF-α) and the upregulation of co-stimulatory molecules (CD80/CD86). Mature APCs further recruit and activate neighboring DCs through IFN-I and associated mediators, promote antigen cross-presentation, and effectively bridge innate and adaptive immunity, resulting in robust $CD4^+$ and $CD8^+$ T-cell responses.

Nanoregulation of the cGAS-STING Pathway

Within the myriad pathways of the innate immune system, the cGAS-STING axis is pivotal for the detection of cytosolic DNA and the subsequent production of IFN-1.[160] There is a growing body of evidence suggesting that nanodelivery systems can potentiate STING signaling through various mechanisms. These include epigenetic reprogramming strategies, such as the co-delivery of demethylating agents to restore the functionality of the STING pathway.[161] Additionally, nanoparticles may either induce DNA damage or promote the generation of immunogenic damage-associated molecular patterns (DAMPs), which facilitate DC cross-presentation and amplify STING-mediated immune responses.[162] These strategies significantly enhance IFN-1 production and have demonstrated efficacy in inhibiting tumor growth and improving survival in multiple tumor models.[162,163] Moreover, nanovaccine systems that combine targeted delivery with microenvironment-responsive properties further improve antigen uptake, lysosomal escape, and cross-presentation by optimizing particle morphology and stimulus-responsive release behaviors, thus counteracting the immunosuppressive TME.[164–166] Although small-molecule cGAS-STING agonists have progressed to clinical trials, the direct activation of this pathway by natural polysaccharides is still uncommon. Notably, Xu et al observed that low-molecular-weight β-glucan derived from brown algae directly enhances cGAS-STING signaling and promotes IFN-1 production.[167] This discovery not only underscores the role of glucans as delivery vehicles but also their intrinsic immunostimulatory capabilities. Such dual functionality underscores their potential in the development of innovative nano-immunomodulators that combine carrier and agonistic properties.

Synergistic Activation of Toll-Like Receptor Signaling

Beyond the STING pathway, TLR signaling is crucial for immune recognition and the initiation of inflammatory responses. Nanoparticle-mediated delivery of TLR7/8 agonists has proven effective in activating the MyD88-dependent signaling cascade, which in turn promotes DC maturation and enhances antitumor immune responses.[168,169]

Although the direct use of glucan-based nanoparticles for delivering TLR agonists is still relatively limited, emerging evidence points to their potential advantages in modulating innate immunity. Certain β-glucans can activate the MyD88-dependent NF-κB pathway through TLR2/4 engagement, acting synergistically with Dectin-1 to amplify inflammatory responses.[128,170] Furthermore, interactions between the STING and TLR pathways have been identified, where STING-induced IFN-1 production further enhances TLR-mediated immune signaling.[171] Additionally, aminated dextran-coated iron oxide nanoparticles have demonstrated the ability to directly adsorb the complement component C3b, thereby activating the lectin pathway of the complement system.[172]

These findings collectively indicate that the co-delivery of multiple innate immune agonists through glucan-based nanoparticles is a promising strategy for amplifying immune activation signals at various regulatory levels. This approach holds potential for overcoming immune tolerance within the TME and establishing more potent and long-lasting antitumor immune responses.[173–175]

Targeted Intervention of Immunosuppressive Cell Populations

The abnormal accumulation of immunosuppressive cells within the TME constitutes a significant obstacle to effective antitumor immunity and plays a critical role in facilitating immune evasion. Among these cells, Tregs and myeloid-derived suppressor cells (MDSCs) are pivotal in the immunosuppressive network. These cell populations employ multiple coordinated mechanisms to suppress the activation of effector T cells and diminish their functional activity, thereby aiding tumor immune escape. Recently, glucan-based nanodelivery systems have shown considerable promise in precisely modulating these immunosuppressive cell subsets,[176] providing innovative approaches to counteract the immunosuppressive TME and reinstate effective antitumor immune responses.

Targeted Modulation of Regulatory T Cells

Aberrant infiltration and sustained accumulation of Tregs within tumor tissues are major contributors to immune tolerance and resistance to immunotherapy.[177] Current research on glucan-based nanoparticles in Treg modulation predominately focuses on the delivery of siRNA targeting immune checkpoint molecules, such as PD-1/PD-L1 and LAG3,[178,179] and on combination strategies that incorporate small-molecule agents like BLZ-945.[88,180] These approaches aim to attenuate Treg-mediated immunosuppression. Beyond checkpoint modulation, a wealth of evidence supports the central role of the transforming growth factor-β (TGF-β) signaling pathway in the differentiation, recruitment, and maintenance of the immunosuppressive function of Tregs.[181] As such, targeting the TGF-β signaling pathway is considered an effective strategy to alleviate tumor-induced immune suppression and enhance effector T cell activity. However, the systemic administration of TGF-β inhibitors frequently results in significant off-target effects and systemic toxicity, which limit their clinical applicability.[182] In this context, nanodelivery systems present a viable approach for localized intervention in the TGF-β pathway. For instance, amphiphilic hydroxyethyl starch-polycaprolactone nanoparticles have been used to deliver the TGF-β inhibitor LY2157299 directly to lymphoma lesions, thereby enhancing CAR-T cell functionality.[183] Similarly, nanoparticles modified with the coagulation-targeting peptide A15, which carry TGF-β inhibitors, have shown pronounced tumor-targeting capabilities and antitumor efficacy.[184] Additionally, metal-lipid hybrid nanoparticles have been employed for TGF-β gene editing, reprogramming the TME into an "immune-activated" state and significantly improving the efficacy of subsequent immunotherapies.[185] Given their favorable biocompatibility and intrinsic immune recognition properties, glucan-based nanoparticles are increasingly recognized as ideal delivery platforms for TGF-β pathway inhibitors. These nanoparticles enable precise, tumor-localized interventions that enhance both safety and therapeutic controllability.

Functional Suppression of Myeloid-Derived Suppressor Cells

MDSCs, along with Tregs, constitute critical immunosuppressive populations that play central roles in tumor immune evasion. MDSCs inhibit T cell activation and effector functions through various mechanisms, including the depletion of essential amino acids such as arginine and cysteine, the production of ROS and peroxynitrite, and the secretion of diverse immunosuppressive mediators.[186] Current interventions targeting MDSCs primarily aim to attenuate their immunosuppressive activities or induce their differentiation into mature myeloid cells. For instance, the delivery of curcumin via self-assembled nanofibers or the administration of all-trans retinoic acid using nanocarriers has been demonstrated to promote MDSC reprogramming. These approaches reduce their recruitment and accumulation within the TME, enhance T cell proliferation and activation, and effectively reverse the immunosuppressive milieu.[187,188] Moreover, nanoparticle-mediated targeting of key immunosuppressive enzymes in MDSCs, such as indoleamine 2,3-dioxygenase 1, has significantly potentiated antitumor immune responses.[189] Collectively, nanodelivery-based strategies, including the delivery of differentiation-inducing agents and the inhibition of critical immunosuppressive enzymes, effectively mitigate MDSC-mediated immune suppression. These strategies do so without substantially impairing normal immune cell function, thereby restoring T cell-mediated antitumor activity.[190–192]

Overall, precise interventions targeting immunosuppressive cell populations, including Tregs and MDSCs, represent an important strategy for reversing tumor-induced immune suppression. Glucan-based nanoparticles, by enhancing delivery specificity and reducing systemic toxicity, offer distinct advantages in modulating immunosuppressive cell functions. However, their long-term safety, delivery selectivity, and potential synergistic effects with other immunotherapeutic strategies, such as ICIs or adoptive cell therapies, require systematic evaluation in future studies and clinical translation efforts.

Combination Immunotherapeutic Strategies Enabled by Glucan-Based Nanoparticles

Although tumor immunotherapy has yielded breakthrough outcomes in specific patient populations, monotherapy often fails to address tumor heterogeneity, the immunosuppressive TME, and the emergence of therapeutic resistance. These challenges limit the breadth and durability of clinical responses. Consequently, combination strategies that integrate distinct mechanisms of action have increasingly become a promising approach to enhance overall therapeutic efficacy. By coordinating multiple treatment modalities, it is possible not only to amplify antitumor immune responses but also to reduce the required doses of individual agents, thereby minimizing associated toxicities.

In this context, nanodelivery systems, particularly those functionalized with glucan-based platforms, provide an ideal vehicle for the synergistic integration of diverse immunotherapeutic strategies. Owing to their favorable biocompatibility, programmable structural design, and intrinsic immunomodulatory properties, dextran-based nanosystems enable precise delivery of immunoregulatory agents while simultaneously serving as a "synergistic hub" that bridges distinct therapeutic modalities. Such integration facilitates the transformation of localized therapeutic effects into systemic antitumor immune responses. This section will focus on recent advances and the underlying synergistic mechanisms of glucan-based nanoplatforms in combination immunotherapy strategies, including ICI, photothermal or PDT, and CAR-T cell therapy (Figure 6).

Synergistic Strategies with Immune Checkpoint Inhibitors

ICIs have significantly improved clinical outcomes across various tumor types. However, their efficacy as monotherapy is often limited by low response rates and the development of resistance. The integration of ICIs with nanodelivery systems or strategies that induce immunogenic cell death (ICD) presents a promising approach to enhance therapeutic efficacy while reducing systemic toxicity.

Firstly, substantial evidence supports the role of β-glucan as a natural inducer of trained immunity, capable of reshaping innate immune memory through epigenetic reprogramming. This reprogramming effectively counteracts the profoundly immunosuppressive TME. For instance, in refractory models such as hepatocellular carcinoma, β-glucan-mediated immune training has significantly improved ICI responsiveness.[193] This mechanism serves as an intrinsic

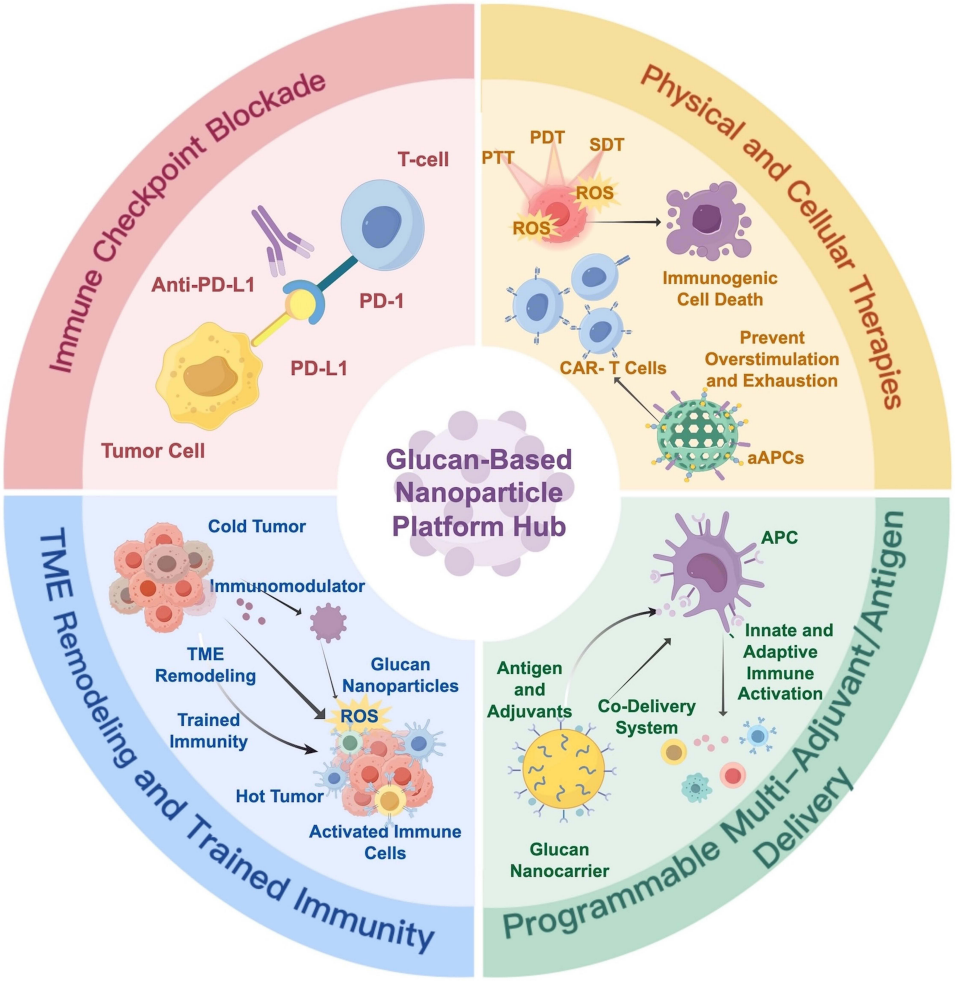

Figure 6 Glucan-based nanoparticle platforms as a central hub for multimodal combinational immunotherapy. This schematic illustrates how the platform integrates ICI, physical and cell-based therapies (e.g, PTT/PDT-induced immunogenic cell death [ICD] and CAR-T cell expansion), and key application pathways within a multi-component programmable delivery system. This platform can enhance local tumor immune activation and improve the response to checkpoint blockade therapy by delivering PD-L1 siRNA, immunomodulatory molecules, or ICD inducers. Concurrently, physical therapies such as PTT/PDT can induce immunogenic cell death in tumor cells, promoting the release of tumor antigens and DAMPs, thereby enhancing APC maturation and T-cell activation. Furthermore, dextran- or mannitol-based nanostructures can be used for in vitro expansion of CAR-T cells, co-delivery of antigens and adjuvants, and remodeling of the tumor immune microenvironment. By modulating immunosuppressive states, training immune cells, and activating effector immune cells, they promote the transition from a "cold" to a "hot" tumor-like immune state in certain models.

driving force for transforming "cold" tumors into "hot" tumors, thus expanding the therapeutic window for checkpoint blockade.

Secondly, at the level of precision delivery, glucan-based nanoparticles serve as efficient carriers for the targeted delivery of anti-PD-1/PD-L1 antibodies or small-molecule immunomodulators to specific tumor tissues or immune cell populations. This targeted approach minimizes systemic exposure and increases the local effective drug concentration within the tumor immune microenvironment. For example, a representative study demonstrated that amine-containing small molecules were grafted onto a dextran backbone through acetal linkages, co-loaded with PD-L1 siRNA, and integrated with imaging probes to create a degradable theranostic nanoplatform capable of real-time visualization and precise gene silencing.[26] Similarly, Yan et al designed pH-sensitive amphiphilic poly(β-amino ester) micelles co-loaded with an MDSC inhibitor and a PD-L1 inhibitor. The outer layer was electrostatically coated with dextran sulfate, resulting in a cascade acid-responsive composite nanoparticle. This system effectively prolonged drug half-life, enhanced deep tumor penetration, and comprehensively activated both innate and adaptive immune axes, ultimately achieving significant tumor growth suppression.[153] Beyond direct drug delivery, glucan-based nanoplatforms can also indirectly potentiate checkpoint blockade by amplifying ICD effects. ICD induction promotes the synchronized release of DAMPs

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and tumor neoantigens, thereby initiating a robust antitumor immune cascade. Recently, Deng et al developed a photoresponsive camptothecin-loaded dextran nano-immunomodulator, which significantly enhanced ICD in tumor cells through precise control of drug release kinetics.[194] Notably, the combination of ICD inducers with ICIs has been shown to produce pronounced synergistic antitumor effects,[195] effectively reversing tumor-associated immune suppression while inhibiting metastasis and recurrence.

In summary, glucan-based nanoplatforms offer a versatile strategy to overcome the resistance and toxicity associated with ICI by enabling precise delivery of immunomodulators and intelligently integrating ICD-inducing mechanisms.

Integration with Physical Modalities and Cell-Based Therapies

Glucan-based nanoplatforms exhibit unique advantages in integrating photothermal therapy (PTT), PDT, and cell-based therapies. Their principal strength resides in their capacity to transform localized physical or chemical therapeutic interventions into enhanced systemic antitumor immune responses, thus connecting focal treatment effects with sustained immunological activation.

Immunological Synergy Induced by Photothermal Therapy

PTT employs photothermal conversion materials to generate localized hyperthermia upon exposure to near-infrared irradiation, thereby inducing ICD in tumor cells. This process facilitates the release of tumor-associated antigens (TAAs) and initiates an "in situ vaccination" effect.[196] During ICD, calreticulin relocates to the cell surface, and DAMPs such as ATP and high-mobility group box 1 are liberated. Collectively, these signals enhance DC maturation and antigen presentation, leading to the vigorous activation of antigen-specific CTLs.[197]

Thus, apart from its direct tumor-ablative capacity, PTT can amplify tumor immunogenicity and restructure the tumor immune microenvironment to promote systemic antitumor immune responses. Nonetheless, the extent of immune activation is significantly influenced by the photothermal conversion efficiency, biocompatibility, and tumor-targeting capability of the photothermal nanoagents.[198] For instance, Jin et al developed a theranostic nanoplatform that, when combined with an anti-PD-L1 ICI, markedly enhanced T-cell infiltration and inflammatory cytokine secretion at tumor sites, while concurrently suppressing the growth of both primary and distant tumors. These findings provide compelling evidence for surmounting resistance to immunotherapy through synergistic PTT-based strategies.[199]

Photodynamic Therapy-Driven Systemic Immune Activation

PDT is a noninvasive local treatment strategy for tumors that utilizes photosensitizers to generate ROS when irradiated with light of a specific wavelength. This process results in membrane damage, mitochondrial dysfunction, and programmed cell apoptosis. However, conventional hydrophobic photosensitizers often exhibit poor in vivo stability and limited tumor accumulation, which hampers their broader application in tumor immunotherapy. The use of functionalized glucan-based nanocarriers has been shown to significantly enhance the loading efficiency of photosensitizers and enable controlled biodistribution, thus addressing these limitations and providing a critical material foundation for improving the efficacy of PDT.[200–202]

Expanding upon this foundation, Jin et al developed a nanoplatform coated with dextran sulfate that encapsulated the photosensitizer chlorin e6.[203] This system specifically targeted TAMs and generated substantial ROS upon laser irradiation, not only enhancing PDT-mediated tumor cell destruction but also reshaping the tumor immune microenvironment through TAM modulation. This dual functionality facilitated synergistic local tumor ablation and immune activation. The study confirmed the feasibility of using dextran-coated photosensitizers in PDT and suggested that reprogramming myeloid cells may enhance downstream immune responses. Further research has indicated that combining PDT with immunotherapy provides significant benefits in eliciting systemic antitumor immunity.[204] Various nano-delivery platforms that integrate PDT with immunomodulatory agents have been effective in suppressing primary tumor growth and in controlling distant metastatic lesions.[205,206] Importantly, the therapeutic effect of PDT is largely confined to the irradiated area. This spatial restriction, when combined with precise control of light exposure, facilitates efficient and localized treatment while minimizing collateral damage to normal tissues, including non-targeted macrophages. In a related development, Wang et al engineered a dextran-black TiO_2 composite hydrogel that integrates PDT with PTT and

sonodynamic therapy, significantly enhancing ROS generation and photothermal conversion efficiency. This multimodal platform represents a synergistic approach to local therapy that is particularly effective for infectious wounds and tumors.[207]

In conclusion, glucan-based PDT platforms exhibit significant advantages when integrated with immunotherapeutic strategies. The further development of systems that enable co-delivery with ICIs could greatly enhance PDT-induced immune activation, leading to robust and durable systemic antitumor responses and potentially eliciting a pronounced abscopal effect against distant metastatic lesions.

Engineering Synergy with CAR-T Cell Therapy

CAR-T cell therapy has demonstrated significant clinical success in treating hematological malignancies. Nevertheless, the conventional manufacturing of CAR-T cells typically depends on intensive ex vivo stimulation to facilitate rapid T-cell expansion. This method can lead to overactivation and functional exhaustion, which may impair the cells' persistence and antitumor efficacy in vivo, particularly in solid tumors.

To overcome these challenges, Zheng et al developed a dextran-based nanoscale artificial APC platform that efficiently expands functional T cells.[29] This platform replicates the natural antigen presentation process, enabling robust T-cell activation while minimizing the exhaustion caused by overstimulation, thus significantly enhancing the therapeutic potential of CAR-T cells. Remarkably, the dextran-based nano-aAPC system demonstrated excellent biocompatibility, showing no apparent cytotoxicity during coculture with T cells. Its nanoscale size facilitates the efficient removal of nano-aAPCs through simple centrifugation and washing steps after T-cell expansion, obviating the need for additional magnetic bead separation. This simplification of the CAR-T cell manufacturing process could reduce the costs associated with clinical translation. Moreover, carboxymethyl dextran-coated magnetic nanoparticles have been used effectively for $CD3^+$ T-cell isolation and, when conjugated with antibodies, allow in vivo tracking via MRI, showcasing their theranostic potential.[208] Overall, these studies suggest that glucan-based nanosystems, whether through biomimetic antigen presentation platforms or magnetic separation strategies, provide significant advantages in enhancing CAR-T cell expansion efficiency, preserving cellular functionality, and streamlining production processes. These innovations offer promising avenues for addressing the current limitations in solid tumor immunotherapy.

Multi-Antigen/Multi-Adjuvant Co-Delivery and Temporally Programmable Release

The synergistic delivery of multiple antigens and adjuvants, combined with a design that allows for controlled sequential release, has emerged as a pivotal research area in tumor immunotherapy. The essence of this strategy involves encapsulating or conjugating multiple TAAs and immune adjuvants onto a single delivery platform. By responding intelligently to the TME or intracellular stimuli, this approach achieves synergistic and precise activation of the immune system, thereby amplifying the overall effectiveness of immunotherapy.

Various studies have successfully implemented antigen-adjuvant co-delivery strategies using glucan-based nanodelivery systems. For example, vinyl sulfone-functionalized acetalated dextran (Ac-DEX) microparticles have been meticulously engineered to create a broad-spectrum subunit influenza vaccine platform.[209] This system employs a "dual-particle" synergistic delivery strategy: the COBRA hemagglutinin antigen is covalently attached to the surface of microparticles to improve antigen presentation efficiency, while the immunoadjuvant cyclic GMP-AMP (cGAMP) is encapsulated within separate Ac-DEX microparticles. Such compartmentalization protects cGAMP from premature degradation in vivo and facilitates its targeted release within the acidic intracellular environment of APCs. Consequently, STING signaling is effectively activated, resulting in a significantly enhanced antigen-specific immune response.

Moreover, integrating glucan-based co-delivery systems with localized delivery modalities, such as microneedles, facilitates site-specific drug release, while minimizing systemic toxicity. Chen et al developed a smart, stimulus-responsive platform that incorporates a microneedle-based delivery strategy.[210] This system employed acetalated dextran to co-load a hydrophobic photosensitizer (ZnPc) and a hydrophilic ICI (anti-CTLA-4 antibody), which were then integrated into a microneedle array for localized co-delivery. The platform exhibited pH-responsive behavior and demonstrated pronounced antitumor efficacy in animal models, significantly reducing systemic toxicity.

Beyond the benefits of multi-component synergistic delivery, glucan-based nanosystems also offer significant advantages in controlled release and temporally programmed therapeutic design. By modulating crosslinking density, pore architecture, and drug loading modalities, or by incorporating stimuli-responsive elements such as pH, ROS, or enzyme-sensitive linkages, these systems can achieve sustained release and localized retention of therapeutic agents. Such capabilities enable the maintenance of stable immune stimulation intensity, which is particularly beneficial for tumor immunotherapy that requires prolonged intervention. Dosta et al described a dual-sensitive nanoparticle system capable of disassembling under TME-specific conditions and subsequently forming nanogels in situ, thereby significantly prolonging local retention and enabling sustained release of therapeutic agents.[93] He et al achieved rapid drug release within the acidic lysosomal environment of tumor cells by tuning the chemical structure and crosslinking degree of dextran.[211] Notably, their system was capable of crossing the blood-brain barrier and maintaining sustained drug delivery at tumor sites, offering a promising strategy for the treatment of central nervous system malignancies, such as glioblastoma. Furthermore, Ma et al developed a dextran-aspirin prodrug nanoplatform that exhibited in situ retention for over 12 hours in colorectal cancer models, continuously releasing salicylic acid. This system exerted long-term antitumor effects by modulating the gut microbiota and inflammatory microenvironment.[212]

In summary, glucan-based multi-antigen/multi-adjuvant co-delivery systems, with their programmable sustained-release capabilities, enable precise modulation of both innate and adaptive immunity through modular loading and intelligent stimulus-responsive release mechanisms. This integrative design strategy provides a robust engineering foundation for the development of efficient, safe, and durable tumor immunotherapy approaches. However, although most combination therapy regimens have demonstrated good efficacy in preclinical models, few studies have compared the synergistic efficacy, safety profiles, and cost-effectiveness of different combination regimens. It remains to be seen whether the results of many studies can be independently replicated, and there is a lack of standardized evaluation systems for determining optimal dose ratios and administration sequences.

Clinical Applications and Translational Challenges of Glucan-Based Nanoparticles

Preclinical Validation of Therapeutic Efficacy and Safety Profiles

Glucan-based nanoparticles, recognized for their multifunctional properties that combine favorable biocompatibility with significant engineering versatility, have shown effective tumor-targeting capabilities, pronounced antitumor activities, and relatively controllable safety profiles in various preclinical animal models. These results provide a crucial experimental basis for their potential advancement toward clinical translation. Table 3 summarizes the advantages and disadvantages of glucan-based nanoparticles compared to other types of nanoparticles in various applications.

Overall, glucan-based nanoparticles are characterized by their safety and biocompatibility.[220,221] However, the biological activity of dextran is influenced by its source, purity, molecular weight, branching degree, solubility, conformation, and particle size. Additionally, they still have shortcomings in terms of mechanical properties, stability, and standardization, which must be addressed through precise engineering design. Furthermore, it is worth emphasizing that the unique value of the glucan-based system lies in its material-immune interface: β-glucan can interact with pattern recognition receptors (such as Dectin-1 and complement receptor 3),[222] while α-glucan primarily serves as a relatively inert and chemically modifiable scaffold, suitable for modular engineering and delivery applications.

In terms of efficacy in animal studies, the primary advantage of glucan-based nanoparticles is their tumor-selective accumulation due to their role as delivery carriers, which leads to enhanced therapeutic benefits. For example, the dextran-dihydroartemisinin-docetaxel dual-drug conjugate system can achieve highly effective tumor suppression in nude mouse xenograft models by improving the in vivo distribution of hydrophobic antitumor drugs. In clinically relevant patient-derived xenograft models, EPI-loaded dextran nanoparticles also demonstrated superior antitumor activity compared to the free drug.[223] Five days after administration, it achieved a 70% inhibition rate of patient-derived ovarian cancer growth in a mouse model, whereas free EPI achieved only a 40% inhibition rate. This finding is particularly significant as it indicates that glucan-based nanodelivery systems can achieve therapeutic advantages, even in highly heterogeneous tumor models. Similarly, albumin-dextran-coated nanoparticles significantly delayed tumor growth in

Table 3 Advantages and Disadvantages of Glucan-Based Nanoparticles Compared to Other Common Types of Nanoparticles in Various Applications

Nanosystems	Core Materials	Key Advantages	Typical Limitations	Typical Applications	References
Glucan-based nanoparticles	Natural polysaccharides	Excellent biocompatibility and biodegradability; High water solubility and good colloidal stability; Low immunogenicity	Weak structural mechanical properties; In vivo stability depends largely on the modification strategy.	Drug carriers, targeted delivery, immunological carriers	[213,214]
Lipid nanoparticles	Phospholipids/ Lipids	Amphiphilic properties allow for the simultaneous loading of both hydrophobic and hydrophilic drugs; easy to customize	Prone to being covered by a protein cap; rapidly cleared from the body; stability is affected by the external environment	Drug Delivery	[215,216]
Polylactic-co-glycolic acid (PLGA) nanoparticles	Synthetic polymers	Physical and chemical properties can be precisely controlled; high drug-loading capacity; controllable degradation kinetics	Organic residues must be strictly controlled; metabolites can create an acidic environment.	Sustained-release systems, targeted delivery	[217]
Chitosan nanoparticles	Natural polysaccharides	Low toxicity; specific receptor binding affinity	Solubility is affected by pH and ionic strength.	Targeted release, oral	[218]
Gold nanoparticles	Metal/Oxide	Excellent optical, magnetic, and electrical properties	Potential cytotoxicity; not biodegradable or its degradation products are difficult to remove	Bioimaging, radioluminescence, photothermal therapy	[219]

a murine colorectal cancer model,[224] further substantiating the broad applicability of dextran-based platforms across various tumor types.

Concerning safety, Numerous studies have consistently reported that the administration of glucan-based nanoparticles did not result in significant body weight loss or histopathological damage to major organs in experimental animals.[225,226] For instance, dextran-coated iron oxide nanoparticles have been used for ultra-high-resolution imaging of brain tumor vasculature without inducing evident toxicity in animal models.[227] Furthermore, the stimulus-responsive design not only enhances therapeutic precision but also helps to minimize systemic toxici, for example, pH-responsive fluoxetine-dextran nanoparticles demonstrate favorable safety profiles while supporting both antidepressant and antitumor applications.[223] Despite excellent efficacy data, the study by Kosnik, W. et al was terminated early due to severe adverse effects, indicating that even in preclinical models, the dextran-based nanoparticle formulation failed to completely eliminate the systemic toxicity of epirubicin.[225] Despite excellent efficacy data, the study by Kosnik, W. et al was terminated early due to severe adverse effects, indicating that even in preclinical models, the dextran-based nanoparticle formulation failed to completely eliminate the systemic toxicity of epirubicin.[228] The optimization of pharmacokinetic behavior is also a crucial mechanism for reducing the toxicity of dextran-based nanosystems. Investigations have shown that dextran-based dual-drug delivery systems significantly extend systemic circulation time and decrease nonspecific distribution to normal tissues, thereby effectively mitigating systemic toxicity.[225,229] Despite excellent efficacy data, the study by Kosnik, W. et al was terminated early due to severe adverse effects, indicating that even in preclinical models, the dextran-based nanoparticle formulation failed to completely eliminate the systemic toxicity of epirubicin.[223] This result serves as a clear illustration that preclinical efficacy advantages do not equate to safe translation. Toxicity optimization of dextran carriers still faces practical challenges, and one cannot draw the optimistic conclusion that "clinical trials can proceed safely" based solely on tumor suppression data from animal models. Despite excellent efficacy data, the study by Kosnik, W. et al was terminated early due to severe adverse effects, indicating that even in preclinical models, the dextran-based nanoparticle formulation failed to completely eliminate the systemic toxicity of epirubicin.[229]

Glucan-Based Formulations Advancing Into Clinical Trials for Cancer Therapy

Although preclinical investigations have provided compelling evidence for the therapeutic potential of glucan-based nanoparticles, the biological differences between animal models and human diseases necessitate their rigorous validation through systematic clinical studies. In this regard, several glucan-related formulations have recently entered clinical evaluation, providing direct insights into their efficacy and safety profiles.

Currently, glucan-derived formulations entering clinical phases are predominantly administered as oral β-glucan or its derivatives. These agents are primarily used as immunomodulators, either as monotherapy or in combination with vaccines, cytokines, or monoclonal antibodies, aiming to enhance antitumor or anti-infective immune responses. Clinical evidence to date suggests that applications of β-glucan in oncology focus primarily on two areas. Firstly, as an immunomodulatory adjunct to chemotherapy, β-glucan has been observed to significantly elevate levels of IL-2, IFN-γ, and $CD4^+$ T cells. Notably, patients with low baseline serum granzyme A expression have shown better therapeutic responses and prolonged overall survival. It is important to acknowledge that approximately 30% of patients in this study experienced grade ≥3 treatment-related adverse events, with nausea being the most frequently reported symptom (53.3%).[230] Secondly, in the context of nutritional intervention, β-glucan-fortified oral nutritional supplements have significantly increased energy intake (792.55 kcal/day) and protein intake (40.72 g/day) in patients with advanced malignancies. These benefits were particularly pronounced in individuals with head and neck or upper gastrointestinal cancers, in advanced-stage disease, or in those receiving multiple lines of therapy. Nonetheless, improvements in certain surgical outcome parameters remained limited.[231,232]

Table 4 summarizes the bioactive β-glucan formulations that have progressed into clinical trials for cancer therapy. Regarding efficacy and safety data, in high-risk neuroblastoma, the combination of β-glucan as an immunostimulant with anti-GD2 therapy, administered orally in conjunction with the 3F8 regimen, demonstrated good overall tolerability with no significant additive toxicity. Preliminary antitumor signals were observed, providing a safety basis for vaccine

Table 4 Bioactive β-Glucan Preparations That Have Entered Clinical Trials for Cancer Treatment

NCT Number	Study Title	Study Status	Conditions	Interventions	Phases	Study Type
NCT04387682	MDSCs in oral squamous cell carcinoma Patients	UNKNOWN	Squamous Cell Carcinoma of the Oral Cavity	DIETARY SUPPLEMENT: β-glucan	Not Applicable	INTERVENTIONAL
NCT06199128	Efficacy and Safety of Carboxymethyl Beta-glucan and Policarbophil in HPV Positive Patients	COMPLETED	Human Papillomavirus Infection	DIETARY SUPPLEMENT: carboxymethyl β-glucan	_	OBSERVATIONAL
NCT04936529	A Study of a Vaccine in Combination With β-glucan and GM-CSF in People With Neuroblastoma	RECRUITING	Neuroblastoma	DIETARY SUPPLEMENT: β-glucan;DRUG: GM-CSF;BIOLOGICAL: OPT-821	PHASE2	INTERVENTIONAL
NCT06057948	A Study of a Vaccine in Combination With Beta-glucan in People With Neuroblastoma	RECRUITING	Neuroblastoma High-risk Neuroblastoma; Metastatic Neuroblastoma	BIOLOGICAL: OPT-821 (QS-21); DIETARY SUPPLEMENT: oral β-glucan	PHASE2	INTERVENTIONAL
NCT01829373	Lung Cancer Vaccine Plus Oral Dietary Supplement	COMPLETED	Lung Cancer	BIOLOGICAL: vaccine 1650-G	PHASE1	INTERVENTIONAL
NCT00492167	Beta-Glucan and Monoclonal Antibody 3F8 in Treating Patients With Metastatic Neuroblastoma	COMPLETED	Neuroblastoma	BIOLOGICAL:β-glucan;BIOLOGICAL: monoclonal antibody 3F8;OTHER: immunohistochemistry staining method;OTHER: laboratory biomarker analysis	PHASE1	INTERVENTIONAL
NCT04771546	Efficacy of Intravaginal Carboxymethyl-β-glucan and Polycarbophil on Low-grade Cervical Lesions	UNKNOWN	Human Papilloma Virus	DEVICE: Colpofix	Not Applicable	INTERVENTIONAL
NCT00911560	Bivalent Vaccine With Escalating Doses of the Immunological Adjuvant OPT-821, in Combination With Oral β-glucan for High-Risk Neuroblastoma	ACTIVE NOT RECRUITING	Neuroblastoma	BIOLOGICAL: adjuvant OPT-821 in a vaccine containing two antigens (GD2L and GD3L) covalently linked to KLH;BIOLOGICAL: oral β-glucan	PHASE1; PHASE2	INTERVENTIONAL
NCT04781023	Efficacy of an Intravaginal Treatment With Carboxymethyl-β-glucan and Polycarbophil in HR-HPV Clearance	UNKNOWN	Human Papilloma Virus	DEVICE: Colpofix	Not Applicable	INTERVENTIONAL

combination therapy (NCT00492167).[233] Differences in study designs across various cancer types also reflect the varying clinical roles of β-glucan. Neuroblastoma studies focus on antigen-targeted immune enhancement. Oral squamous cell carcinoma studies center on regulating MDSCs and improving immune suppression as core endpoints (NCT04387682).[234] HPV-related research targets viral clearance and the resolution of precancerous lesions, falling under the category of preventive interventions (NCT06199128). In lung cancer vaccines, β-glucan is used as an adjuvant in the 1650-G vaccine to enhance immune responses (NCT01829373).[235] Additionally, a Phase II study combining the GD2/GD3 vaccine with β-glucan increased anti-GD2 IgG1 titers without increasing toxicity. However, this did not translate into significant progression-free survival/overall survival benefits, suggesting that immune enhancement requires more precise dosing schedules and identification of the target patient population (NCT00911560).[236] Overall, neuroblastoma exhibits the strongest link between preclinical mechanisms and trial design, yielding the most reliable signals, due to well-defined targets, clear combination logic, and quantifiable immunological endpoints. For other cancer types, research remains primarily focused on mechanism exploration and lacks standardized efficacy endpoints.[237]

In summary, these clinical studies provide preliminary evidence supporting the immunomodulatory potential of glucan-based formulations, their limitations, including small sample sizes, relatively short follow-up periods, and some endpoints failing to reach statistical significance, underscore the necessity for larger-scale, rigorously designed randomized controlled trials to more definitively establish their clinical value.

In addition, dextran, an α-glucan, is extensively utilized in clinical settings, particularly in iron formulations and combination supportive therapeutic systems. Dextran-based formulations and β-glucan immunotherapy trials serve different clinical purposes. β-glucan is typically used to enhance or modulate immune responses, whereas dextran primarily functions as a carrier, chelating matrix, or lymphatic tracing platform in these studies.[238,239] Table 5 presents an overview of dextran (α-glucan)-based formulations that have entered clinical trials for cancer-related applications.

As presented in Table 5, the trials included herein focus not on direct antitumor efficacy such as tumor regression, progression-free survival, or overall survival, but on sentinel lymph node identification, diagnostic accuracy, procedural feasibility, and administration safety. Among these, Tc-99m-tilmanocept represents a representative dextran-based agent with relatively mature clinical evidence. It is structured with a dextran backbone conjugated to mannose ligands and DTPA chelating groups, enabling targeting of lymph node macrophages or dendritic cells via mannose-CD206 recognition. Studies in breast cancer, melanoma, and head and neck tumors have mainly evaluated its detection performance and safety in sentinel lymph node localization, demonstrating the clinical value of dextran as a precision tracing platform (NCT00671918; NCT01106040; NCT02287675; NCT04261179).[240] Research in colorectal cancer, endometrial cancer, pediatric solid tumors, and Kaposi's sarcoma has further expanded its applications to lymphoid tissue targeting, PET/CT imaging, special-population localization, and lymphatic drainage mapping (NCT01902953; NCT05446324; NCT02509598; NCT02201420; NCT03157167). Studies in oral squamous cell carcinoma have also combined sentinel lymph node biopsy with personalized neck radiotherapy strategies, suggesting that such tracers can contribute to the optimization of treatment decisions (NCT07121595).[241]

The reason these trials tend to yield clear clinical signals is primarily the direct correlation between material structure, mechanism of action, and clinical endpoints. Overall, the clinical advantages of dextran lie not in direct immune activation, but in its preclinical properties, such as high modifiability, the ability to conjugate with targeting ligands, and biocompatibility. These features directly support its successful translation into lymphatic tracing and drug delivery systems, with a clear translational pathway and high degree of standardization.

Practical Constraints, Regulatory Challenges, and Manufacturing Bottlenecks

Although glucan-based nanoparticles have demonstrated positive results in most preclinical studies, their further translation into clinical applications faces multiple practical challenges. First, their efficacy is highly system- and model-dependent and is not consistently reliable across all experimental designs.[28,242,243] Differences in dosing regimens and tumor immunogenicity can lead to varying degrees of efficacy. Furthermore, even minor variations in particle size, structure, and preparation methods can significantly affect targeting and immunogenicity, potentially leading to insufficient reproducibility across studies or differing clinical trial outcomes among various cancers. Additionally, current research remains primarily focused on short-term efficacy and acute toxicity assessments. Their long-term safety, chronic

Table 5 Dextran (α-Glucan) Formulations That Have Entered Clinical Trials for Cancer Therapy

NCT Number	Study Title	Study Status	Conditions	Interventions	Phases	Study Type
NCT00401544	Darbepoetin Alfa With or Without Intravenous (IV) Iron	COMPLETED	Anemia;Non-Myeloid Malignancies	DRUG: darbepoetin alfa;DRUG: IV iron dextran	PHASE2	INTERVENTIONAL
NCT01902953	Tc-99m Tilmanocept as Lymphoid Tissue Targeting Agents in Colon Cancer (CNC)	COMPLETED	Colon Cancer;Rectal Cancer	DRUG: Tc-99m Tilmanocept and VBD Sln dissection	PHASE2	INTERVENTIONAL
NCT05446324	Feasibility of Gallium-68-tilmanocept PET/CT for Sentinel Lymph Node Detection in Endometrial Cancer	UNKNOWN	Endometrial Cancer	DRUG: Gallium-68-tilmanocept	PHASE3	INTERVENTIONAL
NCT02287675	Sentinel Lymph Node Biopsy Findings in Patients With Breast Cancer	COMPLETED	Breast Cancer	DRUG: Tc-99m Tilmanocept;DRUG: Sulfur Colloid	PHASE4	INTERVENTIONAL
NCT02065232	Sentinel Lymph Node Mapping Post-Injection Site Pain	COMPLETED	Breast Cancer	DRUG: Tilmanocept; DRUG: Sulfur Colloid	_	OBSERVATIONAL
NCT00671918	Trial of Tc-99m Tilmanocept in Intraoperative Localization of Lymph Nodes in Breast Cancer and Melanoma	COMPLETED	Breast Cancer; Melanoma	DRUG: Tc-99m Tilmanocept	PHASE3	INTERVENTIONAL
NCT01106040	Breast and Melanoma Trial With Tc-99m Tilmanocept to Identify Lymph Nodes	COMPLETED	Breast Cancer; Melanoma	DRUG: Tc-99m Tilmanocept	PHASE3	INTERVENTIONAL
NCT04261179	Study Comparing Tc-99m Tilmanocept vs. Albumin Nanocolloid in Head and Neck, Melanoma and Breast Cancer	UNKNOWN	Head Cancer;Neck Cancer;Melanoma; Breast Cancer	DRUG: Tc-99m Tilmanocept;DRUG: Nanocoll	PHASE4	INTERVENTIONAL
NCT03199560	Tilmanocept vs Sulfur Colloid in Sentinel Lymph Node Biopsy	UNKNOWN	Sentinel Lymph Node Biopsy;Breast Cancer	DRUG: Tc 99m tilmanocept;DRUG: Tc 99m filtered sulfur colloid	PHASE4	INTERVENTIONAL
NCT02509598	A Study of Tc-99m Tilmanocept as a Lymphoid Tissue Targeting Agent in Pediatric Patients With Melanoma, Rhabdomyosarcoma, or Other Solid Tumors Who Are Undergoing Lymph Node Mapping	COMPLETED	Rhabdomyosarcoma; Melanoma	DRUG: Tc99m tilmanocept;DRUG: Vital Blue Dye (optional); PROCEDURE: Lymph Node Mapping	PHASE2	INTERVENTIONAL

(*Continued*)

Table 5 (Continued).

NCT Number	Study Title	Study Status	Conditions	Interventions	Phases	Study Type
NCT02201420	Evaluation of Tc 99m Tilmanocept Localization in Primary Cutaneous Kaposi's Sarcoma and Lymphatic Drainage by SPECT/CT	COMPLETED	Kaposi's Sarcoma	DRUG: Tc 99m tilmanocept	PHASE2	INTERVENTIONAL
NCT03157167	An Evaluation of Tc 99m Tilmanocept by IV and Subcutaneous Injection in Kaposi Sarcoma (KS)	COMPLETED	Kaposi Sarcoma;HIV Infections	DRUG: Tc99m-tilmanocept	PHASE1	INTERVENTIONAL
NCT07121595	Personalized Neck Radiation Therapy Directed by Sentinel Lymph Node Biopsy for the Treatment of Oral Cavity Squamous Cell Carcinoma, PRECEDENT Trial	RECRUITING	Oral Cavity Squamous Cell Carcinoma;Stage I Lip and Oral Cavity Cancer AJCC v8;Stage II Lip and Oral Cavity Cancer AJCC v8;Stage III Lip and Oral Cavity Cancer AJCC v8;Stage IVA Lip and Oral Cavity Cancer AJCC v8	PROCEDURE: Biospecimen Collection;DRUG: Carboplatin;DRUG: Cisplatin; PROCEDURE: Computed Tomography; PROCEDURE: Modified Barium Swallow;DRUG: Paclitaxel; PROCEDURE: Positron Emission Tomography;OTHER: Questionnaire Administration; RADIATION: Radiation Therapy; PROCEDURE: Sentinel Lymph Node Biopsy; PROCEDURE: Single Photon Emission Computed Tomography; RADIATION: Technetium Tc 99m-labeled Tilmanocept; OTHER: Technetium Tc-99m Sulfur Colloid	PHASE2	INTERVENTIONAL

immunological effects, and stability under different physiological and pathological conditions still require validation through more systematic and standardized studies. In addition, from a regulatory standpoint, there is currently no universally accepted definition of nanomedicine, nor is there a standardized framework. This misalignment may lead to inconsistent characterization methodologies and consequent delays in the approval processes for clinical trials.[96,244] In terms of large-scale manufacturing, the selection of starting materials, ensuring batch-to-batch consistency, and the

standardization of critical quality attributes significantly heighten the complexity of clinical translation and commercial-scale production.[245] Furthermore, further research is needed to determine how to effectively integrate dynamic control strategies into the industrial production process of glucan-based nanomedicines.[95]

In summary, most current studies remain at the stage of in vitro cell experiments and animal studies. Although glucan itself has been approved for use in certain anticancer applications, glucan-based nanoparticles as a novel tumor immunomodulatory delivery system still lack essential research data for clinical translation. These data include large-scale preparation processes, in vivo distribution characteristics, and pharmacokinetic profiles. Therefore, there is still a long way to go before they can be used in actual clinical practice.

Conclusions and Future Perspectives

Glucan-based nanoparticles, characterized by their intrinsic immunomodulatory properties and high engineering versatility. Extensive preclinical studies have shown that these nanosystems can remodel the tumor immune microenvironment at multiple levels. They achieve this by targeting immunosuppressive cell populations, enhancing antigen presentation efficiency, amplifying innate immune signaling, and synergistically activating adaptive immune responses.

As a result, they significantly enhance the overall efficacy of immunotherapy. We have innovatively developed a comprehensive review framework for glucan-based nanoparticle tumor immunotherapy that focuses on specific diseases, delves into underlying mechanisms, leads the field, and is translation-oriented, thereby addressing the gaps and shortcomings in existing reviews.

The heterogeneity of the nanotumor microenvironment,[246] immune responses, and drug clearance mechanisms vary significantly across different species.[247] Consequently, the differences between preclinical models and the human physiological environment are the primary reason for difficulties in translation. Therefore, the pharmacokinetic and pharmacodynamic profiles of glucan-based nanoparticles in mouse or rat models cannot be directly extrapolated to humans. Furthermore, from a materials science perspective, glucan-based nanoparticles still face several structural and chemical limitations. The significant steric differences among dextran hydroxyl groups result in poor grafting controllability and substantial performance variations between batches of reaction products.[53] Additionally, the varying reactivity of hydroxyl groups at different positions leads to heterogeneous hydrophilicity and degradation behavior in the nanoparticles, thereby affecting their in vivo pharmacokinetics and functional performance.[59]

Despite these challenges, certain highly engineered dextran-derived systems (such as Ac-DEX micro/nanoparticles) have demonstrated excellent versatility and scalability, providing a solid foundation for clinical translation. Overall, dextran-based nanoparticles offer a multi-level intervention strategy for reversing the tumor immunosuppressive microenvironment, and their application prospects are promising. However, further improvements are needed in terms of standardized preparation, safety assessment, elucidation of mechanisms of action, and translational research.

Against this backdrop, future research should focus on several key areas to further enhance the translational potential of glucan-based nanotherapeutics. First, regarding the targeted intervention of immunosuppressive cell populations, further research should concentrate on improving the selectivity of glucan-based nanosystems for Tregs and MDSCs. The incorporation of response modules that are highly sensitive to specific enzymes, metabolites, or lesion-associated signals could enable precise modulation of the immunosuppressive network. This approach minimizes unintended interactions with normal immune cells and broadens the therapeutic safety margin. It should also be noted that increased target specificity may be accompanied by unintended immune interference or side effects, necessitating the validation of safety thresholds across multiple preclinical models. Second, it remains unclear whether glucan-based nanoparticles exert selective and specific regulatory effects on other tumor-associated immune cell populations, such as DCs and natural killer cells. Advanced methodologies, including single-cell sequencing-based multi-omics approaches, are crucial for delineating these cell-type-specific interactions in forthcoming research. Moreover, the development of multifunctional integrated nanosystems continues to be a vital pathway for enhancing therapeutic efficacy. Future platforms based on dextran should increasingly adopt modular design principles, facilitating the coordinated delivery of multiple immunoadjuvants, immunomodulatory agents, or therapeutic drugs within a single system. Such strategically programmed amplification and integration of immune signals are imperative to effectively address tumor heterogeneity and its dynamic evolution. Importantly, the clinical translation of these technologies will ultimately determine the realization

of significant advancements in this field. The complexity of multifunctional systems may also increase production difficulties, quality control challenges, and potential toxicity risks. Comprehensive assessments of in vivo immunogenicity, metabolic fate, and long-term safety of glucan-based nanodelivery systems are essential. Additionally, the establishment of standardized quality control frameworks and optimization of administration routes will significantly impact regulatory approval and clinical applicability. Furthermore, given the rapid advancements in mRNA vaccines, personalized tumor antigen identification, and emerging immunoregulatory technologies, the potential applications of glucan-based nanoplatforms in next-generation cancer vaccines and combination immunotherapy strategies deserve particular attention.

In summary, glucan-based nanoparticles have evolved beyond mere delivery vehicles into sophisticated engineered therapeutic platforms that actively engage in immune modulation. With the ongoing integration of materials science, immunology, and clinical oncology, these systems are set to play a pivotal role in precision tumor immunotherapy. Their development holds substantial promise for fostering efficient, safe, and sustainable cancer immunointervention strategies.

Abbreviations

TME, tumor microenvironment; ICIs, Immune checkpoint inhibitors; CAR-T, Chimeric antigen receptor T; APCs, antigen-presenting cells; DCs, dendritic cell; ODEX, Oxidized dextran; ODEX-DOX, oxidized dextran-doxorubicin; CD147-ODEX-DOX, CD147 monoclonal antibody-conjugated oxidized dextran-doxorubicin; DOX, doxorubicin; ROS, reactive oxygen species; FR, folate receptor; TLR, Toll-like receptor; STING, stimulator of interferon genes; IFN-1, type I interferon; PEG, polyethylene glycol; CTLs, cytotoxic T lymphocytes; TAMs, tumor-associated macrophages; Tregs, regulatory T cells; siRNA, small interfering RNA; SR-A/CD204, scavenger receptor A; MRI, magnetic resonance imaging; DAMPs, damage-associated molecular patterns; MDSCs, myeloid-derived suppressor cells; TGF-β, transforming growth factor-β; ICD, immunogenic cell death; PTT, Photothermal therapy; PDT, photodynamic therapy; TAAs, tumor-associated antigens; Ac-DEX, functionalized acetalated dextran; cGAMP, cyclic GMP-AMP; IV, Intravenous; CNC, Colon Cancer; KS, Kaposi Sarcoma.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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References

1. Wu D, Huang C, Guan K. Mechanistic and therapeutic perspectives of miRNA-PTEN signaling axis in cancer therapy resistance. *Biochem Pharmacol*. 2024;226:116406. doi:10.1016/j.bcp.2024.116406

2. Tang B, Ma W, Lin Y. Emerging applications of anti-angiogenic nanomaterials in oncotherapy. *J Control Release*. 2023;364:61–78. doi:10.1016/j.jconrel.2023.10.022
3. Ren Y, Mao X, Lin W, Chen Y, Chen R, Sun P. Targeting estrogen-related receptors to mitigate tumor resistance: a comprehensive approach to bridging cellular energy metabolism. *Biochim Biophys Acta Rev Cancer*. 2025;1880(1):189256. doi:10.1016/j.bbcan.2024.189256
4. Ma S, Xie F, Wen X, et al. GSTA1/CTNNB1 axis facilitates sorafenib resistance via suppressing ferroptosis in hepatocellular carcinoma. *Pharmacol Res*. 2024;210:107490. doi:10.1016/j.phrs.2024.107490
5. Yue T, Sun Y, Dai Y, Jin F. Mechanisms for resistance to BCMA-targeted immunotherapies in multiple myeloma. *Blood Rev*. 2025;70:101256. doi:10.1016/j.blre.2025.101256
6. Peng Z, Li M, Li H, Gao Q. PD-1/PD-L1 immune checkpoint blockade in ovarian cancer: dilemmas and opportunities. *Drug Discov Today*. 2023;28(8):103666. doi:10.1016/j.drudis.2023.103666
7. Liu S, Zhao Y, Gao Y, Li F, Zhang Y. Targeting metabolism to improve CAR-T cells therapeutic efficacy. *Chin Med J*. 2024;137(8):909–920. doi:10.1097/cm9.0000000000003046
8. Carstens EJ, Takahashi K, Sakamoto N, et al. Modeling and addressing on-target/off-tumor toxicity of claudin 18.2 targeted immunotherapies. *Nat Commun*. 2025;16(1):9651. doi:10.1038/s41467-025-65148-6
9. Ghemrawi R, Abuamer L, Kremesh S, et al. Revolutionizing cancer treatment: recent advances in immunotherapy. *Biomedicines*. 2024;12(9):2158. doi:10.3390/biomedicines12092158
10. Rui R, Zhou L, He S. Cancer immunotherapies: advances and bottlenecks. *Front Immunol*. 2023;14:1212476. doi:10.3389/fimmu.2023.1212476
11. Yang M, Miao YR, Xie GY, et al. ICBatlas: a comprehensive resource for depicting immune checkpoint blockade therapy characteristics from transcriptome profiles. *Cancer Immunol Res*. 2022;10(11):1398–1406. doi:10.1158/2326-6066.Cir-22-0249
12. Cousin S, Guégan JP, Shitara K, et al. Identification of microenvironment features associated with primary resistance to anti-PD-1/PD-L1 + antiangiogenesis in gastric cancer through spatial transcriptomics and plasma proteomics. *Mol Cancer*. 2024;23(1):197. doi:10.1186/s12943-024-02092-x
13. Borghaei H, de Marinis F, Dumoulin D, et al. SAPPHIRE: Phase III study of sitravatinib plus nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *Ann Oncol*. 2024;35(1):66–76. doi:10.1016/j.annonc.2023.10.004
14. McFaline-Figueroa JR, Sun L, Youssef GC, et al. Neoadjuvant anti-PD1 immunotherapy for surgically accessible recurrent glioblastoma: clinical and molecular outcomes of a stage 2 single-arm expansion cohort. *Nat Commun*. 2024;15(1):10757. doi:10.1038/s41467-024-54326-7
15. Mo D, Yang X, Xu G, et al. Signal detection of immune thrombocytopenia associated with immune checkpoint inhibitors. *Sci Rep*. 2024;14(1):23699. doi:10.1038/s41598-024-75271-x
16. Pfister F, Carnell LR, Löffler L, et al. Loading of CAR-T cells with magnetic nanoparticles for controlled targeting suppresses inflammatory cytokine release and switches tumor cell death mechanism. *MedComm*. 2025;6(1):e70039. doi:10.1002/mco2.70039
17. Jin L, Gu S, Ruan Q, et al. GPRC5D-targeted CAR T-cell therapy (CT071) in patients with relapsed or refractory multiple myeloma: a first-in-human, single-centre, single-arm, Phase 1 trial. *Lancet Haematol*. 2025;12(10):e798–e807. doi:10.1016/s2352-3026(25)00176-0
18. Lu Q, Kou D, Lou S, et al. Nanoparticles in tumor microenvironment remodeling and cancer immunotherapy. *J Hematol Oncol*. 2024;17(1). doi:10.1186/s13045-024-01535-8
19. Qin H, Teng Y, Dai R, Wang A, Liu J. Glycan-based scaffolds and nanoparticles as drug delivery system in cancer therapy. *Front Immunol*. 2024;15. doi:10.3389/fimmu.2024.1395187
20. Chihara G, Maeda Y, Hamuro J, Sasaki T, Fukuoka F. Inhibition of mouse sarcoma 180 by polysaccharides from Lentinus edodes (Berk.) sing. *Nature*. 1969;222(5194):687–688. doi:10.1038/222687a0
21. Carvalho LT, Vieira TA, Zhao Y, Celli A, Medeiros SF, Lacerda TM. Recent advances in the production of biomedical systems based on polyhydroxyalkanoates and exopolysaccharides. *Int J Biol Macromol*. 2021;183:1514–1539. doi:10.1016/j.ijbiomac.2021.05.025
22. Mehvar R. Dextrans for targeted and sustained delivery of therapeutic and imaging agents. *J Control Release*. 2000;69(1):1–25. doi:10.1016/s0168-3659(00)00302-3
23. Bachelder EM, Beaudette TT, Broaders KE, Dashe J, Fréchet JM. Acetal-derivatized dextran: an acid-responsive biodegradable material for therapeutic applications. *J Am Chem Soc*. 2008;130(32):10494–10495. doi:10.1021/ja803947s
24. Cui L, Cohen JA, Broaders KE, Beaudette TT, Fréchet JM. Mannosylated dextran nanoparticles: a pH-sensitive system engineered for immunomodulation through mannose targeting. *Bioconjug Chem*. 2011;22(5):949–957. doi:10.1021/bc100596w
25. Li B, Cai Y, Qi C, et al. Orally administered particulate beta-glucan modulates tumor-capturing dendritic cells and improves antitumor T-cell responses in cancer. *Clin Cancer Res*. 2010;16(21):5153–5164. doi:10.1158/1078-0432.Ccr-10-0820
26. Pacheco-Torres J, Penet MF, Krishnamachary B, Mironchik Y, Chen Z, Bhujwalla ZM. PD-L1 siRNA theranostics with a dextran nanoparticle highlights the importance of nanoparticle delivery for effective tumor PD-L1 downregulation. *Front Oncol*. 2020;10:614365. doi:10.3389/fonc.2020.614365
27. Lin M, Li Y, Long H, et al. Cell membrane-camouflaged DOX-loaded β-glucan nanoparticles for highly efficient cancer immunochemotherapy. *Int J Biol Macromol*. 2023;225:873–885. doi:10.1016/j.ijbiomac.2022.11.152
28. Dowdall N, Hoare T. β-1,3 glucan microparticles & nanoparticles: fabrication methods & applications in immunomodulation & targeted drug delivery. *Adv Healthc Mater*. 2025;14(14):e2501006. doi:10.1002/adhm.202501006
29. Zheng T, Ramanathan K, Ormhøj M, et al. Dextran-based T-cell expansion nanoparticles for manufacturing CAR T cells with augmented efficacy. *Nat Commun*. 2026;17(1):1103. doi:10.1038/s41467-025-67868-1
30. Song Z, Sun J, Williams GR, et al. Glucan-based biomaterials and their applications in the biomedical field. *Int J Biol Macromol*. 2025;318:144940. doi:10.1016/j.ijbiomac.2025.144940
31. Kong Y, Pan S, Wu S. Advances in the use of dietary β-glucan in aquaculture: structural insights, immunological benefits, and feed applications. *Dev Comp Immunol*. 2025;172:105476. doi:10.1016/j.dci.2025.105476
32. Han B, Baruah K, Cox E, Vanrompay D, Bossier P. Structure-functional activity relationship of β-glucans from the perspective of immunomodulation: a mini-review. *Front Immunol*. 2020;11:658. doi:10.3389/fimmu.2020.00658
33. Adachi Y, Ishii T, Ikeda Y, et al. Characterization of beta-glucan recognition site on C-type lectin, dectin 1. *Infect Immun*. 2004;72(7):4159–4171. doi:10.1128/iai.72.7.4159-4171.2004

34. Ameri Shah Reza M, Najafi S, Kahfi M, Safari M, Mahjoor M. Beta-glucans in oncology: revolutionizing treatment with immune power & tumor targeting. *Naunyn-Schmiedeberg's Arch Pharmacol*. 2025;399:1711–1720. doi:10.1007/s00210-025-04519-8
35. Tintoré M, Cuñé J, Vu LD, et al. A Long-Chain Dextran Produced by Weissella cibaria Boosts the Diversity of Health-Related Gut Microbes Ex Vivo. *Biology*. 2024;13(1):51. doi:10.3390/biology13010051
36. Maheshwari G, Sowrirajan S, Joseph B. Extraction and isolation of β-glucan from grain sources-a review. *J Food Sci*. 2017;82(7):1535–1545. doi:10.1111/1750-3841.13765
37. Bornemann S. α-Glucan biosynthesis and the GlgE pathway in Mycobacterium tuberculosis. *Biochem Soc Trans*. 2016;44(1):68–73. doi:10.1042/bst20150181
38. Patil V, Hernandez-Franco JF, HogenEsch H, Renukaradhya GJ. Alpha-D-glucan-based vaccine adjuvants: current status and future perspectives. *Front Immunol*. 2022;13:858321. doi:10.3389/fimmu.2022.858321
39. Tian H, Yu L, Zhang M, He J, Sun X, Ni P. Dextran-doxorubicin prodrug nanoparticles conjugated with CD147 monoclonal antibody for targeted drug delivery in hepatoma therapy. *Colloids Surf B Biointerfaces*. 2023;228:113400. doi:10.1016/j.colsurfb.2023.113400
40. Yan S, Wang Q, Zhang S, et al. Oxidized dextran improves the stability and effectively controls the release of curcumin loaded in soybean protein nanocomplexes. *Food Chem*. 2024;431:137089. doi:10.1016/j.foodchem.2023.137089
41. Pronina EA, Vorotnikov YA, Pozmogova TN, et al. No catalyst added hydrogen peroxide oxidation of dextran: an environmentally friendly route to multifunctional polymers. *Acs Sustain Chemist Eng*. 2020;8(13):5371–5379. doi:10.1021/acssuschemeng.0c01030
42. Pronina EV, Vorotnikov YA, Pozmogova TN, et al. Multifunctional oxidized dextran as a matrix for stabilization of octahedral molybdenum and tungsten iodide clusters in aqueous media. *Int J Mol Sci*. 2023;24(12):10010. doi:10.3390/ijms241210010
43. Li N, Yan XY, Cheng MY, et al. Construction of a microenvironment-responsive antibacterial hydrogel packed with immunomodulatory carbonized polymer dots for periodontitis treatment from multiple perspectives. *Adv Funct Mater*. 2025;35(22):2418407. doi:10.1002/adfm.202418407
44. Wang L, Fan L, Filppula AM, et al. Dual physiological responsive structural color hydrogel particles for wound repair. *Bioact Mater*. 2025;46:494–502. doi:10.1016/j.bioactmat.2025.01.002
45. Wang G, Inturi S, Serkova NJ, et al. High-relaxivity superparamagnetic iron oxide nanoworms with decreased immune recognition and long-circulating properties. *ACS Nano*. 2014;8(12):12437–12449. doi:10.1021/nn505126b
46. Lin CY, Battistoni CM, Liu JC. Redox-responsive hydrogels with decoupled initial stiffness and degradation. *Biomacromolecules*. 2021;22(12):5270–5280. doi:10.1021/acs.biomac.1c01180
47. Mocanu G, Nichifor M, Stanciu MC. New shell crosslinked micelles from dextran with hydrophobic end groups and their interaction with bioactive molecules. *Carbohydr Polym*. 2015;119:228–235. doi:10.1016/j.carbpol.2014.11.047
48. Wang X, Li Z, Shi T, et al. Injectable dextran hydrogels fabricated by metal-free click chemistry for cartilage tissue engineering. *Mater Sci Eng C Mater Biol Appl*. 2017;73:21–30. doi:10.1016/j.msec.2016.12.053
49. Li H, Li X, Jain P, et al. Dual-degradable biohybrid microgels by direct cross-linking of chitosan and dextran using Azide-Alkyne cycloaddition. *Biomacromolecules*. 2020;21(12):4933–4944. doi:10.1021/acs.biomac.0c01158
50. Zhong L, Banigo AT, Zoetebier B, Karperien M. Bioactive hydrogels based on tyramine and maleimide functionalized dextran for tissue engineering applications. *Gels*. 2024;10(9):566. doi:10.3390/gels10090566
51. Zhao B, Zhang Y, Li D, Mo X, Pan J. Hofmeister effect-enhanced gelatin/oxidized dextran hydrogels with improved mechanical properties and biocompatibility for wound healing. *Acta Biomater*. 2022;151:235–253. doi:10.1016/j.actbio.2022.08.009
52. Wang S, Liu Y, Sun Q, et al. Triple cross-linked dynamic responsive hydrogel loaded with selenium nanoparticles for modulating the inflammatory microenvironment via PI3K/Akt/NF-κB and MAPK signaling pathways. *Adv Sci*. 2023;10(31):e2303167. doi:10.1002/advs.202303167
53. Azadpour B, Kashanian F, Habibi-Rezaei M, et al. Covalently-bonded coating of L-arginine modified magnetic nanoparticles with dextran using co-precipitation method. *Materials*. 2022;15(24):8762. doi:10.3390/ma15248762
54. Chung JT, Rafiei M, Chau Y. Self-adjuvanted L-arginine-modified dextran-based nanogels for sustained local antigenic protein delivery to antigen-presenting cells and enhanced cellular and humoral immune responses. *Biomater Sci*. 2024;12(7):1771–1787. doi:10.1039/d3bm01150j
55. Lu A, Li S. Polysaccharides as a hydrophilic building block of amphiphilic block copolymers for the conception of nanocarriers. *Pharmaceutics*. 2024;16(4):467. doi:10.3390/pharmaceutics16040467
56. Cai L, Li J, Quan S, et al. Dextran-based hydrogel with enhanced mechanical performance via covalent and non-covalent cross-linking units carrying adipose-derived stem cells toward vascularized bone tissue engineering. *J Biomed Mater Res A*. 2019;107(6):1120–1131. doi:10.1002/jbm.a.36580
57. Zheng Y, Wang L, Liu X, et al. Arming abraxane with cationic spermidine conjugate and homologous cell membrane for enhanced triple-negative breast cancer therapy. *Adv Healthc Mater*. 2026;15(12):e01853. doi:10.1002/adhm.202501853
58. Thodikayil AT, Hemlata H, Murali N, Minocha S, Betal S, Saha S. Nano enabled dual-responsive drug carrier originated from acetalated dextran/carboxylated nanocellulose-based core-shell microspheres. *ACS Biomater Sci Eng*. 2026;12(2):936–954. doi:10.1021/acsbiomaterials.5c01495
59. Zhao C, Cao W, Zheng H, et al. Acid-responsive nanoparticles as a novel oxidative stress-inducing anticancer therapeutic agent for colon cancer. *Int J Nanomedicine*. 2019;14:1597–1618. doi:10.2147/ijn.S189923
60. Li Y, Li DM, Han Y, Zeng XA, Han Z. Structural and functional properties of sodium caseinate glycosylated by dextran aldehyde. *Food Chem*. 2023;404(Pt A):134589. doi:10.1016/j.foodchem.2022.134589
61. Yurkshtovich TL, Pristromova YI, Golub NV, Solomevich SO, Kosterova RI. Preparation and properties of Dialdehyddextran. *Russ J Appl Chemist*. 2022;95(12):1800–1808. doi:10.1134/s1070427222120060
62. Meng H, Su J, Shen Q, et al. A smart MMP-9-responsive hydrogel releasing M2 macrophage-derived exosomes for diabetic wound healing. *Adv Healthc Mater*. 2025;14(10):e2404966. doi:10.1002/adhm.202404966
63. Shen D, Chen H, Li M, et al. Effects of different molecular weight oxidized dextran as crosslinkers on stability and antioxidant capacity of curcumin-loaded nanoparticles. *Foods*. 2023;12(13):2533. doi:10.3390/foods12132533
64. Chen Y, Sun H, Tang S, et al. Nanofiltration membranes with enhanced performance by constructing an interlayer integrated with dextran nanoparticles and polyethyleneimine coating. *J Membrane Sci*. 2022;654:120537. doi:10.1016/j.memsci.2022.120537

65. You C, Zhang Z, Guo Y, et al. Application of extracellular matrix cross-linked by microbial transglutaminase to promote wound healing. *Int J Biol Macromol*. 2024;266(Pt 2):131384. doi:10.1016/j.ijbiomac.2024.131384
66. Genç H, Hazur J, Karakaya E, et al. Differential responses to bioink-induced oxidative stress in endothelial cells and fibroblasts. *Int J Mol Sci*. 2021;22(5):2358. doi:10.3390/ijms22052358
67. Kono H, Noda J, Wakamori H. Detailed structural characterization of oxidized sucrose and its application in the fully carbohydrate-based preparation of a hydrogel from carboxymethyl chitosan. *Molecules*. 2022;27(18):6137. doi:10.3390/molecules27186137
68. Chao JY, Yue TJ, Lu XB, Ren WM. Elemental sulfur utilization: construction of a reprocessable covalent crosslinked polydisulfide with enhanced mechanical properties. *Polymer Chemist*. 2025;16(33):3701–3708. doi:10.1039/d5py00085h
69. Du W, Yang H, Lu C, et al. Aldehyde-mediated adaptive membranes with self-healing and antimicrobial properties for endometrial repair. *Int J Biol Macromol*. 2023;229:1023–1035. doi:10.1016/j.ijbiomac.2022.12.265
70. Chenault HK, Bhatia SK, Dimaio WG, Vincent GL, Camacho W, Behrens A. Sealing and healing of clear corneal incisions with an improved dextran aldehyde-PEG amine tissue adhesive. *Curr Eye Res*. 2011;36(11):997–1004. doi:10.3109/02713683.2011.606590
71. Li DQ, Tohti M, Fu YS, et al. Aldehyde group pendant-grafted pectin-based injectable hydrogel. *Int J Biol Macromol*. 2024;264(Pt 1):130453. doi:10.1016/j.ijbiomac.2024.130453
72. Ren J, Yang H, Wu Y, et al. Dynamic reversible adhesives based on crosslinking network via Schiff base and Michael addition. *RSC Adv*. 2022;12(24):15241–15250. doi:10.1039/d2ra02299k
73. Pandit AH, Nisar S, Imtiyaz K, et al. Injectable, self-healing, and biocompatible N,O-carboxymethyl chitosan/multialdehyde guar gum hydrogels for sustained anticancer drug delivery. *Biomacromolecules*. 2021;22(9):3731–3745. doi:10.1021/acs.biomac.1c00537
74. Chen KH, Nguyen N, Huang TY, et al. Macrophage-hitchhiked orally administered β-glucans-functionalized nanoparticles as "precision-guided stealth missiles" for targeted pancreatic cancer therapy. *Adv Mater*. 2023;35(40):e2304735. doi:10.1002/adma.202304735
75. Wang SQ, Liu YH, Sun QW, et al. Triple cross-linked dynamic responsive hydrogel loaded with selenium nanoparticles for modulating the inflammatory microenvironment via PI3K/Akt/NF-?B and MAPK signaling pathways. *Adv Sci*. 2023;10(31). doi:10.1002/advs.202303167
76. Dong P, Lv H, Jia W, et al. Polysaccharide dextran-based conjugate for selective co-delivery of two synergistic drugs docetaxel and docosahexaenoic acid to tumor cells. *Drug Deliv*. 2023;30(1):40–50. doi:10.1080/10717544.2022.2152133
77. Delorme V, Lichon L, Mahindad H, et al. Reverse poly(ε-caprolactone)-g-dextran graft copolymers. Nano-carriers for intracellular uptake of anticancer drugs. *Carbohydr Polym*. 2020;232:115764. doi:10.1016/j.carbpol.2019.115764
78. Long LX, Yuan XB, Chang J, et al. Self-assembly of polylactic acid and cholesterol-modified dextran into hollow nanocapsules. *Carbohydr Polym*. 2012;87(4):2630–2637. doi:10.1016/j.carbpol.2011.11.032
79. Gericke M, Schulze P, Heinze T. Nanoparticles based on hydrophobic polysaccharide derivatives-formation principles, characterization techniques, and biomedical applications. *Macromol Biosci*. 2020;20(4):e1900415. doi:10.1002/mabi.201900415
80. Zou W, Williams D, Cox A. Mitigating base-catalysed degradation of periodate-oxidized capsular polysaccharides: conjugation by reductive amination in acidic media. *Vaccine*. 2019;37(8):1087–1093. doi:10.1016/j.vaccine.2018.12.072
81. Bergal A, Andac M. Detailed investigation and influence of oxidation degree on synthesis, characterization and antibacterial activity of β-cyclodextrin. *Carbohydr Res*. 2023;533:108936. doi:10.1016/j.carres.2023.108936
82. Liu Y, Li C, Yang X, Yang B, Fu Q. Stimuli-responsive polymer-based nanosystems for cardiovascular disease theranostics. *Biomater Sci*. 2024;12(15):3805–3825. doi:10.1039/d4bm00415a
83. Wei D, Sun Y, Zhu H, Fu Q. Stimuli-responsive polymer-based nanosystems for cancer theranostics. *ACS Nano*. 2023;17(23):23223–23261. doi:10.1021/acsnano.3c06019
84. Yan H, Xu P, Cong H, Yu B, Shen Y. Research progress in construction of organic carrier drug delivery platform using tumor microenvironment. *Materials Today Chemist*. 2024;37:101997. doi:10.1016/j.mtchem.2024.101997
85. Chen Z, Wang X, Zhao N, Chen H, Guo G. Advancements in pH-responsive nanocarriers: enhancing drug delivery for tumor therapy. *Expert Opin Drug Deliv*. 2023;20(11):1623–1642. doi:10.1080/17425247.2023.2292678
86. Ding H, Tan P, Fu S, et al. Preparation and application of pH-responsive drug delivery systems. *J Control Release*. 2022;348:206–238. doi:10.1016/j.jconrel.2022.05.056
87. Zou X, Cai S, Wang T, et al. Natural antibacterial agent-based nanoparticles for effective treatment of intracellular MRSA infection. *Acta Biomater*. 2023;169:410–421. doi:10.1016/j.actbio.2023.08.004
88. Sun X, Zhang J, Zhao X, et al. Binary regulation of the tumor microenvironment by a pH-responsive reversible shielding nanoplatform for improved tumor chemo-immunotherapy. *Acta Biomater*. 2022;138:505–517. doi:10.1016/j.actbio.2021.11.017
89. Zhang W, Shi Y, Li H, et al. In situ injectable nano-complexed hydrogel based on chitosan/dextran for combining tumor therapy via hypoxia alleviation and TAMs polarity regulation. *Carbohydr Polym*. 2022;288:119418. doi:10.1016/j.carbpol.2022.119418
90. Nayak S, Caz N, Derveaux E, et al. Reactive oxygen species responsive dextran-thioketal conjugate nanocarriers for the delivery of hydrophilic payloads. *Carbohydr Polym*. 2025;356:123375. doi:10.1016/j.carbpol.2025.123375
91. Zhang P, Mukwaya V, Guan Q, et al. Dextran-based nanodrugs with mitochondrial targeting/glutathione depleting synergy for enhanced photodynamic therapy. *Carbohydr Polym*. 2025;348(Pt A):122854. doi:10.1016/j.carbpol.2024.122854
92. Dai X, Li Y, Liu X, Zhang Y, Gao F. Intracellular infection-responsive macrophage-targeted nanoparticles for synergistic antibiotic immunotherapy of bacterial infection. *J Mater Chem B*. 2024;12(21):5248–5260. doi:10.1039/d4tb00409d
93. Dosta P, Dion MZ, Prado M, et al. Matrix metalloproteinase- and pH-sensitive nanoparticle system enhances drug retention and penetration in glioblastoma. *ACS Nano*. 2024;18(22):14145–14160. doi:10.1021/acsnano.3c03409
94. Gao Z, Hou X, Tang J, et al. β-glucan nanotubes improve oral doxorubicin delivery for colorectal cancer by microbiota-mediated colon targeting and reduced toxicity. *Carbohydr Polym*. 2026;374:124705. doi:10.1016/j.carbpol.2025.124705
95. Qin H, Zhou J, Pang A, Huang L, Liu Z, Zheng Y. Microbial dynamic regulatory tools: design, applications, and prospects. *ACS Synth Biol*. 2025;14(7):2418–2432. doi:10.1021/acssynbio.5c00219
96. Musazzi UM, Franzè S, Condorelli F, Minghetti P, Caliceti P. Feeding next-generation nanomedicines to Europe: regulatory and quality challenges. *Adv Healthc Mater*. 2023;12(30):e2301956. doi:10.1002/adhm.202301956
97. Darwitan A, Tan YF, Wong YS, Nedumaran AM, Czarny B, Venkatraman S. Targeting efficiency of nanoliposomes on atherosclerotic foam cells: polyethylene glycol-to-ligand ratio effects. *Expert Opin Drug Deliv*. 2020;17(8):1165–1176. doi:10.1080/17425247.2020.1777982

98. Martín-Sabroso C, Torres-Suárez AI, Alonso-González M, Fernández-Carballido A, Fraguas-Sánchez AI. Active targeted nanoformulations via folate receptors: state of the art and future perspectives. *Pharmaceutics*. 2021;14(1):14. doi:10.3390/pharmaceutics14010014
99. Toti US, Guru BR, Grill AE, Panyam J. Interfacial activity assisted surface functionalization: a novel approach to incorporate maleimide functional groups and cRGD peptide on polymeric nanoparticles for targeted drug delivery. *Mol Pharm*. 2010;7(4):1108–1117. doi:10.1021/mp900284c
100. Kesharwani P, Chandra J, Karim S, Gupta G, Karwasra R, Sharma A. αvβ3 integrin targeting RGD peptide-based nanoparticles as an effective strategy for selective drug delivery to tumor microenvironment. *J Drug Deliv Sci Technol*. 2024;96:105663. doi:10.1016/j.jddst.2024.105663
101. Deng D, Li G, Xia X, et al. Nitrated T cell epitope linked vaccine targeting CD47 elicits antitumor immune responses and acts synergistically with vaccine targeting PDL1. *Int Immunopharmacol*. 2024;128:111374. doi:10.1016/j.intimp.2023.111374
102. Wang T, Wang SQ, Du YX, et al. Gentulizumab, a novel anti-CD47 antibody with potent antitumor activity and demonstrates a favorable safety profile. *J Transl Med*. 2024;22(1):220. doi:10.1186/s12967-023-04710-6
103. Mohanto S, Gowda BHJ, Hani U, et al. Advancements in polysaccharide-based nanoparticles for the treatment of breast cancer: a comprehensive review. *Pharmaceuticals*. 2025;18(11):1712. doi:10.3390/ph18111712
104. Yang C, Ma H, Liang Z, et al. Cyclic RGD modified dextran-quercetin polymer micelles for targeted therapy of breast cancer. *Int J Biol Macromol*. 2025;308(Pt 1):142272. doi:10.1016/j.ijbiomac.2025.142272
105. Butzbach K, Konhäuser M, Fach M, et al. Receptor-mediated uptake of folic acid-functionalized dextran nanoparticles for applications in photodynamic therapy. *Polymers*. 2019;11(5):896. doi:10.3390/polym11050896
106. Zhang X, Hu Q, He X, et al. CD16 CAR-T cells enhance antitumor activity of CpG ODN-loaded nanoparticle-adjuvanted tumor antigen-derived vaccinevia ADCC approach. *J Nanobiotechnology*. 2023;21(1):159. doi:10.1186/s12951-023-01900-8
107. Hernandez-Franco JF, Xie S, Thimmapuram J, Ragland D, HogenEsch H. Mechanism of activation of porcine dendritic cells by an α-D-glucan nanoparticle adjuvant and a nanoparticle/poly(I:C) combination adjuvant. *Front Immunol*. 2022;13:990900. doi:10.3389/fimmu.2022.990900
108. Hsu NS, Tang C, Mendes RV, et al. Tumour-specific STING agonist synthesis via a two-component prodrug system. *Nat Chem*. 2025;17(12):1941–1951. doi:10.1038/s41557-025-01930-9
109. Rabanel JM, Piec PA, Landri S, Patten SA, Ramassamy C. Transport of PEGylated-PLA nanoparticles across a blood brain barrier model, entry into neuronal cells and in vivo brain bioavailability. *J Control Release*. 2020;328:679–695. doi:10.1016/j.jconrel.2020.09.042
110. Al-Shadidi JRMH, Hussain Z, Ahmed IS, Rawas-Qalaji M, Thu HE, Khan S. Polyethylene glycol-mediated functionalization of nanodelivery systems for improving their pharmacokinetic profile and anticancer efficacy. *Int J Polym Mater Polym Biomater*. 2025;74(10):938–956. doi:10.1080/00914037.2024.2383413
111. Ho K-W, Liu Y-L, Liao T-Y, Liu E-S, Cheng T-L. Strategies for non-covalent attachment of antibodies to PEGylated nanoparticles for targeted drug delivery. *Int J Nanomed*. 2024;Volume 19:10045–10064. doi:10.2147/ijn.s479270
112. Kou T, Faisal M, Song J, Blennow A. Polysaccharide-based nanosystems: a review. *Crit Rev Food Sci Nutr*. 2024;64(1):1–15. doi:10.1080/10408398.2022.2104209
113. Hamdan F, Gandolfi S, D'Alessio F, et al. Leveraging glucan-induced trained immunity for the epigenetic and metabolic rewiring of macrophages to enhance colorectal cancer vaccine response. *Nat Commun*. 2026;17(1). doi:10.1038/s41467-026-68466-5
114. Liu H, Shi Y, Ji G, Wang J, Gai B. Ultrasound-triggered with ROS-responsive SN38 nanoparticle for enhanced combination cancer immunotherapy. *Front Immunol*. 2024;15:1339380. doi:10.3389/fimmu.2024.1339380
115. Zhou J, Zhuang Z, Gao R, Li R, Chen Y. β-Glycosidase sensitive oral nanoparticles for combined photothermal and chemo treatment of colorectal cancer. *J Mater Chem B*. 2024;12(6):1624–1635. doi:10.1039/d3tb02393a
116. Luo PK, Ho HM, Chiang MC, et al. pH-responsive β-glucans-complexed mRNA in LNPs as an oral vaccine for enhancing cancer immunotherapy. *Adv Mater*. 2024;36(33):e2404830. doi:10.1002/adma.202404830
117. Roquito T, Colaço M, Costa JP, Borges O. Curcumin-encapsulated glucan nanoparticles as an oxidative stress modulator against human hepatic cancer cells. *Colloids Surf B Biointerfaces*. 2025;245:114326. doi:10.1016/j.colsurfb.2024.114326
118. Xu Y, Wang B, Huang Y, et al. Targeting antigen-presenting cells to enhance the tumor-spleen immunity cycle through liposome-neoantigen vaccine. *Adv Sci*. 2025;12(19). doi:10.1002/advs.202500021
119. You YL, Byun HJ, Chang YB, et al. Euglena gracilis-derived β-glucan ameliorates particulate matter (PM(2.5))-induced airway inflammation by modulating nuclear factor kappa B, mitogen-activated protein kinase, and nuclear factor erythroid 2-related factor 2 signaling pathways in A549 cells and BALB/c mice. *Int J Biol Macromol*. 2025;296:139671. doi:10.1016/j.ijbiomac.2025.139671
120. Shi Z, Lin J, Li W, et al. Cinnamaldehyde triggers cell wall remodeling and enhances macrophage-mediated phagocytic clearance of Candida albicans. *Front Cell Infect Microbiol*. 2025;15:1647320. doi:10.3389/fcimb.2025.1647320
121. Isegawa Y. Activation of immune and antiviral effects by euglena extracts: a review. *Foods*. 2023;12(24):4438. doi:10.3390/foods12244438
122. Qiu D, Zhang S, Huang C, et al. Dectin-1 facilitates lung fungal-mediated pulmonary fibrosis. *Immunity*. 2025;58(7):1811–1829.e8. doi:10.1016/j.immuni.2025.05.007
123. Geller AE, Shrestha R, Woeste MR, et al. The induction of peripheral trained immunity in the pancreas incites anti-tumor activity to control pancreatic cancer progression. *Nat Commun*. 2022;13(1):759. doi:10.1038/s41467-022-28407-4
124. Fanucchi S, Fok ET, Dalla E, et al. Immune genes are primed for robust transcription by proximal long noncoding RNAs located in nuclear compartments. *Nat Genet*. 2019;51(1):138–150. doi:10.1038/s41588-018-0298-2
125. Benjaskulluecha S, Boonmee A, Pattarakankul T, Wongprom B, Klomsing J, Palaga T. Screening of compounds to identify novel epigenetic regulatory factors that affect innate immune memory in macrophages. *Sci Rep*. 2022;12(1):1912. doi:10.1038/s41598-022-05929-x
126. Flores-Gomez D, Hobo W, van Ens D, et al. Interleukin-1β induces trained innate immunity in human hematopoietic progenitor cells in vitro. *Stem Cell Rep*. 2024;19(12):1651–1664. doi:10.1016/j.stemcr.2024.09.004
127. Mata-Martínez P, Bergón-Gutiérrez M, Del Fresno C. Dectin-1 signaling update: new perspectives for trained immunity. *Front Immunol*. 2022;13:812148. doi:10.3389/fimmu.2022.812148
128. Vuscan P, Kischkel B, Hatzioannou A, et al. Potent induction of trained immunity by Saccharomyces cerevisiae β-glucans. *Front Immunol*. 2024;15:1323333. doi:10.3389/fimmu.2024.1323333
129. van Houten P, Changoer P, van Emst L, et al. Induction of trained immunity in myeloid cells and their progenitors from thyroid cancer patients. *Front Immunol*. 2025;16:1706496. doi:10.3389/fimmu.2025.1706496

130. Kalafati L, Kourtzelis I, Schulte-Schrepping J, et al. Innate immune training of granulopoiesis promotes anti-tumor activity. *Cell*. 2020;183(3):771–785.e12. doi:10.1016/j.cell.2020.09.058
131. Jesus S, Panão Costa J, Colaço M, et al. Exploring the immunomodulatory properties of glucan particles in human primary cells. *Int J Pharm*. 2024;655:123996. doi:10.1016/j.ijpharm.2024.123996
132. Andriana P, Fair-Mäkelä R, Liljenbäck H, et al. Macrophage mannose receptor CD206 targeting of fluoride-18 labeled mannosylated dextran: a validation study in mice. *Eur J Nucl Med Mol Imaging*. 2024;51(8):2216–2228. doi:10.1007/s00259-024-06686-x
133. Wollman J, Wanniarachchi K, Pradhan B, et al. Mannose receptor (MRC1) mediates uptake of dextran by bone marrow-derived macrophages. *Mol Biol Cell*. 2024;35(12):ar153. doi:10.1091/mbc.E24-08-0355
134. Rovera G, de Koster EJ, Rufini V, et al. (99m)Tc-Tilmanocept performance for sentinel node mapping in breast cancer, melanoma, and head and neck cancer: a systematic review and meta-analysis from a European expert panel. *Eur J Nucl Med Mol Imaging*. 2023;50(11):3375–3389. doi:10.1007/s00259-023-06290-5
135. Pena ES, Ontiveros-Padilla L, Lukesh NR, et al. Optimizing delivery in a multivalent subunit influenza vaccine using mixed polymeric microparticle degradation rates. *J Control Release*. 2025;384:113936. doi:10.1016/j.jconrel.2025.113936
136. Batty CJ, Amouzougan EA, AC M, Ross TM, Bachelder EM, Ainslie KM. Sustained delivery of CpG oligodeoxynucleotide by acetalated dextran microparticles augments effector response to Computationally Optimized Broadly Reactive Antigen (COBRA) influenza hemagglutinin. *Int J Pharm*. 2023;630:122429. doi:10.1016/j.ijpharm.2022.122429
137. Scotland BL, Shaw JR, Dharmaraj S, et al. Cell and biomaterial delivery strategies to induce immune tolerance. *Adv Drug Deliv Rev*. 2023;203:115141. doi:10.1016/j.addr.2023.115141
138. Sinha A, Simnani FZ, Singh D, et al. The translational paradigm of nanobiomaterials: biological chemistry to modern applications. *Materials Today Bio*. 2022;17:100463. doi:10.1016/j.mtbio.2022.100463
139. Ma Y, Chen Y, Li Z, Zhao Y. Rational design of lipid-based vectors for advanced therapeutic vaccines. *Vaccines*. 2024;12(6):603. doi:10.3390/vaccines12060603
140. Heo MB, Cho MY, Lim YT. Polymer nanoparticles for enhanced immune response: combined delivery of tumor antigen and small interference RNA for immunosuppressive gene to dendritic cells. *Acta Biomaterialia*. 2014;10(5):2169–2176. doi:10.1016/j.actbio.2013.12.050
141. Kim J, Song SG, Park S, et al. Antigen cross-presentation by type-2 innate lymphoid cells facilitates the activation of antitumor CD8+ T cells. *Cancer Res*. 2025;85(14):2659–2678. doi:10.1158/0008-5472.can-24-4194
142. Mahata D, Mukherjee D, Biswas D, et al. Activation and differentiation of cognate T cells by a dextran-based antigen-presenting system for cancer immunotherapy. *Eur J Immunol*. 2023;53(12). doi:10.1002/eji.202350528
143. Meng Y, Huang J, Ding J, Zhou H, Li Y, Zhou W. Mn-phenolic networks as synergistic carrier for STING agonists in tumor immunotherapy. *Materials Today Bio*. 2024;26:101018. doi:10.1016/j.mtbio.2024.101018
144. Wu Y, Li Y, Yan N, et al. Nuclear-targeted chimeric peptide nanorods to amplify innate anti-tumor immunity through localized DNA damage and STING activation. *J Control Release*. 2024;369:531–544. doi:10.1016/j.jconrel.2024.04.008
145. Han S, Wang W, Wang S, et al. Tumor microenvironment remodeling and tumor therapy based on M2-like tumor associated macrophage-targeting nano-complexes. *Theranostics*. 2021;11(6):2892–2916. doi:10.7150/thno.50928
146. Xiao H, Guo Y, Li B, et al. M2-like tumor-associated macrophage-targeted codelivery of STAT6 inhibitor and IKKβ siRNA induces M2-to-M1 repolarization for cancer immunotherapy with low immune side effects. *ACS Central Sci*. 2020;6(7):1208–1222. doi:10.1021/acscentsci.9b01235
147. Li K, Xu W, Lu K, et al. CSF-1R inhibition disrupts the dialog between leukaemia cells and macrophages and delays leukaemia progression. *J Cell Mol Med*. 2020;24(22):13115–13128. doi:10.1111/jcmm.15916
148. Zhang Q, Guo Y, Zhu L, et al. A nucleic acid nanogel dually bears siRNA and CpG motifs for synergistic tumor immunotherapy. *Biomater Sci*. 2021;9(13):4755–4764. doi:10.1039/d1bm00531f
149. Wei Q, Shen N, Yu H, Wang Y, Tang Z, Chen X. FXIIIa substrate peptide decorated BLZ945 nanoparticles for specifically remodeling tumor immunity. *Biomater Sci*. 2020;8(20):5666–5676. doi:10.1039/d0bm00713g
150. Yang R, Chen L, Wang Y, et al. Tumor microenvironment responsive metal nanoparticles in cancer immunotherapy. *Front Immunol*. 2023;14:1237361. doi:10.3389/fimmu.2023.1237361
151. Zheng Y, Han Y, Wang T, et al. Reprogramming Tumor-Associated Macrophages via ROS-Mediated Novel Mechanism of Ultra-Small $Cu_{2-x}Se$ Nanoparticles to Enhance Anti-Tumor Immunity. *Adv Funct Mater*. 2021;32(12). doi:10.1002/adfm.202108971
152. Han S, Bao X, Zou Y, et al. d-lactate modulates M2 tumor-associated macrophages and remodels immunosuppressive tumor microenvironment for hepatocellular carcinoma. *Sci Adv*. 2023;9(29):eadg2697. doi:10.1126/sciadv.adg2697
153. Yan W, Li Y, Zou Y, et al. Breaking tumor immunosuppressive network by regulating multiple nodes with triadic drug delivery nanoparticles. *ACS Nano*. 2023;17(18):17826–17844. doi:10.1021/acsnano.3c03387
154. Kheshti AMS, Hajizadeh F, Barshidi A, et al. Combination cancer immunotherapy with dendritic cell vaccine and nanoparticles loaded with interleukin-15 and anti-beta-catenin siRNA significantly inhibits cancer growth and induces anti-tumor immune response. *Pharm Res*. 2022;39(2):353–367. doi:10.1007/s11095-022-03169-2
155. Chen S, Lv Y, Wang Y, et al. Tumor acidic microenvironment-responsive promodulator iron oxide nanoparticles for photothermal-enhanced chemodynamic immunotherapy of Cancer. *ACS Biomater Sci Eng*. 2023;9(2):773–783. doi:10.1021/acsbiomaterials.2c01287
156. Deng H, Yang X, Wang H, et al. Tailoring the surface charges of iron-crosslinked dextran nanogels towards improved tumor-associated macrophage targeting. *Carbohydr Polym*. 2024;325:121585. doi:10.1016/j.carbpol.2023.121585
157. Zhou J, Meli VS, Yu-Tin Chen E, et al. Magnetic resonance imaging of tumor-associated-macrophages (TAMs) with a nanoparticle contrast agent. *RSC Adv*. 2022;12(13):7742–7756. doi:10.1039/d1ra08061j
158. Ota Y, Inagaki R, Takanashi Y, et al. Targeting tumor-associated macrophages with the immune-activating nanomedicine for achieving strong antitumor activity with rapid clearance from the body. *ACS Nano*. 2024;18(34):23757–23772. doi:10.1021/acsnano.4c08811
159. Liu M, Luo F, Ding C, et al. Dectin-1 activation by a natural product β-glucan converts immunosuppressive macrophages into an M1-like phenotype. *J Immunol*. 2015;195(10):5055–5065. doi:10.4049/jimmunol.1501158
160. Wang Q, Yu Y, Zhuang J, Liu R, Sun C. Demystifying the cGAS-STING pathway: precision regulation in the tumor immune microenvironment. *Molecular Cancer*. 2025;24(1). doi:10.1186/s12943-025-02380-0

161. Yu H, Liu W, Ding K, et al. Sequential release hydrolipo system for STING gene epigenetic reprogramming and immune activation in glioblastoma. *Adv Sci*. 2025;12(5):e2408323. doi:10.1002/advs.202408323
162. Li Z, Chen H, Wang C, et al. Augmenting cGAS/STING-mediated innate immunity by copper-based nanoplatform for synergistic cancer immunotherapy via inducing irreversible DNA damage. *J Control Release*. 2025;386:114075. doi:10.1016/j.jconrel.2025.114075
163. Liang S, Tian Y, Zhao F, et al. A programmable nanoreactor orchestrates cascade of DNA sensing to amplify cGAS-STING activation for cancer immunotherapy. *Adv Sci*. 2026;13(17):e18356. doi:10.1002/advs.202518356
164. Liu Z, Liu B, Feng Y, et al. Dual-targeted self-adjuvant heterocyclic lipidoid@polyester hybrid nanovaccines for boosting cancer immunotherapy. *ACS Nano*. 2024;18(24):15557–15575. doi:10.1021/acsnano.4c00392
165. Chen B, Guo K, Zhao X, et al. Tumor microenvironment-responsive delivery nanosystems reverse immunosuppression for enhanced CO gas/immunotherapy. *Exploration*. 2023;3(6):20220140. doi:10.1002/exp.20220140
166. Zhao X, Zhang J, Chen B, Ding X, Zhao N, Xu FJ. Rough nanovaccines boost antitumor immunity through the enhancement of vaccination cascade and immunogenic cell death induction. *Small Methods*. 2023;7(5):e2201595. doi:10.1002/smtd.202201595
167. Xu L, Lyu J, Qiu Z, et al. Laminaran potentiates cGAS-STING signaling to enhance antiviral responses. *Int Immunopharmacol*. 2025;147:114014. doi:10.1016/j.intimp.2025.114014
168. Lv Z, Li M, Zhu J, et al. Engineering TLR7/8 agonist-loaded and tumor-anchored gold nanosensitizers for enhanced radioimmunotherapy. *Small*. 2025;21(33):e2503133. doi:10.1002/smll.202503133
169. Zhang Y, Li Y, Xu Z, et al. PPS-TLR7/8 agonist nanoparticles equip robust anticancer immunity by selectively prolonged activation of dendritic cells. *Biomaterials*. 2025;316:123032. doi:10.1016/j.biomaterials.2024.123032
170. Stothers CL, Burelbach KR, Owen AM, et al. β-glucan induces distinct and protective innate immune memory in differentiated macrophages. *J Immunol*. 2021;207(11):2785–2798. doi:10.4049/jimmunol.2100107
171. Danielson M, Nicolai CJ, Vo TT, Wolf NK, Burke TP. Cytosolic bacterial pathogens activate TLR pathways in tumors that synergistically enhance STING agonist cancer therapies. *iScience*. 2024;27(12):111385. doi:10.1016/j.isci.2024.111385
172. Li Y, Wu W, Liu Q, et al. Specific surface-modified iron oxide nanoparticles trigger complement-dependent innate and adaptive antileukaemia immunity. *Nat Commun*. 2024;15(1):10400. doi:10.1038/s41467-024-54810-0
173. Wang S, Wang Z, Li Z, et al. Amelioration of systemic antitumor immune responses in cocktail therapy by immunomodulatory nanozymes. *Sci Adv*. 2022;8(21):eabn3883. doi:10.1126/sciadv.abn3883
174. Anwar F, Naqvi S, Shams S, et al. Nanomedicines: intervention in inflammatory pathways of cancer. *Inflammopharmacology*. 2023;31(3):1199–1221. doi:10.1007/s10787-023-01217-w
175. Doi M, Tanaka H, Ohoto T, et al. Reactivation of anticancer immunity by resetting interorgan crosstalk in immune-suppressive cells with a nanoparticulated anti-inflammatory drug. *Small*. 2023;19(16):e2205131. doi:10.1002/smll.202205131
176. Zeng Y, Xiang Y, Sheng R, et al. Polysaccharide-based nanomedicines for cancer immunotherapy: a review. *Bioact Mater*. 2021;6(10):3358–3382. doi:10.1016/j.bioactmat.2021.03.008
177. Ohue Y, Nishikawa H. Regulatory T (Treg) cells in cancer: can Treg cells be a new therapeutic target? *Cancer Sci*. 2019;110(7):2080–2089. doi:10.1111/cas.14069
178. Barshidi A, Karpisheh V, Noukabadi FK, et al. Dual blockade of PD-1 and LAG3 immune checkpoints increases dendritic cell vaccine mediated T cell responses in breast cancer model. *Pharm Res*. 2022;39(8):1851–1866. doi:10.1007/s11095-022-03297-9
179. Hassannia H, Ghasemi Chaleshtari M, Atyabi F, et al. Blockage of immune checkpoint molecules increases T-cell priming potential of dendritic cell vaccine. *Immunology*. 2020;159(1):75–87. doi:10.1111/imm.13126
180. Liu X, Huangfu Y, Wang J, et al. Supramolecular polymer-nanomedicine hydrogel loaded with tumor associated macrophage-reprogramming polyTLR7/8a nanoregulator for enhanced anti-angiogenesis therapy of orthotopic hepatocellular carcinoma. *Adv Sci*. 2023;10(22):e2300637. doi:10.1002/advs.202300637
181. Jiang R, Huang Q, Shen R, et al. PCV2 infection induces the differentiation of Treg cells via the TGF-β/Smad3 pathway. *mBio*. 2025;16(9):e0136625. doi:10.1128/mbio.01366-25
182. Zhao Z, Ukidve A, Kim J, Mitragotri S. Targeting strategies for tissue-specific drug delivery. *Cell*. 2020;181(1):151–167. doi:10.1016/j.cell.2020.02.001
183. Tang Y, Yao W, Hang H, Xiong W, Mei H, Hu Y. TGF-β blocking combined with photothermal therapy promote tumor targeted migration and long-term antitumor activity of CAR-T cells. *Mater Today Bio*. 2023;20:100615. doi:10.1016/j.mtbio.2023.100615
184. Xu Y, Lv J, Liu Y, et al. Coagulation-targeted TGF-β signaling pathway inhibitor nanomedicine for inhibiting the growth and lung metastasis of breast cancer. *Nano Lett*. 2025;25(1):504–513. doi:10.1021/acs.nanolett.4c05355
185. Kim D, Wu Y, Shim G, Oh YK. Genome-editing-mediated restructuring of tumor immune microenvironment for prevention of metastasis. *ACS Nano*. 2021;15(11):17635–17656. doi:10.1021/acsnano.1c05420
186. He S, Zheng L, Qi C. Myeloid-derived suppressor cells (MDSCs) in the tumor microenvironment and their targeting in cancer therapy. *Mol Cancer*. 2025;24(1):5. doi:10.1186/s12943-024-02208-3
187. Wang T, Wang J, Jiang H, et al. Targeted regulation of tumor microenvironment through the inhibition of MDSCs by curcumin loaded self-assembled nano-filaments. *Mater Today Bio*. 2022;15:100304. doi:10.1016/j.mtbio.2022.100304
188. Peng SY, Chen L, Deng RH, et al. Non-depleting reformation of immunosuppressive myeloid cells to broaden the application of anti-PD therapy. *Nanoscale*. 2021;13(8):4420–4431. doi:10.1039/d1nr00830g
189. Xu X, Liu L, Wang H, et al. Engineered DBCO+PD-1 Nanovesicles Carrying 1-MT for Cancer-Targeted Immunotherapy. *ACS Biomater Sci Eng*. 2022;8(11):4819–4826. doi:10.1021/acsbiomaterials.2c00639
190. Lu J, Luo Y, Rao D, et al. Myeloid-derived suppressor cells in cancer: therapeutic targets to overcome tumor immune evasion. *Exp Hematol Oncol*. 2024;13(1). doi:10.1186/s40164-024-00505-7
191. Deshpande NU, Bianchi A, Amirian H, et al. Cell-specific nanoengineering strategy disrupts tolerogenic signaling from myeloid-derived suppressor cells to invigorate antitumor immunity in pancreatic cancer. *bioRxiv*. 2024. doi:10.1101/2024.05.25.594901
192. Wang Z, Li M, Hua D, Hu X, Wang Y. Targeting myeloid-derived suppressor cells: a promising strategy for cancer treatment. *Bratislava Med J*. 2026;127(2):512–527. doi:10.1007/s44411-025-00485-y

193. Hsieh CH, Chuang PC, Liu YW. Beyond Adaptive Immunity: trained Innate Immune Responses as a Novel Frontier in Hepatocellular Carcinoma Therapy. *Cancers*. 2025;17(7):1250. doi:10.3390/cancers17071250
194. Xu D, Ju J, Chen W, et al. A light-controlled dextran nano-immunomodulator amplifies immunogenic cell death for cancer immunotherapy. *Carbohydr Polym*. 2025;366:123885. doi:10.1016/j.carbpol.2025.123885
195. Qi J, Jin F, Xu X, Du Y. Combination cancer immunotherapy of nanoparticle-based immunogenic cell death inducers and immune checkpoint inhibitors. *Int J Nanomedicine*. 2021;16:1435–1456. doi:10.2147/ijn.S285999
196. Wang Z, You T, Su Q, et al. Laser-activatable in situ vaccine enhances cancer-immunity cycle. *Adv Mater*. 2023;35(52):e2307193. doi:10.1002/adma.202307193
197. Chen X, Ouyang H, Zhang Y, et al. Antigen-specific T cell activation through targeted delivery of in-situ generated antigen and calcium ionophore to enhance antitumor immunotherapy. *J Control Release*. 2024;365:544–557. doi:10.1016/j.jconrel.2023.12.002
198. Ye H, Xu D, Zhang X, et al. One-pot solvothermal synthesis of polyvinyl pyrrolidone and ethylene glycol-modified Cu2SnS3 (PE/CTS) nanomaterials for photothermal immunotherapy. *Nano Today*. 2025;65:102876. doi:10.1016/j.nantod.2025.102876
199. Li T, Guo L, Li J, et al. Precision USPIO-PEG-SLe(x) nanotheranostic agent targeted photothermal therapy for enhanced Anti-PD-L1 immunotherapy to treat immunotherapy resistance. *Int J Nanomedicine*. 2024;19:1249–1272. doi:10.2147/ijn.S445879
200. Chen Y, Gao Y, Li Y, Wang K, Zhu J. Synergistic chemo-photodynamic therapy mediated by light-activated ROS-degradable nanocarriers. *J Mater Chem B*. 2019;7(3):460–468. doi:10.1039/c8tb03030h
201. Yeshchenko O, Khort P, Fedotov O, et al. Third-generation anticancer photodynamic therapy systems based on star-like anionic polyacrylamide polymer, gold nanoparticles, and temoporfin photosensitizer. *Molecules*. 2024;29(10):2224. doi:10.3390/molecules29102224
202. Liu J, Zhou B, Guo Y, et al. SR-A-targeted nanoplatform for sequential photothermal/photodynamic ablation of activated macrophages to alleviate atherosclerosis. *ACS Appl Mater Interfaces*. 2021;13(25):29349–29362. doi:10.1021/acsami.1c06380
203. Park K, Ahn JW, Kim JH, Kim JW. Tumor-associated macrophage-targeted photodynamic cancer therapy using a dextran sulfate-based nano-photosensitizer. *Int J Biol Macromol*. 2022;218:384–393. doi:10.1016/j.ijbiomac.2022.07.159
204. Song M, Yoon H, Yoon H, Lee HM, Chae YJ, Chang JE. Enhanced anticancer efficacy of photodynamic therapy in combination with immunotherapy. *J Photochem Photobiol B*. 2024;261:113048. doi:10.1016/j.jphotobiol.2024.113048
205. Zhou Z, Liu Y, Song W, et al. Metabolic reprogramming mediated PD-L1 depression and hypoxia reversion to reactivate tumor therapy. *J Control Release*. 2022;352:793–812. doi:10.1016/j.jconrel.2022.11.004
206. Liu Y, Pan Y, Cao W, et al. A tumor microenvironment responsive biodegradable CaCO(3)/MnO(2)- based nanoplatform for the enhanced photodynamic therapy and improved PD-L1 immunotherapy. *Theranostics*. 2019;9(23):6867–6884. doi:10.7150/thno.37586
207. Wang TY, An YN, Yeh YC. Ultrasound- and NIR-Responsive Polydextran/Black TiO(2) nanocomposite hydrogels for triple-modal antibacterial therapy. *ACS Appl Mater Interfaces*. 2025;17(35):49910–49929. doi:10.1021/acsami.5c15341
208. Moradi N, Muhammadnejad S, Delavari H, Pournoori N, Oghabian MA, Ghafouri H. Bio-conjugation of anti-human CD3 monoclonal antibodies to magnetic nanoparticles by using cyanogen bromide: a potential for cell sorting and noninvasive diagnosis. *Int J Biol Macromol*. 2021;192:72–81. doi:10.1016/j.ijbiomac.2021.09.129
209. Batty CJ, Lifshits LM, Hendy DA, et al. Vinyl sulfone-functionalized acetalated dextran microparticles as a subunit broadly acting influenza vaccine. *AAPS J*. 2023;25(1). doi:10.1208/s12248-023-00786-6
210. Chen SX, Ma M, Xue F, et al. Construction of microneedle-assisted co-delivery platform and its combining photodynamic/immunotherapy. *J Control Release*. 2020;324:218–227. doi:10.1016/j.jconrel.2020.05.006
211. He W, Li X, Morsch M, et al. Brain-targeted codelivery of Bcl-2/Bcl-xl and Mcl-1 inhibitors by biomimetic nanoparticles for orthotopic glioblastoma therapy. *ACS Nano*. 2022;16(4):6293–6308. doi:10.1021/acsnano.2c00320
212. Ma S, Yao H, Si X, et al. Orally available dextran-aspirin nanomedicine modulates gut inflammation and microbiota homeostasis for primary colorectal cancer therapy. *J Control Release*. 2024;370:528–542. doi:10.1016/j.jconrel.2024.05.002
213. Banerjee A, Bandopadhyay R. Use of dextran nanoparticle: a paradigm shift in bacterial exopolysaccharide based biomedical applications. *Int J Biol Macromol*. 2016;87:295–301. doi:10.1016/j.ijbiomac.2016.02.059
214. Kraisomdet P, Pratess T, Na Nakorn P, et al. Amphiphilic dextran-vinyl laurate-based nanoparticles: formation, characterization, encapsulation, and cytotoxicity on human intestinal cell line. *Prog Biomater*. 2020;9(1–2):15–23. doi:10.1007/s40204-020-00128-1
215. Fan Y, Marioli M, Zhang K. Analytical characterization of liposomes and other lipid nanoparticles for drug delivery. *J Pharm Biomed Anal*. 2021;192:113642. doi:10.1016/j.jpba.2020.113642
216. Cardoso RV, Pereira PR, Freitas CS, Paschoalin VMF. Trends in drug delivery systems for natural bioactive molecules to treat health disorders: the importance of nano-liposomes. *Pharmaceutics*. 2022;14(12):2808. doi:10.3390/pharmaceutics14122808
217. Lee WR, Chou WL, Lin ZC, Sung CT, Lin CY, Fang JY. Laser-assisted nanocarrier delivery to achieve cutaneous siRNA targeting for attenuating psoriasiform dermatitis. *J Control Release*. 2022;347:590–606. doi:10.1016/j.jconrel.2022.05.032
218. Trovagunta R, Marquez R, Tolosa L, et al. Corrigendum to "Lignin self-assembly phenomena and valorization strategies for pulping, biorefining, and materials development: part 1. The physical chemistry of lignin self-assembly" [Advances in Colloid and Interface Science 322 (2024) 103247/https://doi.org/10.1016/j.cis.2024.103247]. *Adv Colloid Interface Sci*. 2026;352:103837. doi:10.1016/j.cis.2026.103837
219. Poletto G, Evangelista L, Venturini F, et al. Nanoparticles and Radioisotopes: a Long Story in a Nutshell. *Pharmaceutics*. 2022;14(10):2024. doi:10.3390/pharmaceutics14102024
220. Boutros JA, Magee AS, Cox D. Comparison of structural differences between yeast β-glucan sourced from different strains of saccharomyces cerevisiae and processed using proprietary manufacturing processes. *Food Chem*. 2022;367:130708. doi:10.1016/j.foodchem.2021.130708
221. Anaya EU, Amin AE, Wester MJ, Danielson ME, Michel KS, Neumann AK. Dectin-1 multimerization and signaling depends on fungal β-glucan structure and exposure. *Biophys J*. 2023;122(18):3749–3767. doi:10.1016/j.bpj.2023.07.021
222. Lin H, Han R, Wu W. Glucans and applications in drug delivery. *Carbohydr Polym*. 2024;332:121904. doi:10.1016/j.carbpol.2024.121904
223. Kośnik W, Sikorska H, Kiciak A, Ciach T. Nanoparticle-encapsulated epirubicin efficacy in the inhibition of growth of orthotopic ovarian patient-derived xenograft in immunocompromised mice. *Int J Mol Sci*. 2024;25(1):645. doi:10.3390/ijms25010645
224. Pangua C, Espuelas S, Simon JA, et al. Enhancing bevacizumab efficacy in a colorectal tumor mice model using dextran-coated albumin nanoparticles. *Drug Deliv Transl Res*. 2025;15(7):2354–2371. doi:10.1007/s13346-024-01734-3

225. Dong P, Liu J, Lv H, et al. The enhanced antitumor activity of the polymeric conjugate covalently coupled with docetaxel and docosahexaenoic acid. *Biomater Sci*. 2022;10(13):3454–3465. doi:10.1039/d2bm00337f
226. Wang S, Liu J, Lv H, et al. Complete regression of xenografted breast tumors by dextran-based dual drug conjugates containing paclitaxel and docosahexaenoic acid. *Eur J Med Chem*. 2022;240:114567. doi:10.1016/j.ejmech.2022.114567
227. Zhao Y, Pan J, Han B, et al. Ultrahigh-resolution visualization of vascular heterogeneity in brain tumors via magnetic nanoparticles-enhanced susceptibility-weighted imaging. *ACS Nano*. 2024;18(32):21112–21124. doi:10.1021/acsnano.4c02611
228. Shoaib M, Arif H, Awan AN, Khan MM, Batool S, Ahmed S. Synthesis and optimization of fluoxetine-loaded polymeric nanoparticles for dual therapeutic applications in cancer and depression. *Daru*. 2025;33(2):18. doi:10.1007/s40199-025-00561-2
229. Liu J, Zhang N, Wu J, et al. A novel dextran-based dual drug conjugate targeted tumors with high biodistribution ratio of tumors to normal tissues. *Int J Nanomedicine*. 2022;17:4895–4910. doi:10.2147/ijn.S379758
230. Chu Y, He X, Xue Y, et al. An exploratory clinical study of beta-glucan combined with camrelizumab and SOX chemotherapy as first-line treatment for advanced gastric adenocarcinoma. *Front Immunol*. 2024;15:1448485. doi:10.3389/fimmu.2024.1448485
231. Milla SP, Luna PPG, Casariego AV, et al. Adherence and impact of an oral nutritional supplement enriched in leucine, EVOO, EPA and DHA, and beta-glucans on the coverage of energy and protein requirements in patients with cancer and malnutrition: alisenoc study. *Nutrition*. 2024;120:112355. doi:10.1016/j.nut.2024.112355
232. Singh VA, Ong BK, Yasin NF. Oxidised cellulose in musculoskeletal oncology procedure: does it reduce postoperative blood loss? *Musculoskelet Surg*. 2024;108(4):483–489. doi:10.1007/s12306-024-00840-2
233. Cardenas FI, Mauguen A, Cheung IY, et al. Phase I trial of oral yeast-derived β-glucan to enhance Anti-GD2 immunotherapy of resistant high-risk neuroblastoma. *Cancers*. 2021;13(24):6265. doi:10.3390/cancers13246265
234. Albeituni SH, Ding C, Liu M, et al. Yeast-derived particulate β-glucan treatment subverts the suppression of myeloid-derived suppressor cells (MDSC) by inducing polymorphonuclear MDSC apoptosis and monocytic MDSC differentiation to APC in cancer. *J Immunol*. 2016;196 (5):2167–2180. doi:10.4049/jimmunol.1501853
235. Hirschowitz EA, Mullins A, Prajapati D, et al. Pilot study of 1650-G: a simplified cellular vaccine for lung cancer. *J Thorac Oncol*. 2011;6 (1):169–173. doi:10.1097/JTO.0b013e3181fb5c22
236. Cheung IY, Mauguen A, Modak S, et al. Effect of oral β-glucan on antibody response to ganglioside vaccine in patients with high-risk neuroblastoma: a phase 2 randomized clinical trial. *JAMA Oncol*. 2023;9(2):242–250. doi:10.1001/jamaoncol.2022.5999
237. Hong F, Yan J, Baran JT, et al. Mechanism by which orally administered beta-1,3-glucans enhance the tumoricidal activity of antitumor monoclonal antibodies in murine tumor models. *J Immunol*. 2004;173(2):797–806. doi:10.4049/jimmunol.173.2.797
238. Steimbach L, Borgmann AV, Gomar GG, et al. Fungal beta-glucans as adjuvants for treating cancer patients - A systematic review of clinical trials. *Clin Nutr*. 2021;40(5):3104–3113. doi:10.1016/j.clnu.2020.11.029
239. Leong SP. Detection of melanoma, breast cancer and head and neck squamous cell cancer sentinel lymph nodes by Tc-99m Tilmanocept (Lymphoseek®). *Clin Exp Metastasis*. 2022;39(1):39–50. doi:10.1007/s10585-021-10137-4
240. Agrawal A, Civantos FJ, Brumund KT, et al. [(99m)Tc]tilmanocept accurately detects sentinel lymph nodes and predicts node pathology status in patients with oral squamous cell carcinoma of the head and neck: results of a phase III multi-institutional trial. *Ann Surg Oncol*. 2015;22 (11):3708–3715. doi:10.1245/s10434-015-4382-x
241. Marcinow AM, Hall N, Byrum E, Teknos TN, Old MO, Agrawal A. Use of a novel receptor-targeted (CD206) radiotracer, 99mTc-tilmanocept, and SPECT/CT for sentinel lymph node detection in oral cavity squamous cell carcinoma: initial institutional report in an ongoing Phase 3 study. *JAMA Otolaryngol Head Neck Surg*. 2013;139(9):895–902. doi:10.1001/jamaoto.2013.4239
242. Guo W, Zhang X, Wan L, et al. β-Glucan-modified nanoparticles with different particle sizes exhibit different lymphatic targeting efficiencies and adjuvant effects. *J Pharm Anal*. 2024;14(12):100953. doi:10.1016/j.jpha.2024.02.007
243. Colaço M, Roquito T, Costa JP, Cruz MT, Borges O. The effect of curcumin-loaded glucan nanoparticles on immune cells: size as a critical quality attribute. *Pharmaceutics*. 2023;15(2):623. doi:10.3390/pharmaceutics15020623
244. Dri DA, Rinaldi F, Carafa M, Marianecci C. Nanomedicines and nanocarriers in clinical trials: surfing through regulatory requirements and physico-chemical critical quality attributes. *Drug Deliv Transl Res*. 2023;13(3):757–769. doi:10.1007/s13346-022-01262-y
245. Pikor LA, Arivazhagan S, Mendicino M, Sathiamoorthy S. Navigating the manufacturing, testing and regulatory complexities of regulatory T cells for adoptive cell therapy. *Front Immunol*. 2025;16:1626085. doi:10.3389/fimmu.2025.1626085
246. Abreu TR, Biscaia M, Gonçalves N, Fonseca NA, Moreira JN. In vitro and in vivo tumor models for the evaluation of anticancer nanoparticles. *Adv Exp Med Biol*. 2021;1295:271–299. doi:10.1007/978-3-030-58174-9_12
247. Sharifi S, Caracciolo G, Pozzi D, et al. The role of sex as a biological variable in the efficacy and toxicity of therapeutic nanomedicine. *Adv Drug Deliv Rev*. 2021;174:337–347. doi:10.1016/j.addr.2021.04.028