Cancer Biol Med 2026. doi: 10.20892/j.issn.2095-3941.2025.0512

EDITORIAL

Enhancing cancer immunotherapy through polymer-based antibody conjugation technologies

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Cancer immunotherapy has emerged as a transformative strategy with remarkable clinical potential. Therapeutic approaches, such as monoclonal immunotherapeutic antibodies, dual immune checkpoint blockade, and small-molecule immunomodulators, have demonstrated significant or promising benefits. However, cancer immunotherapy efficacy is often limited by off-target toxicity and insufficient immune activation and antitumor potency. Nanotechnology-based approaches have provided versatile platforms to address these challenges[1], among which polymer-based nanotechnology has gained widespread attention due to biodegradability and excellent biosafety profiles[2]. This approach enables the construction of bispecific antibodies (BsAbs), which target two different antigens simultaneously, or trispecific antibodies (TsAbs), which engage three distinct targets, as well as antibody–drug conjugates (ADCs) with tunable pharmacologic properties by covalent integrating or affinity binding of polymers and antibodies. ADCs can be further categorized based on the payloads, as follows: immunostimulatory ADCs carrying immune agonists to activate anti-tumor immunity; and cytotoxic ADCs delivering cell-killing agents to induce tumor cell death. These conjugates not only improve drug solubility, stability, and the half-life of small molecules, but also enhance tumor accumulation and immune activation, thereby strengthening antitumor immunity. In this editorial we summarize the advances in polymer–antibody conjugates with a focus on preparation strategies, mechanisms for efficacy enhancement, and future perspectives in cancer immunotherapy. We aimed to highlight how polymer engineering can reshape immunotherapies to maximize therapeutic benefit while minimizing adverse effects.

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Received August 31, 2025; accepted October 10, 2025;
published online November 24, 2025.
Available at www.cancerbiomed.org
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Mechanistic insights into enhanced immunotherapy

Polymer-antibody conjugates enhance immunotherapy through multiple mechanisms, including improved checkpoint blockade, enhanced T cell engagement, targeted delivery of immunomodulators, and induction of immunogenic cell death. The key studies demonstrating these therapeutic strategies and the clinical outcomes are summarized in **Table 1**.

Single or dual immune checkpoint therapy

Monoclonal immunotherapeutic antibodies have achieved remarkable success in cancer treatment with the wide clinical use of immune checkpoint inhibitors (anti-PD-1/PD-L1 and anti-CTLA-4) and tumor-targeting antibodies (anti-CD20 and anti-HER2). Nevertheless, these therapies face challenges, including limited response rates, suboptimal tumor targeting, and systemic toxicity. Polymer-based antibody conjugation technology offers a versatile strategy to overcome these barriers through multivalent binding and modular assembly, enabling better mono-, bi-, or multi-specific architectures that strengthen immune cell–tumor interactions.

Xue et al. developed a polymer-assembled PD1/PDL1 bispecific antibody achieving 90.1% tumor suppression[3]. BsAbαPD1/αPDL1-treated mice maintained stable body weight while the free antibody groups showed weight loss, indicating reduced toxicity. BsAbs enhanced tumor accumulation through multivalent binding, activated $CD8^+$ T cells more effectively (90% killing rate), and preserved organ function.

To reduce off-target issues, Zhao et al. designed a switchable immunomodulator (Sw-IM) incorporating environment-responsive chemistry[4]. The polymer uses reversible masking through disulfide bonds or acid-labile maleic anhydride linkers, maintaining therapeutic inactivity during circulation. Only upon encountering tumor microenvironment conditions (high glutathione or acidic pH) do linkers degrade, selectively unleashing immune activation at tumor sites. This spatial control preserved anti-tumor efficacy while significantly reducing hepatosplenic toxicity.

Table 1 Overview of key studies on polymer–antibody conjugates that enhance antitumor immunotherapy

Category	Polymeric nanomedicines	Antibody	Targeting moiety & tumor-associated markers	Mechanism to enhance anti-tumor immunity	Ref.
Single or dual immune checkpoint therapy	PGLU-Fc-III-4C platform	αPD-1, αPD-L1	Fc region of antibodies	Sustained T cell activation enables facile BiTE construction using established mAbs and overcomes complex production methods	3
	SwpH(D)a4-1BB, SwpH(S)a4-1BB (pH-responsive anti-4-1BB conjugates)	α4-1BB	4-1BB/CD137 on T cells	Multivalent binding reduces koff, pH-responsive activation in an acidic TME; reduced systemic toxicity while maintaining efficacy	4
	PD1/CTLA-4 BsAb (PLG-Fc-III-4C based)	αPD1 (nivolumab), αCTLA-4 (ipilimumab)	PD1 on T cells, CTLA-4 on T cells	Multivalent binding enhances checkpoint blockade through increased avidit, precise 3:1 antibody ratio control maintains clinical optimization, tumor-targeted co-delivery of both antibodies *via* PD1-mediated accumulation, simultaneous dual checkpoint blockade at the tumor site	5
	PGLU-Fc-III-4C-PD1/OX40 BsAb	αPD1, αOX40	PD1 (inhibitory), OX40 (costimulatory) on $CD8^+$ T cells	Simultaneous PD1 blockade and OX40 agonism; multivalent binding enhances avidity; increased IFN-γ, TNF-α, and IL-12; enhanced $CD8^+$ T cell activation	6
	G7-aPD-L1	αPD-L1	PD-L1 on tumor cells	Multivalent binding enhances PD-1/PD-L1 blockade; increases T cell IL-2 production; reduces cancer cell chemoresistance to doxorubicin	7
CD3 antibody based T cell engager	PGLU-Fc-III-4C-PDL1/CD3e/4-1BB TsAb	αPDL1, αCD3e, α4-1BB	PDL1 on tumor cells, CD3e and 4-1BB on T cells	T cell engagement to tumor cells; simultaneous PDL1 blockade and T cell co-stimulation; enhanced IFN-γ, perforin, granzyme B	6
	PARylated PARP1-Herceptin/UCHT1 conjugate	αHER2 (Herceptin) + Anti-CD3 (UCHT1)	HER2 (tumor cells) + CD3 (T cells)	Simultaneous engagement of tumor cells and T cells through bispecific binding; enhanced cytotoxicity *via* immune synapse formation	8
	CTNE-25, CTNE-50, CTNE-75, CTNE-100	αCD3F(ab')2, αPDL1 (fixed at 50)	CD3 (T cells), PDL1 (E0771 tumor cells)	Valence-dependent T cell activation; controlled cytokine release; tumor-specific T cell engagement	9
	PTNE-10, PTNE-25, PTNE-50, PTNE-75, PTNE-100	αCD3F(ab')2 (fixed at 50), αPDL1	CD3 (T cells), PDL1 (tumor cells)	Modulation of binding affinity through PDL1 antibody valence variation; tumor targeting optimization	9
Monoclonal antibody polymer drug conjugation	aPDL1-NPLG-SN38	αPDL1 (Clone 10F.2H11)	PDL1 on MC38 tumor cells	Delivers SN38 for ICD induction, releases DAMPs, maintains PD-L1 checkpoint blockade	10
	αCD73-PLG-MMAE	αCD73 (oleclumab)	CD73 on TNBC cells and immune suppressive cells	Blocks adenosine pathway, induces ICD *via* MMAE release, enhances $CD8^+$ T cell infiltration, reduces Tregs	11

Table 1 Continued

Category	Polymeric nanomedicines	Antibody	Targeting moiety & tumor-associated markers	Mechanism to enhance anti-tumor immunity	Ref.
	U6244-021 (ISA-P-EPI)	Isatuximab	CD38 on MM cells	Direct cytotoxicity *via* EPI, preserved antibody-dependent cellular cytotoxicity (ADCC), ICD induction, cell cycle arrest	[12]
	U6244-031 (DARA-P-EPI)	Daratumumab	CD38 on MM cells	Direct cytotoxicity *via* EPI, preserved ADCC, ICD induction, cell cycle arrest	[12]
Cytotoxic drug-induced immunogenic cell death	αPDL1-PLG-IMDQ	αPD-L1	PD-L1 on intratumoral DCs and tumor cells	TLR7/8 activation in DC endosomes, PD-L1/PD-1 blockade, DC maturation, T cell priming	[13]
	aPDL1-PLG/R848 NPs	αPD-L1	PD-L1 on tumor cells	TLR7/8 activation, ultrasound-induced ICD, DC activation, T cell memory	[14]

Immune checkpoint inhibitors reinvigorate T cells by releasing inhibitory signals, which restores cytotoxic function. Once effective, these therapies induce durable responses and prolong survival. However, clinical benefit remains limited with response rates typically <30%. Dual checkpoint blockades (anti-PD-1 with anti-CTLA-4 or anti-LAG-3) demonstrate superior activity but cause high-grade immune-related adverse events from systemic T cell activation. Polymer-based conjugation provides a solution by enabling multivalent binding, stoichiometric control, and sustained activation, while simplifying bispecific assembly. Liu et al. developed polymeric multivalent Fc-binding peptide (PLG-Fc-III-4C) creating BsAbs by mixing polymer with anti-PD1 and anti-CTLA-4 antibodies in aqueous solution[5]. This innovation achieved the optimal 3 αPD1:1 αCTLA-4 ratio, matching the Opdivo plus Yervoy combination. $BsAb_{PD1/CTLA-4}$ achieved 96.8% tumor suppression *vs.* 77.3% for free combination in MC38 models. The system demonstrated 6.3-fold enhanced tumor accumulation through PD1-mediated targeting, while reducing colitis-related adverse events compared to conventional therapy, addressing a major limitation of dual checkpoint blockade.

CD3 antibody-based T cell engager

CD3 is commonly used as a key target in the design of bispecific T cell engagers (BiTEs), which activate T cell-mediated cytotoxicity by simultaneously binding CD3 on T cells and tumor-associated antigens on cancer cells. Conventional BiTEs are typically low-valency constructs with limited binding avidity to targets and efficient and durable T cell activation. To address these limitations, polymer-mediated trispecific T cell engagers (TiTEs) have been developed. Xue et al. improved this approach by constructing PDL1/CD3ε/4-1BB TsAbs using polymer scaffolds[6]. This system integrates 11.4 antibodies on average, delivering triple immune signals (CD3ε for T cell activation, 4-1BB for co-stimulation, and PDL1 for tumor targeting). The multivalent presentation dramatically stabilizes immune synapses, increasing tumor killing from 45% to 80% while minimizing off-target effects. TiTE achieves increased binding avidity, prolonged immunologic synapse formation, and amplified cytotoxic T cell responses, thereby offering a promising strategy to enhance the efficacy of tumor immunotherapy.

Therefore, polymer-antibody conjugates offer key advantages over conventional mono-, bi-, and tri-specific antibodies, such as enhanced affinity through multivalent binding, facile assembly with precise ratio control, spatiotemporal activation in tumor microenvironment, and superior immune synapse stabilization.

Small molecule immunomodulators

Toll-like receptor (TLR) agonists have emerged as potent immunostimulatory adjuvants, bridging innate and adaptive immunity[15]. By activating pattern recognition pathways in dendritic cells (DCs) and other APCs, TLR agonists enhance antigen processing and presentation, thereby promoting *de novo* CTL priming and expansion[16,17]. However, the broader clinical translation of TLR agonists is hampered by rapid systemic clearance, insufficient tumor accumulation, and dose-limiting inflammatory toxicities. Antibody-polymeric drug complexes (pADCs) could be constructed for reducing adverse toxicity, while increasing therapeutic efficiency.

Chu et al. developed αPDL1-PLG-IMDQ by conjugating imidazoquinoline TLR7/8 agonists to anti-PD-L1 antibodies *via* polyglutamic acid carriers[13]. This design achieves multiple objectives simultaneously, as follows: tumor-specific targeting through PD-L1 binding; controlled agonist release within the acidic tumor microenvironment; local dendritic cell activation without systemic inflammation; and synergistic checkpoint blockade. The spatial restriction of immune activation to

tumor sites enabled 97% and 89.4% tumor inhibition in CT26 and 4T1 models, respectively, effectively converting cold tumors to hot tumors without systemic toxicity.

Similarly, Cui et al. developed aPDL1-PLG/R848 nanoparticles addressing the poor solubility and high toxicity of free R848[14]. The polymer formulation not only solubilizes the hydrophobic agonist but also provides tumor-specific delivery, achieving 97.3% tumor inhibition with 50% complete responses when combined with ultrasound-triggered release. These systems demonstrate how polymer platforms transform systemically toxic immune agonists into precisely targeted immunotherapeutics.

Cytotoxic drug-induced immunogenic cell death (ICD)

Some cytotoxic drugs, such as anthracyclines, oxaliplatin, and camptothecin derivatives, can induce ICD, releasing damage-associated molecular patterns (DAMPs) and activating anti-tumor immune responses. However, the non-specific distribution of traditional chemotherapy drugs leads to severe normal tissue toxicity, while drug concentrations at tumor sites are often insufficient to effectively induce ICD. Conventional ADCs are constrained by drug-to-antibody ratios below 10, limiting their ability to deliver sufficient cytotoxic agents for effective ICD induction.

Zhang et al. shattered this limitation with aPDL1-NPLG-SN38, achieving DAR = 72 through polyglutamic acid modification[10]. This increase in drug loading ensures sufficient SN38 concentration at tumor sites to trigger robust ICD and damage-associated molecular pattern (DAMP) release. In addition, the Fc-III-4C conjugation strategy preserves antibody function, maintaining PD-L1 checkpoint blockade, while delivering cytotoxic payloads. This dual mechanism-simultaneous ICD induction and immune checkpoint inhibition-resulted in 2.8-fold higher tumor accumulation and significantly enhanced therapeutic efficacy.

The concept extends beyond simple cytotoxicity to metabolic immune regulation. Xie et al. developed αCD73-PLG-MMAE targeting the adenosine pathway, a critical metabolic checkpoint in tumor immunity[11]. CD73 catalyzes adenosine production, creating a profoundly immunosuppressive microenvironment. The polymer conjugate delivers MMAE for tumor killing, while simultaneously blocking CD73-mediated immunosuppression, effectively converting "cold" tumors to "hot" immune-responsive states. When combined with αPD-1, this metabolic reprogramming achieved 92% tumor suppression *vs.* only 21% for αPD-1 monotherapy, demonstrating the power of targeting metabolic checkpoints alongside conventional immune checkpoints.

Polymer platforms enable the use of less toxic payloads while maintaining efficacy for hematologic malignancies. CD38-targeting pADCs (ISA-P-EPI and DARA-P-EPI) achieved DAR = 30 using HPMA carriers, allowing epirubicin with lower-toxicity to replace traditional highly toxic payloads, while achieving complete tumor eradication[12]. This toxicity reduction expands the therapeutic window and improves patient tolerance.

Polymer-based ADCs have the potential to overcome conventional ADC limitations primarily through dramatically enhanced drug loading, which directly translates to improved therapeutic efficacy by ensuring sufficient drug concentration for robust immunogenic cell death and enhanced anti-tumor immune activation. In addition, polymer platforms preserve antibody functionality *via* non-covalent conjugation strategies, like Fc-III-4C, and minimize organic solvent exposure through aqueous bioorthogonal chemistry, maintaining both antibody integrity and immune effector functions throughout the conjugation process.

Polymer-based antibody conjugation strategies

Various conjugation strategies have been developed to link antibodies with polymers, ranging from covalent approaches to non-covalent methods. The detailed advantages and limitations of each method are summarized in **Table 2**.

Carbodiimide chemistry (EDC/NHS)

EDC/NHS conjugation represents the widely adopted antibody modification strategy, using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) for carboxyl activation. The unstable O-acylisourea intermediate formed by EDC alone exhibits poor reactivity with amines. However, N-hydroxysuccinimide (NHS) enables formation of semi-stable NHS ester intermediates that efficiently react with lysine ε-amino groups, generating stable amide bonds. For example, trastuzumab (anti-HER2) and UCHT1 (anti-CD3) were modified on lysines with BCN *via* NHS-ester chemistry, then coupled to azido-modified poly-ADP-ribose through copper-free SPAAC[8]. The engineered multivalent complexes bridged $HER2^+$ tumor cells and $CD3^+$ T cells, increasing local effective concentration and binding avidity.

In addition, Bu et al. demonstrated this principle through PAMAM dendrimer-based PD-L1 antagonist (G7-aPD-L1), clustering multiple anti-PD-L1 antibodies on a single nanoplatform[7]. This multivalent architecture improved the dissociation constant (KD) by an order of magnitude from 9.6×10^{-10} M to 8.5×10^{-11} M, while koff decreased 32-fold. These kinetic improvements translated to 1.9-fold increased IL-2 secretion and 2.5-fold enhanced tumor targeting *in vivo*. However, NHS/EDC coupling is inherently non-site-specific, yielding heterogeneous DARs and potentially impairing binding/Fc function.

Maleic anhydride-amine ring-opening amidation

Maleic anhydrides react directly with antibody surface lysines through nucleophilic ring opening to form stable amide bonds

with pendant carboxyl groups. This approach offers direct conjugation without pre-activation steps and achieves high drug-antibody ratios through multisite modification. The pH-responsive SwpH(S) a4-1BB used methylmaleic anhydride chemistry-mPEG-MMMA and was directly conjugated to antibodies at pH 9.5, yielding conjugates stable at physiologic pH but selectively cleaving in tumor-acidic environments[4]. Limitations include non-site-specific modification leading to product heterogeneity, anhydride susceptibility to hydrolysis, and conversion of positively charged lysines to negatively charged carboxylates potentially affecting antibody stability.

Click chemistry

Click chemistry refers to a class of highly efficient, reliable, and user-friendly reactions characterized by modularity, high yields, excellent selectivity, mild reaction conditions, and rapid kinetics. Common coupling strategies in click chemistry include copper-catalyzed azide-alkyne cycloaddition, strain-promoted azide-alkyne cycloaddition, thiol-alkene reactions, photoinduced cycloadditions between tetrazoles and alkenes, and thiol-maleimide reaction, also exhibit click-like characteristics. Among these strategies, thiol-maleimide conjugation and strain-promoted azide-alkyne cycloaddition have been widely adopted in the development of ADCs. Thiol-maleimide conjugation encompasses two approaches (natural disulfide reduction and genetically engineered cysteine conjugation). Natural disulfide reduction uses reducing agents to cleave hinge disulfides, generating thiols for maleimide conjugation, while genetic engineering introduces specific cysteine codons at predetermined positions. Advantages include directional conjugation, mild reaction conditions, and stable thioether linkages. Huang et al. developed PLA-based bispecific nano-engagers *via* thiol-maleimide chemistry, revealing that controlling αCD3 valence within 25–50 enables stable T-cell pre-binding without premature activation[9]. The Huang et al. study revealed that controlling αCD3 valence within an intermediate range (25–50) enables stable T-cell pre-binding without premature activation, while αPD-L1 mediates tumor-specific localization.

Strain-promoted azide-alkyne cycloaddition (SPAAC) represents advanced bioorthogonal conjugation. Antibodies

Table 2 Antibody-polymer conjugation chemistries: methods; advantages; and limitations for immunotherapeutic applications

Method	Advantages	Disadvantages	Ref
EDC/NHS amide coupling (–COOH/–NH_2)	Mild reaction conditions (physiologic pH, room temperature) Forms stable amide bonds	Non-site-specific lysine modification yields heterogeneous DARs Random antibody orientation potentially impairs binding/Fc function Requires extensive purification steps Batch-to-batch variability in conjugation efficiency	7,8
Maleic Anhydride-Amine Ring-Opening Amidation	Direct one-step conjugation without pre-activation High drug-antibody ratios achievable Forms stable amide bonds	Non-site-specific lysine modification causes heterogeneity Anhydride hydrolysis in aqueous conditions reduces efficiency Converts cationic lysines to anionic carboxylates, affecting protein stability Variable modification degrees between batches	4
Click Chemistry	Thiol-maleimide: Site-specific conjugation at engineered cysteines; efficient reaction under mild conditions; forms stable thioether bonds SPAAC: Bioorthogonal reaction under physiologic conditions; copper-free chemistry preserves antibody functionality; forms stable triazole linkages	Thiol-maleimide: Disulfide reduction may compromise antibody stability; limited conjugation sites; potential thiol re-oxidation without proper capping SPAAC: Requires antibody pre-modification with NHS-azide or DBCO/BCN; high synthesis costs for strained alkynes; multi-step process increases complexity	4,8,10,18
Fc-III-4C (Fc-specific peptide mediated)	Preserves antibody function (targeting and ADCC/CDC) and structure (no direct modification) Universal platform for multi-specific antibody assembly Rapid assembly (2–4 h in PBS) Maintains effector functions Enables purification-free one-step assembly	Non-covalent binding may dissociate *in vivo* Fc-III-4C peptide synthesis costs Potential competition with endogenous Fc receptors Limited to antibodies with intact Fc regions Possible immunogenicity concerns	3,5,6,10,11,13,14

are pre-modified with NHS-azide or DBCO-NHS reagents, followed by cycloaddition with functionalized polymers forming stable triazole linkages. The reaction proceeds efficiently under physiologic conditions without copper catalysts, achieving high DAR. Limitations include required antibody pre-modification and high synthesis costs for DBCO linkers.

Fc-binding peptide (Fc-III-4C)-mediated conjugation

Fc-III-4C is a 15-amino acid bicyclic peptide that binds specifically to the Fc region of antibodies with high affinity (Kd < 5 nM). This peptide enables the conjugation of antibodies to polymer carriers through non-covalent interactions.

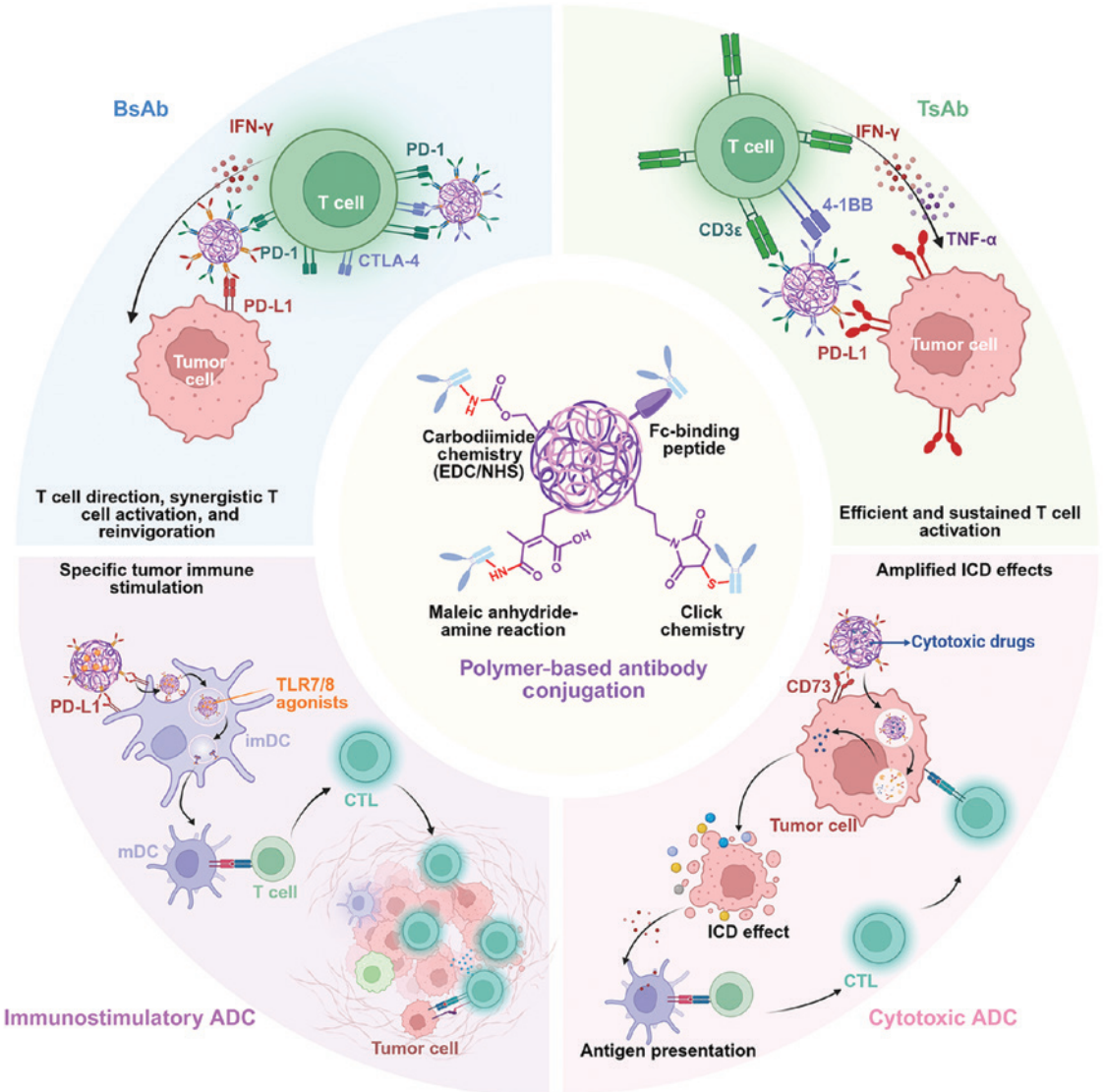


Figure 1 Overview of polymer-based antibody conjugation strategies and the applications in cancer immunotherapy. Central core illustrates various polymer-antibody conjugation chemistries, including carbodiimide coupling (EDC/NHS), click chemistry (azide-alkyne cycloaddition), the maleic anhydride-amine reaction, and Fc-binding peptide (Fc-III-4C)-mediated assembly. Surrounding quadrants demonstrate the diverse therapeutic modalities enabled by these conjugation strategies: (top) bispecific antibodies (BsAbs) and trispecific antibodies (TsAbs) for multi-target engagement and enhanced T cell activation; (bottom left) Immunostimulatory ADCs delivering immune agonists to the tumor microenvironment; (bottom right) Cytotoxic ADCs inducing immunogenic cell death and subsequent anti-tumor immune responses. These polymer-based platforms collectively enhance antibody therapeutic efficacy through improved stability, multivalent binding, controlled drug release, and synergistic immune activation mechanisms.

This approach offers several advantages. Specifically, this approach completely preserves antibody structure and function because no direct modification is required, enables ultra-high drug loading, allows rapid assembly in simple buffer conditions (2–4 h in PBS), and provides precise control over antibody ratios for creating multi-specific combinations. The multivalent presentation enhances binding strength and therapeutic potency. While this platform shows great promise for clinical translation due to simplicity and versatility, potential limitations include peptide synthesis costs, possible immunogenicity, and competition from endogenous antibodies in the circulation. Xue et al. established a universal Fc-III-4C-poly [$_L$-glutamic acid] (PGLU) platform that allows one-step, purification-free self-assembly of multi-specific antibodies in aqueous solution[6]. Using this modular system, Xue et al. constructed PD-1/OX40 BsAbs and PD-L1/CD3ε/4-1BB TsAbs, achieving high valence.

Conclusions and future perspectives

Polymer-based antibody conjugation technology represents a versatile and rapidly evolving platform for advancing cancer immunotherapy. Distinct from purely biotechnological approaches to antibody engineering, polymer-based strategies provide unparalleled flexibility in molecular design, enabling the assembly of a broad spectrum of conjugate architectures. Through precise chemical control, antibodies can be integrated with polymers to generate bi- and multi-specific formats, ADCs with unprecedented drug-to-antibody ratios, or hybrid constructs that combine immune modulation with targeted delivery. Such diversity allows for enhanced multivalent binding, programmable stoichiometry, and spatiotemporally controlled immune activation, thereby addressing many limitations of conventional antibodies and small-molecule immunomodulators.

A key advantage of polymer-based platforms lies in the ability to serve as a molecular bridge connecting multiple antibodies or antibodies with small-molecule agents with a controllable ratio, high DAR, and tumor targeting ability to amplify immune responses through several complementary mechanisms (**Figure 1**), as follows: 1) T cell direction or synergistic T cell activation and reinvigoration; 2) efficient and sustained T cell activation; 3) specific tumor immune stimulation; and 4) amplified ICD effects for enhanced immunotherapy.

Despite these promising advances, clinical translation remains challenging. Current phase I trials illustrate this complexity. XMT-1522, a Dolaflexin platform-based ADC achieving a DAR = 12 demonstrated initial promise but was discontinued following a grade 5 adverse event (NCT02952729). While polymer platforms enable unprecedented drug loading and maintain structural stability, optimizing the therapeutic window remains paramount. Beyond safety optimization, clinical translation requires addressing polymer-specific challenges, including precise control of polymer dispersity, establishing regulatory frameworks for biodegradation products, validating batch-to-batch reproducibility, and demonstrating long-term stability. In addition, the immunogenicity of synthetic polymer backbones and the need for standardized analytical methods to characterize these complex conjugates represent critical hurdles for successful implementation.

Looking ahead, continued refinement of polymer–antibody conjugates-through structural optimization, stability enhancement, and standardized manufacturing will be critical for clinical translation. By reshaping the immunosuppressive tumor microenvironment or directly inducing tumor cell killing, polymer–antibody conjugates can be rationally combined with other immunotherapeutic modalities, such as checkpoint inhibitors, cytokines, or cancer vaccines, to achieve synergistic outcomes. Ultimately, polymer-mediated antibody engineering may open a new frontier in cancer treatment, providing modular and customizable solutions for next-generation BsAbs, ADCs, and combination immunotherapy approaches.

Grant support

This study was financially supported by the Ministry of Science and Technology of China (Grant No. 2022YFE0110200), the National Natural Science Foundation of China (Grant Nos. 52573183, 52273157, 52073279, and 52025035), Jilin province (Grant No. 20240305041YY), as well as the Youth Innovation Promotion Association of Chinese Academy of Sciences (Grant No. 2022224).

Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Na Shen, Zhaohui Tang.
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Cite this article as: Chu H, Chen J, Ye S, Fang X, Shen N, Tang Z. Enhancing cancer immunotherapy through polymer-based antibody conjugation technologies. Cancer Biol Med. 2026; 23: 453-460. doi: 10.20892/j.issn.2095-3941.2025.0512