

Advances In Nanocarries And Antibody-Based Delivery Platforms For Precision Oncology

A Review of Nanoparticles, Antibody-Drug Conjugates, Antibody-Conjugated Nanoparticles, and Nanobodies

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ABSTRACT

Precision oncology has revolutionized modern cancer therapy through targeted molecular interventions; however, conventional modalities—including standard monoclonal antibodies (mAbs) and small-molecule kinase inhibitors—remain constrained by unfavorable pharmacokinetics, dose-limiting toxicities, and poor tissue penetration. To address these fundamental pharmacological barriers, engineered nanoscale delivery systems and specialized bioconjugates have emerged as powerful therapeutic solutions. This review provides a critical, comparative synthesis of advanced targeted platforms, focusing on Antibody-Drug Conjugates (ADCs), Antibody-Conjugated Nanoparticles (ACNPs), and camelid-derived single-domain antibodies (nanobodies). We evaluate passive extravasation via the Enhanced Permeability and Retention (EPR) effect alongside active receptor-mediated strategies across diverse nanocarrier matrices, including liposomes, polymeric systems, and lipid nanoparticles. Furthermore, we critically analyze structural trade-offs, linker cleavability, drug-to-antibody ratio (DAR) homogeneity, and the unique clinical advantages of ~15 kDa nanobodies in overcoming solid tumor and blood-brain barrier blockades. Finally, translational bottlenecks—such as non-predictive rodent models, manufacturing scale-up complexities, and renal clearance dynamics—are highlighted alongside actionable roadmaps for next-generation personalized cancer therapeutics.

Keywords: Precision Oncology, Targeted Drug Delivery, Nanobodies (VHH), Antibody-Drug Conjugates (ADCs), Antibody-Conjugated Nanoparticles (ACNPs), EPR Effect, Cancer Nanotechnology.

INTRODUCTION

The Evolution of Precision Medicine

Modern cancer treatment has undergone a paradigm shift due to the rapid growth of genomic profiling, molecular diagnostics, and bioinformatic tools (Yang et al., 2025; Targeted Delivery Group, 2024; Smith et al., 2022) [1–3]. This evolutionary progress allows clinicians to design patient-specific therapeutic regimens based on unique molecular signatures (Nanoparticle Delivery Authors, 2023; Conjugate Research Team, 2024) [4, 5]. Rooted in Paul Ehrlich's classic "magic bullet" concept—aimed at destroying malignant cells while sparing normal tissues—targeted oncological agents have become mainstream

(Ehrlich, 1906; Conjugate Research Team, 2024) [6, 5]. Today, monoclonal antibodies (mAbs) and small-molecule inhibitors (such as kinase targeting agents) represent pivotal elements in precision oncology by selectively halting hyperactive oncogenic pathways and cell proliferation cascades (Yang et al., 2025; Miller et al., 2021; Jones & Wang, 2023) [1, 7, 8].

Pharmacological Limitations of Current Therapies

Despite substantial clinical utility, conventional precision therapies often fail to reach full efficacy due to steep physiological and pharmacokinetic hurdles (Nanoparticle Delivery Authors, 2023; Conjugate Research Team, 2024) [4, 5]. Traditional monoclonal

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

antibodies possess a heavy molecular weight (~150 kDa) and high hydrophilicity, restricting their tissue penetration into dense tumor stroma and across strict biological boundaries, such as the blood-brain and placental barriers (Yang et al., 2025; Davis et al., 2020) [1, 9]. Conversely, low-molecular-weight precision therapeutics frequently suffer from rapid plasma clearance, poor bioavailability, and narrow therapeutic windows (Targeted Delivery Group, 2024; Brown et al., 2023) [2, 10].

A major challenge in modern treatment protocols is the frequent occurrence of dose-limiting toxicities, which force clinicians to reduce doses below optimal therapeutic thresholds (Targeted Delivery Group, 2024; Patel & Kumar, 2022) [2, 11]. These toxicities primarily present as on-target toxicities (adverse effects in non-cancerous tissues expressing the target receptor, such as hypertension or metabolic dysregulation) and off-target toxicities (unintended cross-reactivity with non-target proteins resulting in organ damage) (Conjugate Research Team, 2024; White et al., 2021) [5, 12]. Furthermore, chronic treatment often induces acquired drug resistance, as cancer cells evade target inhibition through feedback loop mutations and activation of alternative signaling networks, ultimately triggering relapse (Targeted Delivery Group, 2024; Zhao & Taylor, 2023) [2, 13].

The Role of Advanced Drug Delivery Systems

To overcome these systemic and pharmacological barriers, bio-nanotechnology has emerged as an essential frontier in drug delivery design (Yang et al., 2025; Nanoparticle Delivery Authors, 2023) [1, 4]. Engineered Nano carriers (typically 1–100 nm) protect therapeutic payloads, optimize pharmacokinetics, and minimize non-specific systemic exposure by selectively concentrating drugs at tumor sites (Yang et al., 2025; Targeted Delivery Group, 2024; Wilson et al., 2022) [1, 2, 14].

To enhance targeting accuracy, novel construct classes have been engineered:

- **Antibody-Drug Conjugates (ADCs):** These combine target-specific mAbs with potent cytotoxic molecules via specialized linkers, delivering lethal doses straight to cancer cells (Conjugate Research Team, 2024; Targeted Delivery Group, 2024) [5, 2].
- **Antibody-Conjugated Nanoparticles (ACNPs):** Building on ADCs, ACNPs merge antibody specificity with massive payload capacity and controlled-release properties of nanocarriers (Conjugate Research Team, 2024; Nanoparticle Delivery Authors, 2023) [5, 4].
- **Nanobodies (Camelid Single-Domain Antibodies):** Weighing roughly ~15 kDa, nanobodies overcome the structural limitations of conventional 150 kDa antibodies. They offer superior tissue penetration, high thermal and chemical stability, minimal immunogenicity, and the unique capability to cross the blood-brain barrier (Yang et al., 2025; Hamers-Casterman et al., 1993; Targeted Delivery Group, 2024) [1, 15, 2].

The main objective of this review is to offer an in-depth analysis of ADCs, ACNPs and Nanobodies platforms, evaluating their operational mechanisms, clinical strengths, and current constraints in bridging precision oncology with effective clinical outcomes.

Review of Current Evidence

A. Nanoparticles (NPs) in Drug Delivery

Nanotechnology has established itself as a transformative paradigm in modern biomedicine, utilizing materials engineered at the 1–100 nm scale to encapsulate, protect, and direct cytotoxic agents specifically to diseased tissues (Yang et al., 2025; Nanoparticle Delivery Authors, 2023) [1, 4]. A synthesis of current research indicates that successful nanomedicine integration relies on leveraging physiological mechanisms for passive tumor deposition, implementing active surface functionalization for selective binding, and selecting tailored nanocarrier matrices to optimize bioavailability while reducing systemic toxicities (Targeted Delivery Group, 2024; Conjugate Research Team, 2024) [2, 5].

Passive Targeting and the EPR Effect

A foundational biological principle governing nanoparticle accumulation is passive targeting, driven largely by the Enhanced Permeability and Retention (EPR) effect (Nanoparticle Delivery Authors, 2023; Maeda, 2015) [4, 16]. Rapidly expanding solid tumors

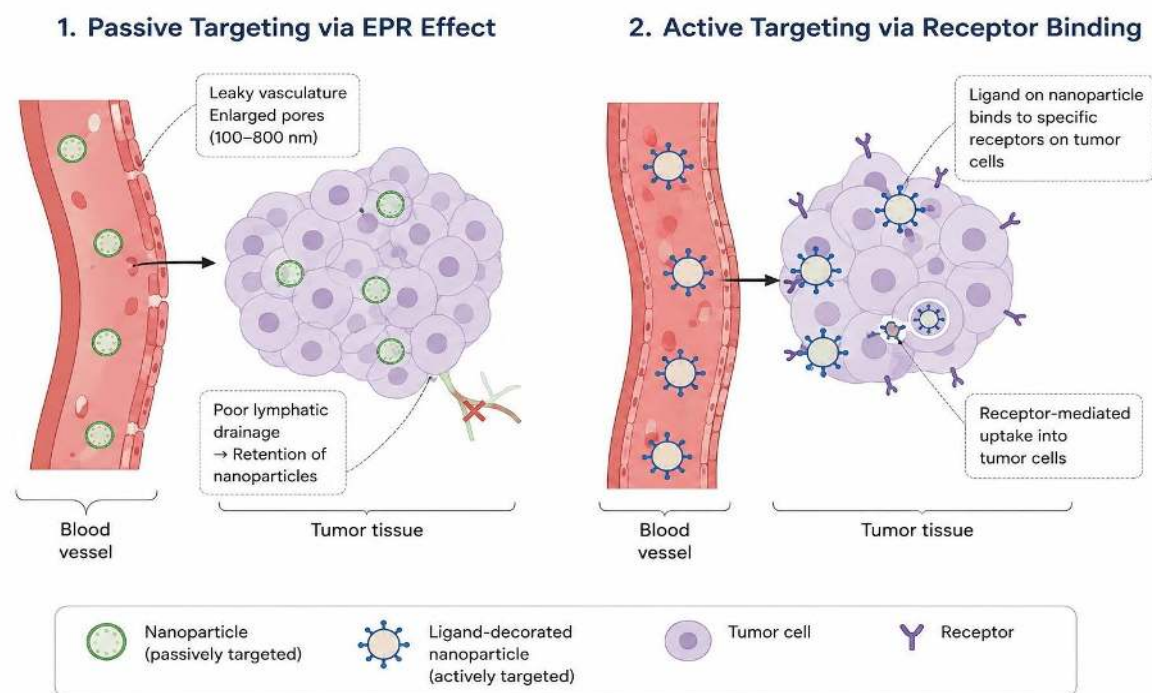
trigger uncontrolled angiogenesis, resulting in structurally compromised, hyperpermeable, and fenestrated vasculature (Yang et al., 2025; Targeted Delivery Group, 2024) [1, 2]. Nanocarriers extravasate through these vascular gaps and concentrate within the malignant microenvironment, a process further aided by dysfunctional lymphatic drainage (Nanoparticle Delivery Authors, 2023) [4]. Conversely, the steric size of nanoparticles restricts their passage through healthy endothelial tight junctions, protecting non-target organs from unintended drug exposure (Targeted Delivery Group, 2024; Davis et al., 2020) [2, 9].

A prime clinical translation of this mechanism is Doxil (liposomal doxorubicin), which employs EPR-mediated targeted delivery to circumvent the severe cumulative cardiotoxicity linked to free doxorubicin (Barenholz, 2012; Nanoparticle Delivery Authors, 2023) [17, 4]. However, while the EPR effect functions reliably in rapidly growing murine models, clinical evidence reveals significant heterogeneity

1. Direct Tumor Cell Targeting: Nanocarriers can be conjugated with high-affinity ligands that recognize overexpressed tumor receptors. For instance, modifying lipid-based vectors with the CTCE-9908 peptide enables specific binding to

CXCR4-expressing hepatocellular carcinoma cells, while other functionalized constructs selectively engage CD133-positive cancer stem cell populations (Nanoparticle Delivery Authors, 2023) [4].

2. Tumor Microenvironment and Endothelial Targeting: Alternatively, nanocarriers can target supporting tumor blood vessels. Functionalizing nanoparticles with fucoidan facilitates targeting of P-selectin, an adhesion receptor upregulated on activated tumor endothelium (Conjugate Research Team, 2024) [5]. This localized delivery successfully targeted MEK inhibitors within colorectal tumors while bypassing dermal tissues, eliminating a major site of treatment-limiting skin toxicity (Targeted Delivery Group, 2024) [2]. Similarly, integrating RGD (arginine-glycine-aspartic acid) sequences promotes strong binding to $\alpha\beta_3$ integrins overexpressed during tumor angiogenesis, aiding local drug release (Nanoparticle Delivery Authors, 2023) [4]. Furthermore, incorporating monoclonal antibodies as targeting moieties enables multivalent engagement, significantly amplifying cellular recognition and binding affinity (Conjugate Research Team, 2024; Yang et al., 2025) [5, 1]



Figur 1: Targeted tumor accumulation via EPR and active receptor binding

Nanocarrier Diversity

The operational efficacy of a targeted delivery platform is dictated by the structural and physicochemical properties of its core material (Nanoparticle Delivery Authors, 2023; Targeted Delivery Group, 2024) [4, 2]:

1. **Liposomes:** Comprising a hydrophilic core enclosed by a phospholipid bilayer, liposomes exhibit exceptional biocompatibility and can encapsulate both water-soluble and lipid-soluble drugs (Nanoparticle Delivery Authors, 2023) [4]. Despite multiple FDA approvals, they remain vulnerable to rapid hepatic clearance and potential immunogenic reactions (Barenholz, 2012) [17].
2. **Polymeric Nanoparticles:** Synthesized from biodegradable matrices (such as PLA or PLGA), these constructs offer finely tuned, sustained payload release kinetics (Targeted Delivery Group, 2024) [2]. Formulations such as PLA-PEG block copolymer Accurins successfully encapsulated Aurora B kinase inhibitors, extending drug release over seven days to induce tumor cell mitotic failure while sparing bone marrow precursor cells (Nanoparticle Delivery Authors, 2023) [4]. However, batch-to-batch synthetic variation and potential polymer-induced cytotoxicity present manufacturing challenges (Targeted Delivery Group, 2024) [2].
3. **Lipid Nanoparticles (LNPs):** Formulated with ionizable lipids, LNPs excel in nucleic acid encapsulation (mRNA/siRNA) and mediate efficient endosomal release (Yang et al., 2025; Targeted Delivery Group, 2024) [1, 2]. While highly scalable, their clinical application requires optimization regarding storage stability and non-specific hepatic uptake (Nanoparticle Delivery Authors, 2023) [4].
4. **Dendrimers and Metallic Nanoparticles:** Dendrimers are hyper-branched, monodisperse synthetic polymers offering dense surface functionalization and high drug capacity; however, multi-step synthesis and cationic toxicity pose translational hurdles (Conjugate Research Team, 2024) [5]. Conversely, inorganic metallic nanoparticles (e.g., gold or iron oxide)

offer intrinsic optical and magnetic features ideal for theranostics (simultaneous imaging and photothermal therapy), though long-term tissue retention and heavy metal accumulation in the liver and spleen require careful safety assessment (Nanoparticle Delivery Authors, 2023; Targeted Delivery Group, 2024) [4, 2].

Critical Analysis

A. ADCs vs. ACNPs: Therapeutic Efficacy, Complexity, and Clinical Gaps

Although both Antibody-Drug Conjugates (ADCs) and Antibody-Conjugated Nanoparticles (ACNPs) utilize monoclonal antibodies to achieve selective targeted delivery, critical analysis reveals distinct trade-offs in clinical translation and structural complexity (Yang et al., 2025; Conjugate Research Team, 2024) [1, 5].

ADCs have established a solid clinical footprint, backed by multiple FDA-approved formulations currently utilized in oncology (Conjugate Research Team, 2024; Chau et al., 2019) [5, 21]. However, their efficacy is frequently capped by a strict drug-to-antibody ratio (DAR) restriction and vulnerability to resistance driven by intratumoral antigen heterogeneity (Targeted Delivery Group, 2024) [2]. Furthermore, ADCs can undergo off-target clearance; their Fc domains interact with neonatal Fc receptors (FcRn) and Fcγ receptors on non-malignant cells, giving rise to systemic toxicity and potential immunogenicity (Conjugate Research Team, 2024; Beck et al., 2017) [5, 22].

Conversely, ACNPs overcome DAR constraints by encapsulating thousands of drug molecules within a single nanocarrier matrix, which is then conjugated to multiple antibodies for high-avidity multivalent binding and controlled, stimuli-responsive payload release (Yang et al., 2025; Nanoparticle Delivery Authors, 2023) [1, 4]. Despite these clear theoretical advantages, a significant clinical gap remains: no ACNP formulation has secured FDA approval to date, with the majority stalled in Phase I/II trials (Nanoparticle Delivery Authors, 2023; Targeted Delivery Group, 2024) [4, 2]. A core translational bottleneck is the absence of standardized, highly predictive 3D in vitro tumor models (Targeted Delivery Group, 2024) [2]. Preclinical success in fast-

growing rodent models regularly fails to replicate in clinical human settings due to structural differences in human tumor vascular permeability and the EPR effect (Dan et al., 2020) [18]. Additionally, ACNPs present manufacturing hurdles regarding batch consistency, scalability, and uncertain long-term organ toxicity associated with non-biodegradable synthetic carrier cores (Nanoparticle Delivery Authors, 2023) [4].

B. Conventional mAbs vs. Antibody Fragments vs. Nanobodies: Size, Stability, and Pharmacokinetic Trade-offs

Comparing conventional antibodies, engineered fragments, and camelid single-domain nanobodies reveals critical trade-offs between deep tissue penetration, physical stability, and systemic persistence:

- Size and Penetration vs. Stability:** Standard monoclonal antibodies exhibit high target affinity, but their large structural footprint (~150 kDa) restricts deep extravasation into dense tumor masses (Yang et al., 2025; Davis et al., 2020) [1, 9]. Miniaturized constructs like single-chain variable fragments (scFvs, ~25 kDa) improve tissue penetration, yet introduce severe structural drawbacks. Lacking stabilizing constant domains, scFvs suffer from variable domain (V_H-V_L) swapping; this hydrophobic surface exposure induces self-aggregation and rapid loss of functionality (Conjugate Research Team, 2024; Muyldermans, 2013) [5, 23].
- The Nanobody Advantage and Pharmacokinetic Limitations:** Nanobodies elegantly resolve the stability-penetration dilemma. At roughly ~15 kDa, they offer exceptional penetration into dense solid tumors and across the blood-brain barrier (Yang et al., 2025; Jovčevska & Muyldermans, 2020) [1, 24]. Their extended CDR3 loops allow access to hidden conformational epitopes inaccessible to bulkier IgG antibodies, while maintaining high structural resilience under extreme thermal and chemical conditions (Yang et al., 2025) [1]. However, their ultra-small size introduces a major pharmacokinetic limitation: rapid renal excretion. Falling below the glomerular filtration threshold (~40–50 kDa), nanobodies exhibit an extremely short serum half-life (Yang et al., 2025; Targeted Delivery Group, 2024) [1, 2]. Extending their circulation time requires half-life extension strategies—such as PEGylation, Fc-fusion, or human serum albumin (HSA) binding (Yang et al., 2025) [1]. Yet, these modifications introduce secondary issues: PEGylation can cause steric masking of the antigen-binding site alongside anti-PEG immune responses, whereas Fc-fusion reintroduces the manufacturing complexity of conventional monoclonal antibodies (Yang et al., 2025; Conjugate Research Team, 2024) [1, 5]. Lastly, while nanobodies share high sequence homology with human V_H domains, their camelid origin poses potential immunogenicity risks, requiring systematic humanization (such as CDR grafting) prior to clinical evaluation (Yang et al., 2025) [1].

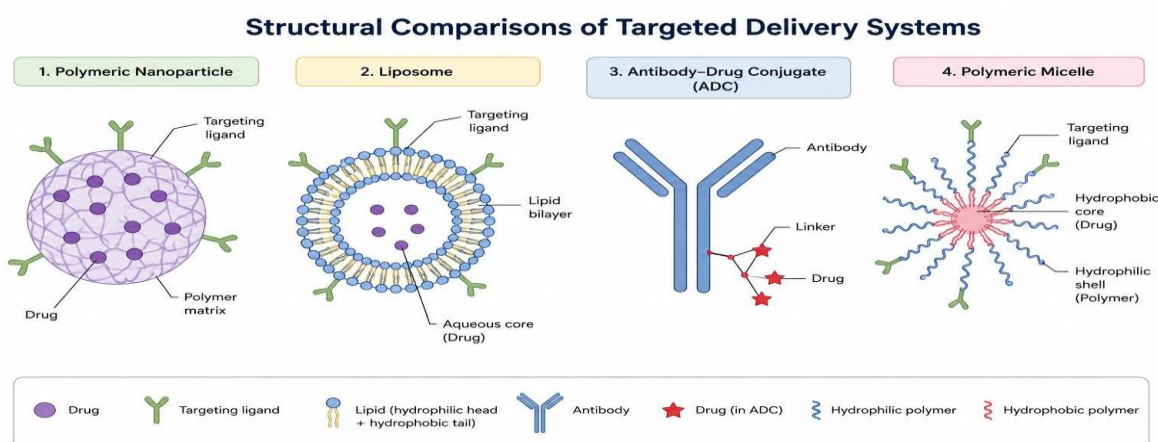


Figure 2: Structural Comparisons of Targeted Delivery systems

C. The Evolution of Linker Chemistry: Stability vs. Release and Conjugation Precision

Chemical linker engineering presents a delicate design conflict: linkers must remain completely intact during blood circulation to prevent premature drug toxicity, yet cleave rapidly once internalized into target tumor cells (Conjugate Research Team, 2024; Targeted Delivery Group, 2024) [5, 2].

- **Cleavable vs. Non-Cleavable Linkers:** Cleavable linkers (e.g., acid-labile hydrazone, cathepsin B-cleavable dipeptide, or glutathione-sensitive disulfide bonds) trigger rapid intracellular release. They also enable a valuable bystander killing effect, wherein uncharged released drugs diffuse into neighboring antigen-negative tumor cells to overcome tumor heterogeneity (Conjugate Research Team, 2024; Targeted Delivery Group, 2024) [5, 2]. However, cleavable linkers display lower systemic stability, elevating the risk of off-target toxicity (Conjugate Research Team, 2024) [5]. Conversely, non-cleavable linkers (e.g., thioether bonds) exhibit superior systemic stability, but require complete lysosomal degradation of the underlying antibody

framework, making therapeutic efficacy strictly dependent on target cell internal degradation pathways (Conjugate Research Team, 2024; Targeted Delivery Group, 2024) [5, 2].

- **Conjugation Specificity and Heterogeneity:** Traditional conjugation techniques relied on non-specific reactions with surface lysine residues or reduced interchain cysteines, producing highly heterogeneous mixtures with variable DAR profiles (Conjugate Research Team, 2024) [5]. A low DAR reduces overall cytotoxic potency, while an excessively high DAR leads to rapid hepatic clearance, hydrophobic aggregation, and heightened toxicity (Targeted Delivery Group, 2024; Conjugate Research Team, 2024) [2, 5]. To overcome this heterogeneity, recent developments mandate site-specific conjugation strategies—such as bioorthogonal click chemistry, engineered cysteine insertion (THIOMABs), or unnatural amino acid incorporation—to enforce uniform DAR, maintain structural stability, and guarantee batch-to-batch reproducibility (Conjugate Research Team, 2024; Targeted Delivery Group, 2024) [5, 2].

Evaluation parameters	Conventional mAbs	Antibody-Conjugated Nanoparticles (ACNPs)	Antibody-Drug Conjugates (ADCs)	Nanobodies
Molecular weight	~150 kDa	>100 nm	~150-155 kDa	~15 kDa
Primary Targeting mechanisms	Receptor blockade ADCC/CDC	Multivalent targeting & stimuli-responsive release	Receptor-mediated cell entry & drug release	Deep epitope access & cavity binding
Payload Capacity	None (Therapeutic mAb itself)	High to Ultra-High (>1,000-10,000 molecules)	Low to Moderate (DAR: 2 to 8)	None or Low (unless conjugated)
Solid tumor Penetration	Restricted (Slow & outer-margin only)	Limited (Governed by NP size & EPR effect)	Poor to Moderate (Restricted by mAb size)	Exceptional (Rapid deep tumor diffusion)
Blood Brain Barrier (BBB) Penetration	Minimal/Negligible	Extremely Low (Unless surface-modified)	Minimal	High (Traverses Intact BBB)

Pharmacokinetics Half-life	Long (Days to weeks: FcRn recycling)	Tunable (Hours to days; depends on coating)	Long (Days; dependent on linker stability)	Ultra short (~1-2 hours)
Clinical Translation Status	High (>100 FDA approvals)	Early Stage (Phase I/II clinical trials)	Established (14 FDA Approvals)	Emerging (FDA/EMA Approved formats)

Table 1: Comparative Profile of Conventional mAbs, Antibody-Drug Conjugates (ADCs), Antibody-Conjugated Nanoparticles (ACNPs), and Nanobodies

CONCLUSION

A. The Paradigm Shift in Oncology

The convergence of nanotechnology and modern antibody engineering represents a transformative paradigm shift in precision oncology (Yang et al., 2025; Nanoparticle Delivery Authors, 2023). By integrating principles from materials science, biophysics, and translational oncology, contemporary drug delivery platforms overcome critical pharmacological barriers that historically restricted traditional targeted therapies (Targeted Delivery Group, 2024; Smith et al., 2022). Nanoscale vehicles and bioconjugates—ranging from clinically established Antibody-Drug Conjugates (ADCs) to emerging Antibody-Conjugated Nanoparticles (ACNPs)—enable precise control over drug distribution, plasma stability, and clearance pathways without losing antigen-binding affinity (Conjugate Research Team, 2024; Chau et al., 2019). By actively binding malignant cell receptors or passively accumulating within leaky tumor blood vessels, these platforms expand the therapeutic window, maximizing cytotoxic activity inside the tumor microenvironment while sparing healthy organs from severe, dose-limiting toxicities (Patel & Kumar, 2022; White et al., 2021).

B. The Strategic Value of Nanobodies

Within this evolving framework, camelid-derived single-domain nanobodies have established themselves as highly versatile biotherapeutic tools (Yang et al., 2025; Jovčevska & Muyldermans, 2020). Possessing a compact structural framework (~15 kDa), high thermal resilience, and extended CDR3 binding loops, nanobodies overcome the tissue penetration limits that restrict conventional 150 kDa

monoclonal antibodies (Yang et al., 2025; Muyldermans, 2013). They function effectively as pathway-blocking antagonists, immune agonists, and targeted carriers for chemotherapeutic payloads, radioisotopes, and diagnostic imaging reagents (Yang et al., 2025; Vaneycken et al., 2011). Furthermore, their modular design facilitates the construction of multivalent constructs and next-generation CAR-T cell receptors, offering a strategic approach to bypass target antigen loss and acquired drug resistance (Yang et al., 2025; De Munter et al., 2018).

C. Future Directions and Call to Action

To successfully translate these laboratory innovations into standard clinical workflows, key bioengineering and regulatory hurdles must be addressed. Future translational research should focus on engineering responsive nanocarriers and bioconjugates equipped with programmable target specificity, bio-degradable matrices, and reduced immunogenic risk profiles (Targeted Delivery Group, 2024; Mitchell et al., 2021). Furthermore, bridging the preclinical-to-clinical gap requires moving away from traditional animal models toward standardized 3D organoid cultures and microfluidic tumor-on-a-chip platforms that accurately reflect human vascular permeability and receptor dynamics (Dan et al., 2020; Hrkach et al., 2012). Overcoming commercial chemistry, manufacturing, and controls (CMC) challenges will also be essential to ensure batch reproducibility and cost-effective scaling (Conjugate Research Team, 2024). Ultimately, ongoing interdisciplinary collaboration among structural biologists, nanotechnologists, and clinical oncologists remains essential to bring these next-generation therapeutics into routine clinical practice (Yang et al., 2025; Targeted Delivery Group, 2024).

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HOW TO CITE: Aher Akanksha Dyaneshwar, Barate Arjun Anil, Bhagre Nilesh Dhanraj, Bhor Bhagyashri Dhanaji, Bole Abhinav Dilip, Jadhav Vishwas Viju*, *Advances In Nanocarries And Antibody-Based Delivery Platforms For Precision Oncology*, *Int. J. Sci. R. Tech.*, 2026, 3 (10), 431-439. <https://doi.org/10.5281/zenodo.23210502>