Antibody Nanocarriers for Cancer Management

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Abstract

Antibodies are extremely valuable tools in modern medicine due to their ability to target diseased cells through selective antigen binding and thereby regulate cellular signaling or inhibit cell-cell interactions with high specificity. However, the therapeutic utility of freely delivered antibodies is limited by high production costs, low efficacy, dose-limiting toxicities, and inability to cross the cellular membrane (which hinders antibodies against intracellular targets). To overcome these limitations, researchers have begun to develop nanocarriers that can improve antibodies' delivery efficiency, safety profile, and clinical potential. This review summarizes recent advances in the design and implementation of nanocarriers for extracellular or intracellular antibody delivery, emphasizing important design considerations, and points to future directions for the field.

Keywords
targeted antibodies; binding affinity; multivalency; nanoparticles; signal cascade interference

Abbreviations
mAb (monoclonal antibody), Food and Drug Administration (FDA), antigen-binding fragment (Fab), nanoparticle (NP), C-X-C chemokine receptor type 4 (CXCR4), EDC/NHS (1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide/N-hydroxysulfosuccinimide), breast cancer (BC), stromal cell-derived factor 1 (SDF1), lipocalin-2 (Lcn2), intercellular adhesion molecule 1 (ICAM1), epidermal growth factor receptor (EGFR), dual-complementary liposomes (DCLs), nanoshell (NS), human epidermal growth factor receptor 2 (HER2), poly(ethylene glycol) (PEG), Frizzled7 (FZD7), triple-negative breast cancer (TNBC), effective dissociation constant (K_D), poly(lactic-co-glycolic acid) (PLGA), poly-L-lysine (PLL), poly-L-arginine (PLA), polyethylenimine (PEI), B-cell lymphoma-2 (Bcl-2), B-cell lymphoma-xL (Bcl-xL), octaarginine (R8), nuclear pore complex (NPC), fragment crystallizable (Fc)

1. Introduction

Antibodies that can target diseased cells through selective antigen binding and thereby regulate cellular signaling or inhibit cell-cell interactions with high specificity are extremely valuable tools in modern medicine. The monoclonal antibody (mAb) market has grown rapidly in the past decade, with an anticipated value in the US of $137-$200 billion by 2022 [1]. Over 120 mAbs have been approved by the Food and Drug Administration (FDA) for treatment of diseases including cancer, autoimmune disorders, and most recently, coronavirus (**Figure 1A, Supplemental Table 1**) [2]. Further, over 2000 mAbs and biosimilars are in preclinical or clinical development, indicating a bright future for antibody therapeutics [3].

An antibody's antigen specificity is defined by the variable domains of the antigen-binding fragment (Fab) within its structure (**Figure 1B**). While polyclonal antibodies bind multiple epitopes on a targeted antigen, mAbs bind a precise epitope, which affords greater specificity, affinity, and biologic effects. However, mAbs are expensive to produce and limited by low efficacy due to poor tissue penetration and inability to cross the cellular membrane [4,5]. To maximize the advantages antibodies provide, technologies such as antibody-drug conjugates are being developed [6] and other methods to enhance mAb stability, delivery, and efficacy are being explored [7].

Nanoparticles (NPs, naturally derived or engineered structures less than ~200 nm in diameter) have emerged as promising therapeutic carriers because they can improve cargo stability, pharmacokinetics, and delivery into diseased tissues [8]. Nanocarriers can be synthesized from diverse materials, including lipids [9–12], polymers [13,14], and metals [15–18], for desirable properties (size, charge, shape, and surface functionality) [8]. While most nanocarrier research has focused on delivery of small molecule drugs or nucleic acids, recent studies investigate large protein and antibody nanocarriers [19,20]. Compared to freely delivered antibodies, antibody-NP conjugates have improved efficacy and reduced toxicity owing to the carriers' ability to protect their cargo *in vivo*, provide multivalent binding effects, and more [8,21]. This review highlights recent work that demonstrates the benefits of antibody nanocarriers for disease management, with an emphasis on oncology applications and a focus on therapeutic antibody use (e.g., to enable signaling inhibition). Antibody nanocarriers for immunoengineering are not discussed, as other reviews on this topic are available [22–24]. The following sections describe advances in extracellular and intracellular antibody delivery, respectively, as well as future directions for the field.

2. Antibody Nanocarriers to Block Extracellular Ligand/Receptor Interactions

2.1. Overview of Nanocarriers for Extracellular Antibody Delivery

Antagonistic antibodies typically mediate biological effects by binding to target receptors on the exterior of a diseased cell, locking them in a ligand-unresponsive state. This blockade of ligand/receptor interactions inhibits downstream cell signaling to alter cellular function [25]. Antibody nanocarriers have proven more effective than freely delivered antibodies because they

can engage multiple receptors simultaneously, resulting in enhanced binding avidity and signaling inhibition [17,26] (**Figure 2**). Besides targeting cell receptors, antibodies and antibody-NP conjugates can also block cell/cell interactions or bind extracellular ligands and sequester them from cellular interactions [25]. This section highlights *in vitro* and *in vivo* studies that demonstrate the immense potential of nanocarriers for extracellular antibody delivery.

2.2. Liposomal Antibody Carriers

Liposomes were among the first class of antibody nanocarriers developed. Liposomes are self-assembled from phospholipids that provide two polar environments: a hydrophilic center and a hydrophobic membrane [27]. Due to their physical composition, liposomes can impart controlled drug release, protect cargos from degradation, and increase pharmacokinetics, circulation, and passive targeting. Hence, they have the most FDA approved and investigational formations [28].

Liposomes functionalized with antibodies, known as "immunoliposomes," exhibit increased cellular specificity and uptake versus unmodified liposomes [29]. Antibodies are added to liposomes primarily by covalent linkages or at times with noncovalent coupling [30]. The use of immunoliposomes to inhibit extracellular ligand/receptor interactions was first reported in 2014 [10]. Guo *et al.* coated liposomes with mouse anti-human C-X-C chemokine receptor type 4 (CXCR4) mAbs *via* EDC/NHS (1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide/N-hydroxysulfosuccinimide) chemistry for NP binding to CXCR4 receptors on metastatic breast cancer (BC) cells *in vitro*; the goal was to block ligand stromal cell-derived factor 1 (SDF1) interaction with CXCR4 to suppress cell migration. The team hypothesized that co-delivery of lipocalin-2 (Lcn2) siRNA could provide synergistic effects, as Lcn2 knockdown decreases BC cell migration and invasion [31]. Transwell migration assays revealed that MDA-MB-436 and MDA-MB-231 cells treated with anti-CXCR4 immunoliposomes exhibited 16-18% reductions in migration compared with untreated cells, and co-delivery of Lnc2 siRNA increased this reduction to an impressive 88%-92% [10]. This demonstrates the potential of antibody nanocarriers to regulate cell behavior through extracellular blockade of ligand/receptor interactions. One limitation of targeting CXCR4, however, is risk of non-specific binding to other CXCR4-expressing cells, including leukocytes, endothelial cells, hematopoietic stem cells, and others [10].

In related work, Auguste and colleagues developed immunoliposomes coated with antibodies targeting two receptors–intercellular adhesion molecule 1 (ICAM1) and epidermal growth factor receptor (EGFR)– to mediate cell binding, internalization, and signaling inhibition (**Figure 3**) [11]. This design offered dual complementarity, and the antibody loading was proportional to the targeted cell's receptor density. The ratio proved impactful in regulating cell binding and internalization *in vitro*, and affected delivery to tumors *in vivo* in spontaneous and experimental metastasis models [11]. The dual-complementary liposomes (DCLs) also cooperatively blocked the ICAM1 and EGFR signaling cascades, inhibiting MDA-MB-231 and MDA-MB-436 proliferation by 30-40%, and reducing invasion by 64% and 46% versus phosphate buffered saline controls [11]. Overall, this study showed that dual antibody delivery is advantageous and demonstrated that matching antibody loading on nanocarriers to cell surface receptor density is an important design parameter.

2.3. Gold Nanoshell Antibody Conjugates

As an alternative to lipid-based nanocarriers, NPs made from inorganic materials including gold [32–34], iron oxide [35,36], carbon [37,38], and more [39] have been developed for biosensing, diagnostic, and therapeutic purposes. Regarding antibody delivery, silica core/gold shell nanoshells (NS) are among the most widely explored inorganic carriers. Because they can efficiently absorb near-infrared light, NS have historically been used to mediate photothermal therapy [40], along with imaging and diagnostic purposes [41]. Antibody-NS conjugates were first developed in the mid-2000s, where two separate papers demonstrated targeting of anti-human epidermal growth factor receptor 2 (HER-2) antibody coated NS to HER-2-expressing SK-BR-3 BC cells *in vitro* [42,43]. Initially, the antibodies strictly imparted cell-selective binding, but more recent studies show that antibody-NS conjugates can enable signal cascade interference. Antibodies can be tethered to the surface of NS (or any gold-coated NP) by hydrophobic interactions, ionic interactions, or covalent interactions through dative binding of a linker [44]. Most often, antibodies are adsorbed to gold-based NPs using heterobifunctional poly(ethylene glycol) (PEG) linkers that contain a sulfur group at one end, as gold-sulfur bonds are notably strong [45].

In 2017, NS coated with antibodies against Frizzled7 (FZD7, a receptor involved in Wnt signaling that is overexpressed on triple-negative breast cancer, TNBC, cells) were demonstrated to be more effective than freely delivered antibodies as they could outcompete freely delivered Wnt3a ligands for targeted FZD7 receptors *in vitro* [17]. Studies performed to calculate the effective dissociation constant (K_D) of FZD7-NS and free FZD7 antibodies to MDA-MB-231 cells revealed FZD7-NS have ~30X greater binding strength for these cells than freely delivered antibodies, which is attributed to multivalent binding effects [17]. To correlate this increased binding avidity with signaling inhibition capacity, the team co-treated MDA-MB-231 cells with Wnt3a ligands and either FZD7-NS or free FZD7 antibodies and observed that FZD7-NS significantly reduced the mRNA and protein expression of downstream Wnt targets, while control NS and free FZD7 antibodies administered at a ~50X higher dose did not have this effect [17]. These findings indicate valency plays a critical role in binding avidity and signal cascade interference.

While the above study indicates FZD7-NS are effective alone, subsequent *in vitro* work demonstrates FZD7-NS are also impactful in combination regimens [18]. When FZD7-NS and the autophagy regulator chloroquine were applied to TNBC cells together, they reduced the expression of several stemness genes and inhibited cell migration and self-renewal [18]. Notably, this study loaded FZD7 antibodies on NS with 5 kDa rather than 2 kDa PEG linkers as reported previously [17]. This amplified antibody loading yet yielded a similar K_D of $6x10^{-10}$ M [17,18]. Future studies should further investigate the relationship between PEG length, antibody loading, and cell binding strength to advance the field. Future work should also investigate whether antibody orientation impacts binding avidity and efficacy. The above papers used non-directional conjugation methods, but linkers such as hydrazide-PEG-dithiol can provide directional antibody orientation to increase accessibility and binding to corresponding receptors [46]. While great progress has been made in the use of inorganic NPs as antibody carriers, more knowledge remains to be acquired to advance the start of the art. For example, beyond improving understanding of how linker length, antibody loading, and antibody orientation impact the efficacy of inorganic antibody nanocarriers, researchers must also study parameters such as

antibody:receptor ratios, NP radius of curvature, and NP shape, as these are likely to impact cell binding and efficacy. Transitioning to *in vivo* studies will also be critical to confirm the promise identified in preclinical *in vitro* studies and to understand the biodistribution, tumor penetration, and therapeutic success of inorganic antibody nanocarriers.

2.4. Poly(lactic-co-glycolic acid) (PLGA) Nanoparticles

Polymer nanocarriers were first developed for drug and nucleic acid delivery in the 1980s, [47–49] and the number of FDA-approved and preclinical formulations has grown substantially ever since. Some of the most common polymers used include PLGA, PEG, poly-L-lysine (PLL), poly-L-arginine (PLA), and polyethylenimine (PEI). Of these, PLGA is particularly popular because of its dual polarity, biocompatibility, and biodegradability into byproducts that are readily metabolized within the body [50]. In general, polymer nanocarriers can be easily surface modified using carbodiimide, maleimide, and click chemistries [51].

Two recent publications exhibit the utility of PLGA nanocarriers for antibody delivery [13,52]. In both, anti-Notch1 antibodies were conjugated to PLGA NPs using EDC/NHS chemistry [13,52]. These antibodies bind to Notch1 receptors overexpressed on TNBC cells to suppress downstream Notch signaling by blocking receptor interactions with Jagged/Delta ligands on neighboring cells [13,52]. In the first study, Notch1-targeted PLGA NPs were loaded with the B-cell lymphoma-2 (Bcl-2)/B-cell lymphoma-xL (Bcl-xL) inhibitor ABT-737 [13]. This system exhibited enhanced binding to MDA-MB-231 TNBC cells versus MCF-10A breast epithelial cells. *In vitro,* Notch1-ABT-NPs decreased the relative metabolic activity of MDA-MB-231 cells to a greater extent than freely delivered antibodies and drugs, indicating nanocarrier advantage. This system also reduced TNBC tumor size and extended animal survival when compared to ABT-NPs functionalized with control IgG antibodies *in vivo* [13]. Following this, Notch1-targeted NPs were loaded with miR-34a, a tumor suppressive nucleic acid cargo and evaluated through *in vitro* studies [52]. Although the Notch1-miR-34a-NPs could decrease TNBC cell proliferation and migration, they did not exhibit the same level of preferential and specific binding to TNBC cells as the ABT-loaded NPs, likely due to reduced antibody loading density on this formulation (4.6 compared to 9.1 μg/mg PLGA) [52]. Future studies should define the optimal particle size and antibody loading density to maximize cell binding and signaling inhibition.

3. Nanocarriers for Intracellular Antibody Delivery

3.1 Overview of Intracellular Antibody Delivery

Beyond targeting extracellular domains, there are also strategies to deliver antibodies into cells for intracellular interference. Antibodies have immense potential to target disease-promoting proteins that are “undruggable” by small molecule therapeutics, but, unfortunately, antibodies have difficulty passing through cellular and endosomal membranes, preventing their interaction with cytosolic targets [53]. Nanocarriers designed to facilitate intracellular antibody delivery can overcome these limitations (**Figure 4**) and avoid the use of more invasive delivery methods such

as membrane permeabilization, electroporation, or microinjection, which disrupt the cell's structure and can cause adverse effects [54]. In this section, nanocarrier platforms that have successfully enabled intracellular antibody transport are discussed.

3.2 Liposomes

Liposomes have shown promise not just for extracellular antibody delivery, but also for intracellular delivery. In one notable development, antibody-loaded liposomes were modified with octaarginine (R8), a cell penetrating peptide, and GALA, a pH-sensitive fusogenic peptide [55], to overcome cellular and endosomal membrane barriers to intracellular delivery. This system demonstrated reduced endosomal entrapment and preserved antibody functionality after *in vitro* delivery to HeLa cervical cancer cells. The modified liposomes successfully delivered anti-nuclear pore complex (NPC) antibodies into the cells, which localized to the nucleus, indicating the antibodies escaped the nanocarrier and maintained their functional integrity.

In a related approach, liposomes were used to deliver anti-S100A4 antibodies and doxorubicin into 4T1 murine TNBC cells [56]. These liposomes are activated by the acidic tumor microenvironment and deliver their cargo into cells in a fusion-dependent manner as opposed to relying on endocytic escape. The fusogenic liposomes were synthesized from 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-Arg-Arg-Arg-Arg and 3-phosphoethanolamine-N-benzaldhyde-[methoxy(PEG)-2000] such that in an acidic environment, the PEG chains detach and the four arginines can fuse with the tumor cell membrane. *In vitro* studies indicated intracellular delivery of the antibodies and drug within 30 seconds of liposome fusion. Further *in vitro* and *in vivo* studies showed a synergistic effect from the dual delivery of doxorubicin and antibodies against S100A4, a protein involved in TNBC metastasis. This and other liposomal formulations are promising tools for intracellular antibody delivery but suffer from low loading capacities that may limit efficacy.

3.3 Protein Nanocarriers

Recently, a protein nanocarrier with extremely high antibody loading:nanocarrier material ratio was reported [57–59], which may overcome the shortcomings of other nanocarriers as increasing the ratio of antibodies to carrier material should maximize efficacy and minimize side effects. This Hex protein nanocarrier uses protein-protein interactions to self-assemble into a hexameric barrel that displays sites with affinity for the fragment crystallizable (Fc) domain of an antibody [57]. This structure theoretically loads six antibodies per hexamer. Detailed *in vitro* studies show the Hex nanocarriers are primarily trafficked through clathrin-mediated endocytosis and can escape endosomes to deliver antibodies to the cytosol. Critically, the antibodies maintain their functionality upon delivery [58]. Further work with this nanocarrier has shown the stoichiometry of the assembled Hex-antibody complexes can be adjusted based on incubation temperature and time, which can better control assembly for future applications [59]. Given this system's high ratio of antibody cargo to carrier material, future development of similar protein nanocarriers could be expected to offer high efficacy and minimal toxicity when tested in animal models.

3.4 Polymer Nanoassemblies

A third platform for intracellular antibody delivery is polymer nanoassemblies, which are formed from self-immolative polymers that contain activated carbonate moieties that support covalent self-assembly upon interaction with lysine residues on antibodies [60]. Dutta *et al.* evaluated a library of random copolymers with six potential activated carbonate candidates and chose pentafluorophenyl-carbonate as the best candidate based on its relatively high antibody conjugation efficiency [60]. *In vitro*, the nanoassemblies effectively delivered antibodies into the cytosol and preserved antibody function in HeLa cervical cancer cells and MCF7 BC cells. Anti-NPC antibodies localized to nuclear membranes in HeLa cells, while anti-phosphoAkt (pAkt) antibodies increased caspase 3/7 levels and reduced cell viability in MCF7 cells, indicating pAkt signaling inhibition. The nanoassemblies modulated pAkt signaling more effectively than native antibodies, demonstrating the benefit of the nanoassembly design [60]. In the future, polymer nanoassemblies like this could be promising delivery vehicles owing to their ability to encapsulate large antibodies, protect them, and ensure their intracellular release.

4. Conclusions

To date, antibodies have shown great promise for cancer treatment, and the number of FDA-approved mAbs is rapidly growing. Antibody nanocarriers can enhance these targeted therapies by improving delivery efficiency and therapeutic efficacy. This review has highlighted recent progress in the development of liposomal, polymeric, protein, and gold-based NPs as tools for extracellular and intracellular antibody delivery**. Table 1** summarizes the advantages and disadvantages of each carrier type, as well as unique design criteria that are relevant for NP-mediated extracellular and intracellular delivery.

While much knowledge has been gained from recent work, more fundamental studies are necessary to enable antibody nanocarriers to reach their full potential. For example, literature shows several design parameters are important for antibody nanocarriers, including antibody:receptor ratios [11], linker length [18], loading density [52], and methods of cell entry and cargo release [56,61]. In further developing antibody nanocarriers, researchers must report antibody loading for their system and continue to evaluate the influence of loading density and antibody orientation on target binding affinity, efficacy, and safety. Additionally, researchers should report the dose required to elicit the desired therapeutic response, which may vary based on the specific characteristics of the NP and the antibody cargo. In transitioning to *in vivo* studies, other factors to consider are the protein corona's impact on NP delivery and the limitations of tissue penetration, as antibody-NPs may engage target cells near vessels after extravasation, limiting the distance they travel into diseased tissues [62,63]. When examining the efficacy, pharmacokinetics, and safety of antibody nanocarriers *in vivo,* researchers must include comparison to freely delivered antibodies to validate the benefits of the nanocarrier design. NP clearance must also be studied in detail since different nanocarriers will exhibit distinct biodistribution patterns. While most NPs (independent of material) are cleared *via* the liver and spleen, inorganic NPs such as those made from gold are not biodegradable like their polymeric or liposomal counterparts and will thus remain in the body for extended periods of time [64]. While

gold NS have shown excellent biocompatibility in human clinical trials [65,66], safety remains to be confirmed for other inorganic nanocarriers and for antibody-coated NS.

In conclusion, antibody nanocarriers have great potential as targeted, high precision therapeutics. As researchers fill existing knowledge gaps through new experimentation, the field will advance to develop more effective antibody nanocarriers for disease management.

Author Contributions

Emily Day: conceptualization, funding acquisition, supervision, writing-review and editing; Megan Dang: conceptualization, investigation, writing-original draft, writing-review and editing; Elise Hoover: conceptualization, investigation, writing-original draft, writing-review and editing; Mackenzie Scully: visualization, writing-review and editing; Eric Sterin: visualization, investigation

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Conflict of Interest Statement

Nothing to declare.

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Figures and Figure Legends

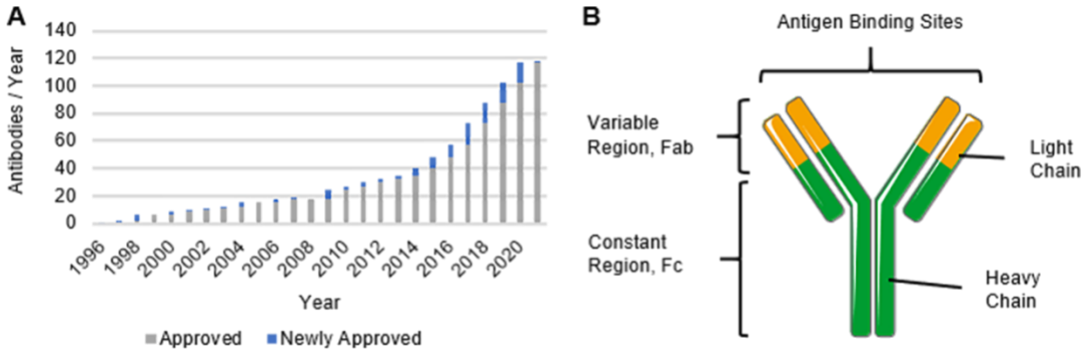

Figure 1. Overview of antibody therapeutics. (A) FDA approved antibodies per year. The number of antibody therapeutics approved yearly has grown at almost an exponential rate over the last two decades. (B) Antibody structure. Antibodies contain unique structural components, including the Fab region that defines antigen-specific binding. Portions of this figure were produced using Servier Medical Art templates (https://smart.servier.com). Servier Medical Art by Servier is licensed under a Creative Commons Attribution 4.0 Unported License.

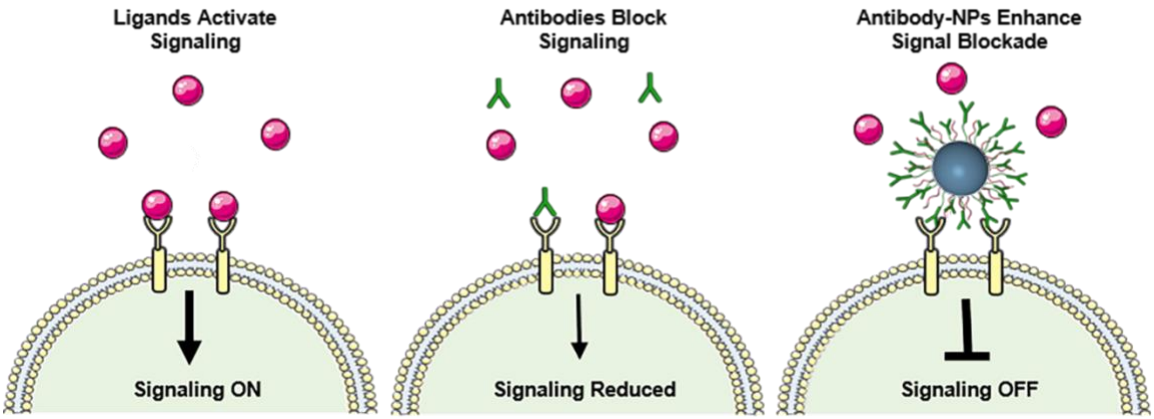

Figure 2. Comparison of antibody nanocarriers and freely delivered antibodies for extracellular receptor targeting and ligand blockade. *(Left)* When extracellular ligands bind receptors that are overexpressed on diseased cells, intracellular signaling cascades that promote disease progression are activated. *(Center)* When freely delivered antibodies compete with the ligands for receptor binding sites, intracellular signaling is reduced. *(Right)* Antibody nanocarriers can engage multiple receptors simultaneously, and this multivalent binding leads to increased binding strength and greater signaling inhibition than is achieved by freely delivered antibodies. Portions of this figure were produced using Servier Medical Art templates (https://smart.servier.com). Servier Medical Art by Servier is licensed under a Creative Commons Attribution 4.0 Unported License.

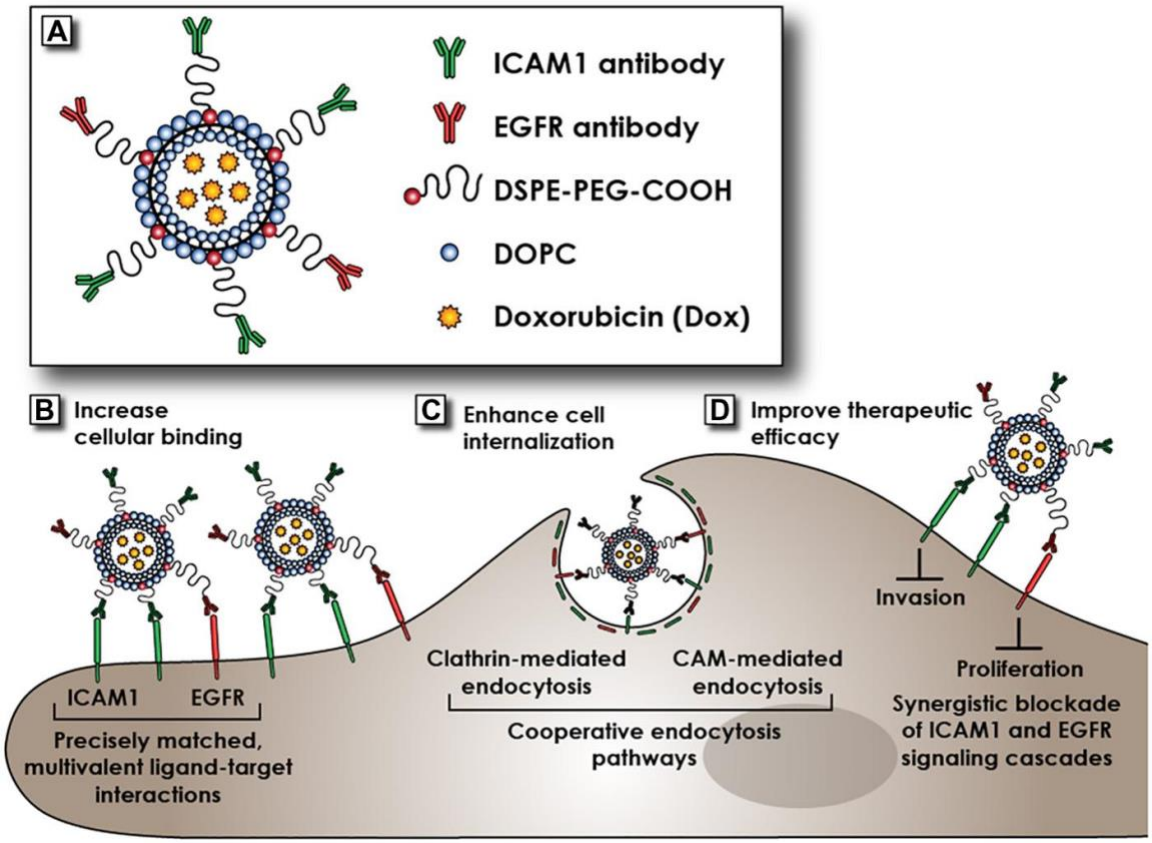

Figure 3. Schematic illustration of dual complementary liposome (DCL) structure and mechanisms of action. (A) Scheme showing the structure of a DCL. (B) DCLs exhibit enhanced cellular binding owing to precisely matched, multivalent ligand-receptor interactions. (C) DCL internalization is enhanced through the cooperative ICAM1 and EGFR endocytosis pathways. (D) DCLs synergistically block the ICAM1 and EGFR signaling cascades to improve therapeutic efficacy. This figure is reproduced with permission from "Dual complementary liposomes inhibit triple-negative breast tumor progression and metastasis" by Guo P, *et al.* (DOI: 10.1126/sciadv.aav5010). The original article published in Science Advances (https://advances.sciencemag.org/) is licensed under a Creative Commons Attribution 4.0 Unported License.

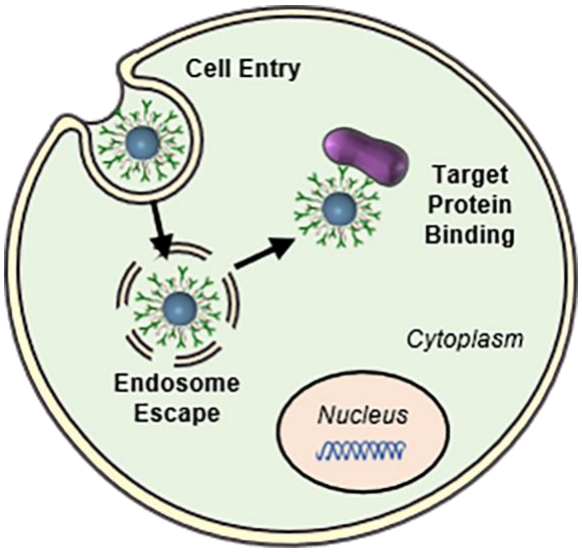

Figure 4. Intracellular delivery of antibodies via nanocarriers. Antibody nanocarriers have been designed to overcome the cellular and endosomal membrane barriers to allow therapeutic antibodies to bind and inhibit targeted proteins intracellularly. Portions of this figure were made using Servier Medical Art templates (https://smart.servier.com). Servier Medical Art by Servier is licensed under a Creative Commons Attribution 4.0 Unported License.

	Nanocarrier type	Advantages	Disadvantages	Unique design criteria
Extracellular Delivery	Liposomes	• Easily modified • pH-sensitive release • Biocompatible & biodegradable	• High production costs • Short half-life • Potential leakage of encapsulated cargo	• Antibodies must be accessible to receptors at cell surface • Antibody:receptor ratio is important to maximize effect • Antibody release from NP may not be required to elicit signaling inhibition *via* ligand blockade
	Gold nanoshells	• Bioinert • Ease of bioconjugation • Intrinsic phototherapeutic and imaging capabilities • High monodispersity & reproducibility	• Antibodies must be loaded on NP exterior • Lack biodegradability; slow/limited clearance from the body	
	PLGA	• Biocompatible & biodegradable • Can co-deliver hydrophobic or hydrophilic molecules depending on synthesis parameters	• Prone to aggregation • More polydisperse & less uniform than other carrier systems	
Intracellular Delivery	Liposomes	• Easily modified • pH-sensitive release • Biocompatible & biodegradable	• High production costs • Short half-life • Potential leakage of encapsulated cargo	• Must be internalized by cells and trafficked to desired intracellular compartment • Antibodies delivered intracellularly must maintain function after release from nanocarrier
	Protein nanocarriers	• High ratio of antibody cargo to carrier material • Extremely customizable	• Small-scale production • Potential immunogenicity	
	Polymer nanoassemblies	• Easily modified with high precision • Controllable release profile	• Can have toxic degradation byproducts • Some formulations prone to aggregation	

Table 1. Advantages and disadvantages of various antibody nanocarriers, along with unique design criteria to consider for extracellular versus intracellular antibody delivery.