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Review article

Control of biomedical nanoparticle distribution and drug release in vivo by complex particle design strategies

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ABSTRACT

The utilization of targeted nanoparticles as a selective drug delivery system is a powerful tool to increase the amount of active substance reaching the target site. This can increase therapeutic efficacy while reducing adverse drug effects. However, nanoparticles face several challenges: upon injection, the immediate adhesion of plasma proteins may mask targeting ligands, thereby diminishing the target cell selectivity. In addition, opsonization can lead to premature clearance and the widespread presence of receptors or enzymes limits the accuracy of target cell recognition. Nanoparticles may also suffer from endosomal entrapment, and controlled drug release can be hindered by premature burst release or insufficient particle retention at the target site. Various strategies have been developed to address these adverse events, such as the implementation of switchable particle properties, regulating the composition of the formed protein corona, or using click-chemistry based targeting approaches. This has resulted in increasingly complex particle designs, raising the question of whether this development actually improves the therapeutic efficacy in vivo. This review provides an overview of the challenges in targeted drug delivery and explores potential solutions described in the literature. Subsequently, appropriate strategies for the development of nanoparticular drug delivery concepts are discussed.

1. Introduction

The use of nanoparticles as drug delivery systems is a promising approach to enhance the efficacy of drugs while limiting adverse drug effects. To precisely control the distribution in vivo, the particles are designed to accumulate in the target tissue or specific target cells through interactions between targeting ligands and cell surface structures [1,2]. However, upon administration, biomedical nanoparticles for therapeutic or diagnostic applications face a variety of obstacles [3]. Depending on the route of administration, such as intramuscular (i.m.) [4], subcutaneous (s.c.) [5], intravenous (i.v.) [6], oral, [7] intravitreal [8], pulmonary [9], or nasal [10], complex biological barriers must be overcome [11]. Oral drug delivery with nanoparticles, for example, is hampered by the acidic gastric environment and the secretion of mucus that protects the gastrointestinal (GI) tract can efficiently trap and remove administered particles [12]. Another example is nanoparticle administration via inhalation, which is challenging due to biological barriers in the respiratory system, such as mucus, ciliated cells, or clearance by resident macrophages [13].

In addition, once nanoparticles enter biological media, the adsorption of proteins on their surface alters the pre-formed particle properties. As a result, not only particle distribution [14], but also toxicity [15], stability [16], clearance [17], and cargo leaching [16] can be affected, which may be a major bottleneck for therapeutic efficacy. Moreover, many target structures are located intracellularly. Since the cell membrane represents a natural barrier, preventing direct entry into the cytoplasm, particle internalization is often essential. [18,19] One challenge at this point is that the majority of nanoparticles are taken up via endocytic uptake pathways. Thus, they may suffer from endosomal entrapment and degradation by acidification and lysosomal enzyme activity. [20,21] In addition, drug release must occur between entry into the cytosol and exocytosis from the target cell. Therefore, premature drug release [22,23], as well as insufficient intracellular particle residence time might be a handicap to therapeutic efficacy. [24].

Due to this multitude of requirements to be fulfilled simultaneously, there has been a paradigm shift in the development of biomedical

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nanoparticles. While early approaches focused on tailoring physicochemical properties, so-called passive targeting, [25–27] or modifying the particle surface with a single targeting ligand to identify target cells in a key-lock principle [28,29], the objective has changed to precisely control the nanoparticles' fate. Thus, multiple factors such as protein attachment, biodistribution, nanoparticle internalization, drug release, or exocytosis are coordinated, which frequently results in highly complex particle designs. [30,31] We outline different strategies to overcome respective hurdles, such as adapting the particle size, charge, or surface, and the implementation of switchable particle characteristics, which are activated by signals such as changes in pH value, redox potential, enzymatic cleavage, ultrasonic, light, temperature, or magnetism. Moreover, we illustrate further innovative strategies, such as optimizing particle distribution and uptake by subsequent ligand attachment in biological media by click chemistry [32,33] or targeting via the specific manipulation of the formed protein corona. [34] Finally, we critically examine the possibilities and limitations of influencing the particles' fate by synthetical nanoparticle design. Since i.v. particle injection is the most common route of application for the development of nanoparticles, which additionally offers the advantage that the entire amount of administered substance reaches the systemic circulation and is not consumed by administration-route specific barriers [35], the review is focused on this route of application.

2. Critical aspects for targeted drug delivery

2.1. Protein corona assembly

Immediately upon the first contact with blood, plasma proteins adsorb to the nanoparticle surface and create altered particle properties, which change their pharmacological profile. [36–38] (Fig. 1a) The composition of the formed protein corona and thus the particles' "biological identity" strongly depends on the particle size, charge [39], and surface chemistry [40], and has a high impact on the NP fate in vivo. The protein adsorption, which affects positively charged particles to a particularly high degree [41], is associated with several challenges: the corona interferes with ligands tethered to the nanoparticle surface, hampering interactions with targeting motifs. [42,43] Furthermore, the adsorption of so-called opsonins promotes an immune response [44–46] and frequently leads to premature clearance by the MPS. [46,47] Since an adequate nanoparticle circulation time is essential to reach the target tissue [48], the prevention of fast MPS-mediated clearance is of major significance. Moreover, the protein corona changes the drug release profile of nanocarriers [49], diminishing the controllability of NP-based

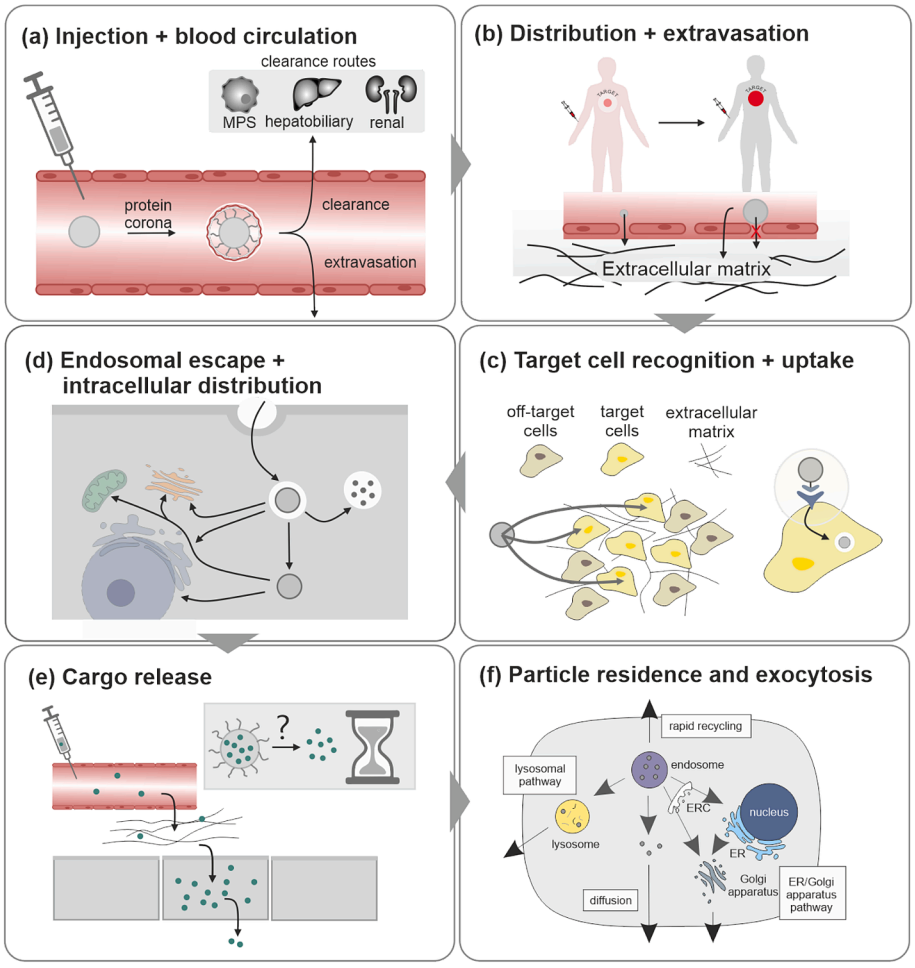


Fig. 1. Critical aspects of nanoparticle distribution and drug release from injection to elimination. (a) Immediately after i.v. injection, the particles are localized in the systemic circulation and various proteins bind to the particle surface. This results in an altered particle structure, which can strongly differ from the original design. (b) The nanoparticles are distributed throughout the body with the objective of extravasating from blood vessels at their target tissue. (c) Due to specific nanoparticle surface modifications, the drug carrier is supposed to identify its target cells and be taken up without premature clearance or accumulation in off-target tissues. (d) As NPs are mainly internalized via endocytic uptake processes, most particles are initially localized inside endosomes, from which they must escape to avoid lysosomal degradation and reach the cytoplasm or specific organelles. (e) For nanoparticles as drug delivery systems, both temporal and spatial control of the drug release are essential for therapeutic efficacy and to minimize adverse drug effects. (f) One decisive factor in this case is the particle residence time, to achieve a suitable time frame for drug release before NP exocytosis and elimination.

drug therapy.

2.2. Extravasation and target cell identification

The NPs must pass the vascular endothelial barrier to reach their target tissue. (Fig. 1b) [50] Extravasation is mainly performed in two different ways: via fenestrations between endothelial cells or transcellularly. Additionally, there are special pathways, such as extravasation via transcytoplasmic holes in glomerular endothelial cells. [51] The endothelial fenestrations are mainly below 10 nm and thus only permeable for very small particles. Larger particles need to pass the vascular endothelial barrier transcellularly through endocytotic pathways such as phagocytosis, clathrin-mediated endocytosis, and the caveolae-mediated pathway and thus partially receptor-dependent. [35] While very small particles with a size below 6 nm are rapidly excreted by renal clearance mechanism, larger particles tend to remain in circulation longer and subsequently undergo hepatobiliary elimination. [35,52] Upon extravasation, the particles are localized in the extracellular

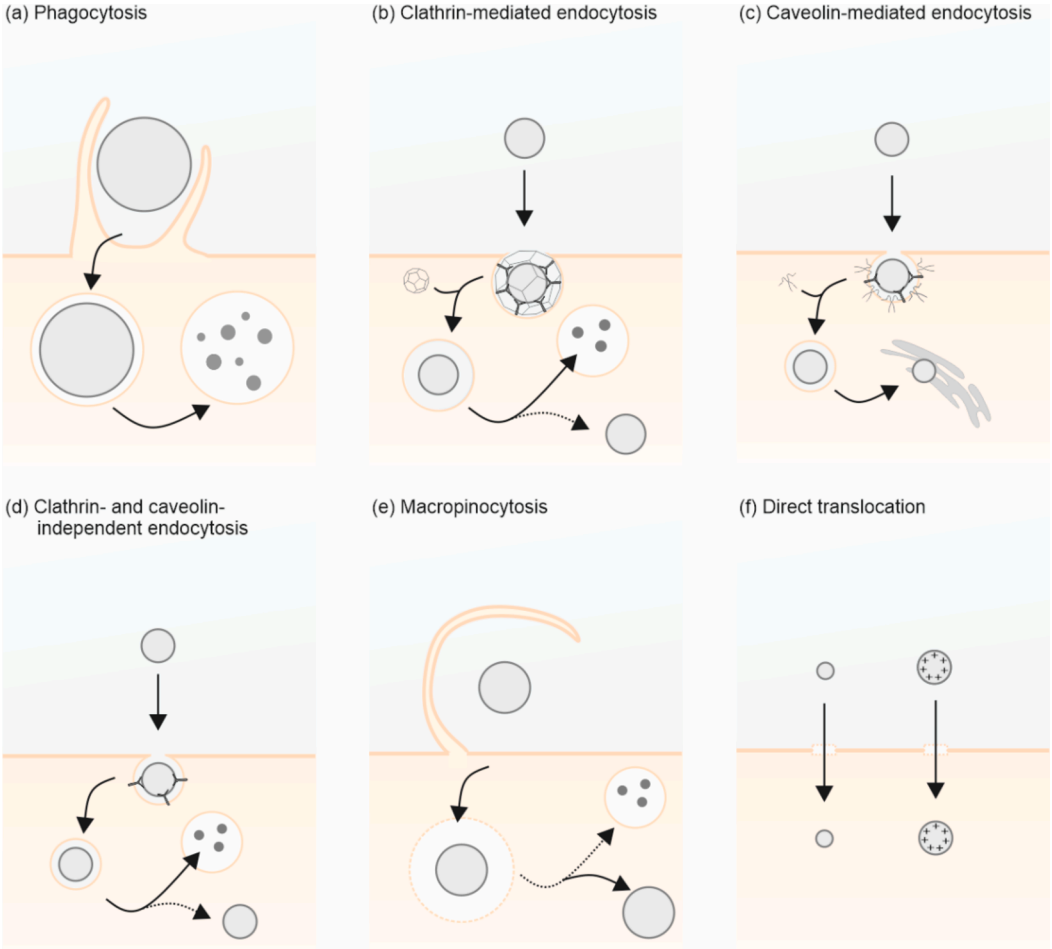


Fig. 2. Schematic overview of nanoparticle internalization pathways. (a) Phagocytosis, the ingestion of large particles through protrusions of the plasma membrane, is mainly important for immune cells such as macrophages, monocytes, neutrophils, or dendritic cells. [77,78] All non-phagocytotic but endocytotic uptake processes are summarized as pinocytosis, which is the engulfment of smaller particles. [79] (b) Clathrin-mediated endocytosis (CME) generally depends on the formation of ligand-receptor complexes [79] and is thus highly important for the internalization of actively targeted nanoparticles. [18] Among other proteins, clathrin generates and stabilizes membrane curvatures, so-called clathrin-coated pits (CCPs). These pits are then pinched off the membrane with the help of a GTPase enzyme called dynamin [80], leading to the budding of vesicles with a size from 100-500 nm into the cytosol. [54] The resulting vesicles ultimately lose their clathrin coat and fuse to early endosomes [81,82], which frequently leads to lysosomal degradation due to endosomal entrapment. [79] The occurrence of clathrin-coated pits has been demonstrated to influence nanoparticle avidity and therefore also distribution in target and off-target cells in cell culture experiments. [83,84] (c) Caveolae-mediated endocytosis is a related process, in which the protein caveolin is the decisive factor for structural stabilization and membrane budding. The flask-shaped plasma membrane invaginations are 50–80 nm in size and therefore enable the uptake of smaller particles than CCPs [85,86], which are reported with sizes of up to 200 nm. [87] Since caveolae-mediated endocytosis results in the formation of caveosomes, which possess a neutral pH and may bypass lysosomes and thus digestive environments, this uptake way is beneficial regarding cargo stability. [79,88,89] However, caveolae-mediated uptake is very slow with half times higher than 20 min. [90] (d) Clathrin/caveolae-independent endocytosis (CCIE) involves vesicle formation supported by actin and actin-associated proteins [91] or lipid rafts. These are cholesterol and sphingolipid-rich domains within the plasma membrane, which are freely diffusing and may be internalized following the binding of ligands to receptors or glycolipids that are localized within the raft. [54,79,90] Lipid raft-mediated uptake is discussed for the internalization of nanoparticles modified with particular cell-penetrating peptides (CPPs) and nucleic acids. [54,92] Furthermore, CCIE is especially interesting for nanoparticles modified with folic acid, which is frequently used for tumor-specific targeting concepts, since the folate receptor internalizes by this route. [93] (e) Macropinocytosis is characterized by the formation of large membrane extensions, which are formed by rearrangement of the cytoskeleton. During re-fusion with the plasma membrane, vesicles between 0.5 and 10 μM in size filled with extracellular fluid are formed and transported into the cell interior. [18,46] These vesicles, called macropinosomes, undergo acidification and fusion similar to endosomes. [18] In macropinocytotic uptake, all particles that are dissolved in the internalized extracellular fluid are taken up, which is why this uptake way is not directly regulated by the activation of a receptor. [46] Furthermore, macropinocytosis is a possible uptake way of particles whose size exceeds that of CCPs or caveolae. (f) Direct translocation is mainly limited to highly positively charged or very small particles. This uptake pathway enables immediate and fast entry into the cytosol.

matrix (ECM), which may nonspecifically interact with particle surfaces and thus hamper target cell internalization. In particular positively charged NPs are affected due to interactions with the negatively charged ECM. [53].

For preferential accumulation in target cells, the particles must discriminate between target and off-target tissue by precise biomolecular recognition strategies (Fig. 1c). [2,54–56] Therefore, ligands which interact with certain cell surface structures, such as receptors or ectoenzymes in a key lock principle, are tethered to the nanoparticle surface. [56–58] Ligand types that are implemented in the nanoparticle design are peptides [59], small molecules [60], aptamers [61], polysaccharides [62], or proteins [63], which can also be categorized in agonists [58], antagonists [64], substrates [65], inhibitors [57], or antibodies [66,67] for the corresponding target structures. In the simplest case, one type of ligand interacts with one target structure, which is especially promising for highly specific targeting motifs or structures that are strongly overexpressed in certain tissues. This plays a particularly important role in cancer therapy, e.g. nanoparticles functionalized with cancer-targeting antibodies, such as anti-CD133 [68], anti-HER2 [69], or anti-CD44 antibodies [70], as cancer tissue differs considerably from healthy tissues regarding morphology, cell metabolism, or the expression of cell surface markers. [71] However, since many receptors or enzymes are expressed not exclusively in one cell type, but ubiquitously in the organism, using only one ligand for target cell identification may cause reduced selectivity.

2.3. Nanoparticle uptake and endosomal entrapment

Many target structures are localized intracellularly. Therefore, efficient nanoparticle uptake is often required. Nanoparticle internalization can be devided in endocytic (Fig. 2a-e) and direct (Fig. 2f) uptake, whereas endocytic uptake pathways play the major role for nanoparticles. [46].

Upon endocytosis, particle binding is followed by their engulfment with subsequent budding of endocytic vesicles to the cell interior. [46] Thus, the internalized particles do not have direct access to the cytoplasm or cellular organelles. [54] Depending on the uptake mechanism, the vesicles are sorted, fused, dissociated, or matured to lysosomes and can either be exocytosed, recycled, or trafficked to different organelles, involving motor proteins, such as kinesin, dynein, and myosin, that shuttle vesicular cargos along microtubules or via actin filaments (Fig. 1d). [19,54] For many applications, the entrapment inside endocytic vesicles is undesirable since target structures are localized inside the cytosol or at specific subcellular organelles. Additionally, the maturation of early endosomes to lysosomes leads to acidification of the vesicles and a combination of lysosomal enzyme activity, and acidic pH values promote cargo degradation, which may be beneficial in some cases [72], but often reduces the therapeutic efficacy. [73].

Direct translocation, on the other hand, promotes direct access to the cytoplasm and organelles, faster delivery kinetics, and minimal lysosomal degradation [54,74,75], but is rarely reported and the permeation mechanisms are poorly described. [74] It is known that direct uptake pathways are particularly important for very small particles since nanoparticles require a critical minimum size of around 5–10 nm to be taken up endocytotically. [76].

2.4. Drug release

There are two conflicting objectives in controlling drug release: to prevent premature release into the bloodstream and to ensure rapid release once the particles have reached their target site (Fig. 1e). Besides the NP type, the exact composition, structure, and physical and chemical interactions of the individual components are important for the drug release characteristics. In this context, the nanoparticle manufacturing method is also an important factor. [94] Drug release can be categorized into diffusion, solvent-controlled, chemical, and stimulated release. [94,95] Diffusion-controlled release, which is forced by a concentration gradient, is important for almost all kinds of drug release from a dosage form, especially for capsule-like systems, where the drug is dispersed or dissolved inside a core. [94,96,97] Due to the concentration dependence, diffusion-controlled release often shows a high initial release that decreases over time. [94] Solvent-controlled release, which means osmotic- or swelling-controlled release, is primarily relevant for carriers with semi-permeable membranes or three-dimensional cross-linked materials like hydrogels [98], whereas drug release via chemical interactions is mainly associated with the degradation of the carrier matrix. The degradability and time are highly material-dependent. [99,100] Since non-biodegradable particles such as metal colloids or ceramics might accumulate and cause cytotoxicity, the usage of biodegradable materials is mostly preferred. [99,100] Frequently utilized materials in this context are biodegradable polymers such as poly (ε-caprolactone) (PCL), polylactide (PLA), and poly(lactide-co-glycolide) (PLGA), mesoporous silica nanoparticles, or lipid nanoparticles. Stimulated drug release, triggered for example by a pH shift in the environment or changes in the redox potential, enables temporal and spatial control of the drug release and thus might be advantageous. [101].

2.5. Exocytosis and intracellular particle residence time

The intracellular particle residence time is a critical factor for the efficacy of a nanotherapeutic system. It is determined by two factors: nanoparticle exocytosis and degradation. [102] The main exocytosis pathways are diffusion, rapid recycling, and the lysosomal- or the ER/Golgi apparatus pathway. (Fig. 1f) [102] The formation, fusion, transport, and excretion of nanoparticle-loaded vesicles in this context are controlled by the endocytic recycling compartment (ERC), which is a microtubular organelle that is distributed in the cytoplasm. [103,104] As described in chapter 2.4, the majority of internalized particles end up in early endosomes, which have the function of controlling the reutilization or degradation of membrane components. [105] Therefore, some of the internalized particles return directly to the plasma membrane and are ejected. [103,104] This exocytosis mechanism, known as rapid recycling, [102] possesses half-life times of two minutes or less [104], hardly offering time for intracellular drug release. The most important exocytosis mechanism is the lysosomal pathway. In this case, the early endosomes undergo a maturation process from early to late endosomes and ultimately to lysosomes. [105] Nanoparticles suffering from endosomal entrapment [106] are digested by lysosomal enzymes and acidic pH values and the vesicle content is expelled. Therefore, the endosomal escape capability is a critical factor for particle residence time. [107] Moreover, optional via the endoplasmic reticulum [108], nanoparticles may be transported to the Golgi apparatus and transported to the cell surface for excretion via secretory vesicles. [102].

3. Nanoparticle design strategies

3.1. Manipulation of the protein corona

Various strategies have been developed to avoid or control the formation of the protein corona, thus preventing premature clearance, and obtaining the synthesized nanoparticle characteristics. [34,109,110] The topic is of utmost significance and has been reviewed in detail. [111] The most commonly used method to hinder protein adsorption is the stealth coating of nanoparticles with polyethylene glycol (PEG) [112–114], but also other hydrophilic polymers can be utilized according to this method [115]. The PEG chains provide a hydrated layer on the particle surface, reducing protein adsorption, [48] frequently referred to as “stealth effect”. [47] The repulsive effect depends on the polymer’s molecular weight, conformation, and surface density, [46] and can prolong the half-life time of blood circulation from a few minutes to several hours. [40,46] A further strategy was presented by

Müller et al. (2017). [110] The research group coated nanoparticles with tunable surfactants to control the unspecific protein adsorption and aggregation of particles by a non-covalent approach that could be applied to any particle type without high synthetic effort. However, the formation of a protein corona does not only have negative effects: the adsorption of so-called dysopsonins actively prevents phagocytosis by immune cells, which prolongs blood circulation. Furthermore, dysopsonins can contribute to reduced toxicity and colloidal stability of NPs (Fig. 3). [116] Typical dysopsonins are for example albumin, clusterin, also called apolipoprotein J, and transferrin, which is why studies were performed that deal with the intentional coating of NP surfaces with these proteins to exploit the protein corona for improved drug delivery. [116–119] Additionally, the protein corona can be utilized for specific nanoparticle targeting. [120] One example is the protein corona manipulation via polysorbate precoating, which facilitates the adsorption of apolipoprotein to the nanoparticle surface and thus enables brain targeting. [121,122] Furthermore, Zhang et al. (2015) [123] developed a retinol-conjugated polyetherimine nanoparticle system that selectively attaches the retinol-binding protein 4 (RBP4), which targets hepatic stellate cells and thus could be used for the treatment of hepatic fibrosis. Therefore, the aim is not necessarily to completely prevent protein attachment, but to ensure that the corona is formed by desired proteins that enable immune escape or that are targeted to distinct cells. The amount, type, and affinity of adsorbed proteins can be altered by changes in the nanoparticle surface chemistry, size, shape, and precoating, which was summarized in recently published reviews by Zhao et al. (2024) [34] or Kim et al. (2023) [48].

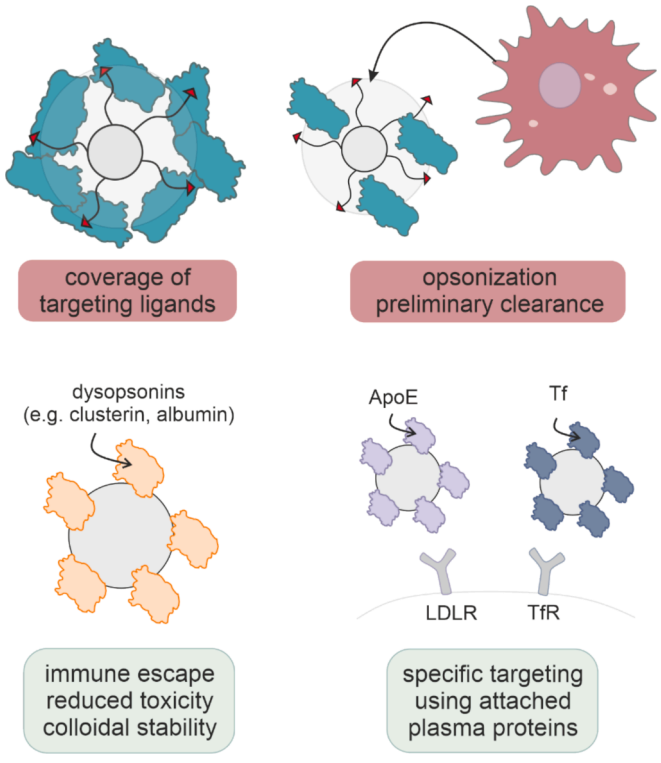


Fig. 3. Consequences of protein corona formation. Protein attachment is frequently correlated with a negative impact due to the coverage of targeting ligands, resulting in suppressed target cell selectivity, or premature MPS clearance due to opsonization. Nevertheless, the protein corona may also have positive effects due to the attachment of dysopsonins or proteins such as transferrin (Tf) or apolipoprotein A (ApoE), which can be utilized for specific nanoparticle targeting. [120].

3.2. Control of nanoparticle extravasation and target cell recognition

To reach their target cells, nanoparticles must pass the endothelial barrier of blood vessels. While larger particles have more interactions with the cell membrane and smaller particles require less energy to form vesicles upon particle uptake, there is an optimal size range for endothelial internalization and thus transcellular extravasation of about 50–70 nm. [35] In certain tissues, such as tumors, glomeruli, or hepatic sinusoids, larger fenestrations facilitate the paracellular extravasation of larger NPs. [51,124,125] Accordingly, it may be advantageous to adjust the particle diameter to the size of the extended fenestrations or to choose a size range that allows transcellular passage through the endothelial barrier.

To identify target cells, targeting ligands are attached to the nanoparticle surface. Depending on the type of ligand, different effects can be observed: antagonistic ligands or enzyme inhibitors mediate binding to the cell membrane without direct uptake. [57,126] In contrast, the interaction of receptor agonists as ligands usually induces receptor-mediated nanoparticle internalization. [127,128] Antibodies used as targeting ligands can also induce cellular uptake. [129,130] Substrates of ectoenzymes attached to the nanoparticle surface are cleaved and subsequently released, so no direct particle uptake is expected. However, enzymatic processing can unveil structures on the nanoparticle surface that subsequently promote cell internalization (Fig. 4). [65] Consequently, besides the target structure, the pharmacological characteristics of the targeting ligands have a major influence on the efficacy of the drug delivery system and must be taken into account in the nanoparticle design. [18,131].

Since most targeting motifs are expressed in a variety of cells throughout the body and are rarely exclusively expressed or at least significantly overexpressed in a single cell type, the combination of different ligands, which is also known as hetero-multivalent targeting, has significant advantages over the use of a single ligand type. [58,132–134] By simultaneous binding of several ligands to different target structures, both targeting efficiency and specificity can be increased. [135] The corresponding theoretical and thermodynamic background was described in an excellent review by Woythe et al. (2021) [136]. However, for multi-target interactions, several attributes should be taken into account: the addressed targeting structures should not have downregulating effects via intracellular receptor consumption pathways, the ligand density should be optimized to the expression density in the target tissue, and the bioconjugation strategy has to be adjusted to facilitate the interaction between ligand and target structure, for example by the setting of spacer length and linker chemistries. [133] A possibility to further increase the target cell selectivity of hetero-multivalent targeting approaches, by steric shielding of one ligand type, was published by Fleischmann et al. (2020) [58]. Only after the binding of a primary ligand to a receptor expressed on the target cell surface, the newly achieved spatial proximity reveals a previously hidden second ligand, which ultimately leads to nanoparticle internalization.

3.3. Promotion of endosomal escape and direct penetration

Since reaching the cytosol is essential for the efficacy of many nanotherapeutics, numerous strategies have been developed to promote endosomal escape or direct penetration of the cell membrane. The most common endosomal escape strategies can be categorized in the so-called “proton sponge effect” or osmotic rupture, the swelling effect, the destabilization of the membrane by pore formation or disruption, and membrane fusion. All aim to destabilize the endocytic vesicles and thus allow nanoparticle trafficking to the cytosol (Fig. 5). [137,138] Besides, new approaches are being developed that should diminish endosomal entrapment, such as the thiol-disulfide exchange strategy: Kanjilal et al. (2022) [139] demonstrated that disulfide bonds as NP functionality may enhance cellular uptake and endosomal escape. The underlying

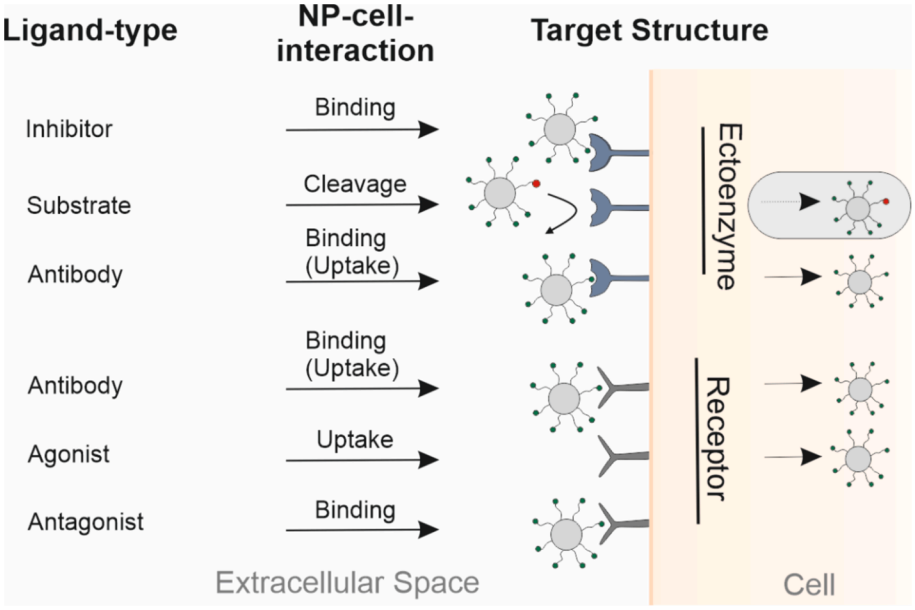


Fig. 4. Nanoparticle-cell interaction based on the ligand type and the target structure. Enzyme inhibitors or antagonistic receptor ligands mainly bind to the target structures expressed on the cell surface, thus anchoring the particle to the target cell surface. For antibodies, both cell surface binding and uptake have been described. Receptor agonists often promote receptor-mediated uptake into the target cells. Enzyme substrates attached to the nanoparticle surface are cleaved, which does not result in immediate uptake. However, the associated release of receptor agonists or other uptake signals may secondarily trigger nanoparticle uptake.

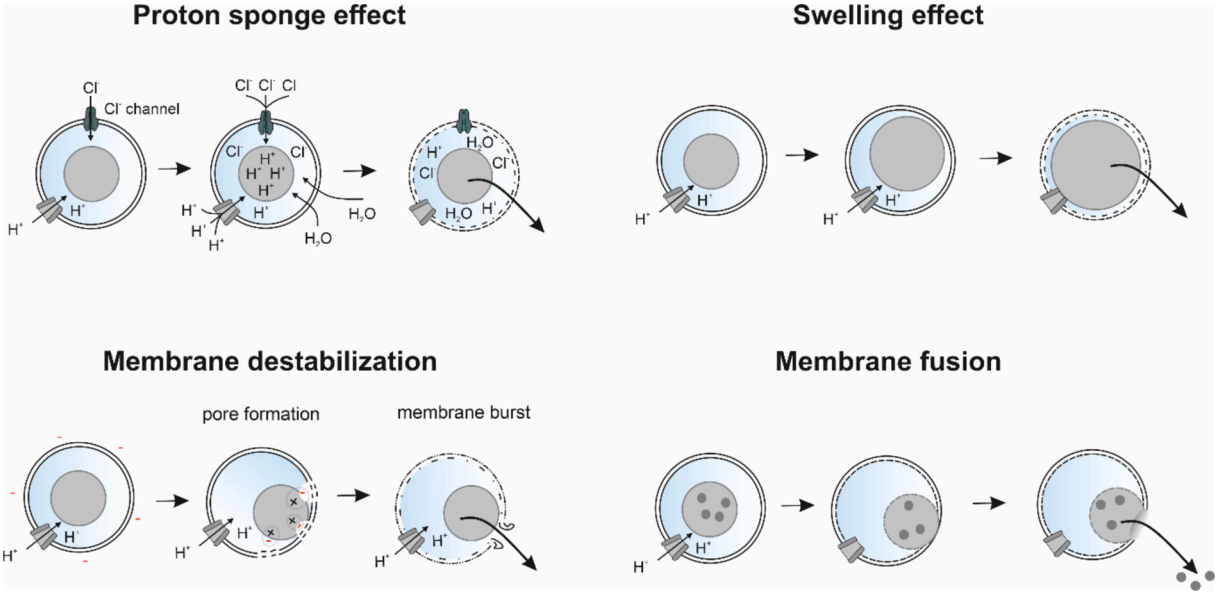


Fig. 5. Mechanisms of endosomal escape. The proton sponge effect is caused by endocytosed compounds that are protonated upon H^+-ion influx during the acidification of endosomes in the maturation to late endosomes or lysosomes. [97] Consequently, those substances possess a buffering capacity that counteracts the acidification of the endosomal compartment. [98] This promotes further ATP-driven influx of protons, accompanied by chloride ions and water molecules. The resulting osmotic pressure ultimately leads to membrane rupture and thus to the release of the entrapped components. [96] The swelling effect describes drug release caused by the swelling of certain structural compounds, mainly polymers, caused by pH shifts or changes in ionic concentrations. [98] The most important mechanism for persistent membrane destabilization, causing pore formation or also membrane rupture, is the membrane "flip-flop" caused by cationic charges. [152] Since the outer layers of endosomes are mainly composed of negatively charged phospholipids, positively charged cargos induce a flip of the outer layers to the intraluminal side of the endosome. The resulting formation of charge-neutral pairs results in membrane reorganization and non-lamellar phase changes, which ultimately cause membrane destabilization. [153,154] Membrane fusion is a process that is inspired by viruses such as the influenza virus, utilizing the hemagglutinin (HA)-2 subunit as a fusogenic agent. [152] HA-2 is converted from a hydrophilic, anionic coil at neutral pH to a hydrophobic helical conformation in an acidic environment, enabling the fusion of the viral membrane with the cellular membrane. [138] This mechanism can be adapted for the endosomal escape of nanoparticles by the attachment of fusogenic peptides to the NP surface, which leads to fusion with the lipid bilayer and release from endosomal entrapment. Many reviews are focusing on these mechanisms to which we would like to refer for more detailed information. [137,138,155,156].

mechanisms are still not clear, but the research group proposed that the covalent contact between the membrane thiols and the nanogel strained the packing of the endosomal membranes and thus promoted cargo leakage. Stahl et al. (2022) [72] used the endosomal enzyme activity to promote endosomal escape: a substrate of the protease cathepsin S (CatS), which is found in early endosomes of dendritic cells, was used as a linker between a model antigen and polymeric nanoparticles as carrier. Enzymatic processing of the nanoparticle surface enabled selective release of the antigen, allowing its endosomal escape.

Another strategy to prevent endosomal entrapment is to adjust the particle design to achieve prioritization for specific uptake pathways. Particularly high nanoparticle surface charges and cell-penetrating peptide modifications promote non-endocytic uptake [75,140,141], using transient holes that are generated in the bilayer membrane in response to strong local potential differences, which are resealed after particle uptake. [142,143] In addition to the particle charge, also the shape has an impact on translocation behavior and can result in varying cell entry mechanisms. [142] This has been shown for dendrimers as an example. A spheroidal shape was more efficient in permeabilizing the plasma membrane than linear poly-l-lysine polymers. [144].

Besides direct internalization, modifications promoting macropinocytosis or caveolae-mediated endocytosis could be favorable regarding subcellular targeting, since macropinosomes possess relatively leaky vesicular structures that facilitate escape into the cytosol. [145] The caveolar pathway to enter cells provides a nonacidic and less digestive route for cellular uptake. [88] The cargo internalized by caveolin-mediated endocytosis may be directly transported to processing organelles such as the Golgi apparatus (GA) or the endoplasmic reticulum (ER), avoiding lysosomal degradation. [79,88] However, while the attachment of cell-penetrating peptides to the particle surface supports direct NP internalization and also particle uptake via macropinocytosis [146,147], the regulation of particle uptake via caveolae-mediated endocytosis and the resulting particle fate is still unclear and controversially discussed. One approach to direct the NP uptake towards caveolae-related endocytosis to circumvent lysosomal degradation was established by Chen et al. (2022) [24]. The research group developed a biomimetic system using NP cancer cell membrane camouflage. However, the factor which likely influenced the rate and route of endocytosis to the greatest extent is the formed protein corona. [148] Additionally, the cell type has an impact. [149–151] At this point, there is a lack of more detailed studies dealing with the control of NP uptake via specific pathways and clarifying the subsequent distribution processes.

3.4. Delay of particle exocytosis

Although low intracellular particle residence time is a limiting factor for therapy efficacy, only a few studies deal with the analysis of nanoparticle exocytosis or the prolongation of particle retention in the target tissue. [54] The nanoparticle size has a high impact in this case. [157] Most studies agree that smaller particle sizes promote faster elimination from the cells. [107,158–160] One reason frequently postulated is that smaller NPs have fewer receptor-ligand interactions, which lead to a lower overall intracellular binding and therefore facilitate the release of the particles. [107,157,158] Therefore, increasing the particle size could be useful to prolong intracellular retention. Furthermore, there is a low number of studies developing strategies to decrease NP exocytosis rates. Chen et al. (2022) [24] discussed that a rapid exocytosis of nanoparticles causes unsatisfactory results of ER-targeting approaches. Therefore, they investigated a strategy to enhance NP-mediated immunotherapy by exocytosis blockade with brefeldin (BFA) by coat protein type I (COPI) vesicle transport inhibition. Thus, they achieved an 11-fold increase in intracellular retention of the NPs at 24 h. Yanes et al. (2013) [161] decreased the exocytosis rates of mesoporous silica nanoparticles to prolong the retention in cancer cells and thus enhance drug delivery. The combination of camptothecin-loaded particles with bafilomycin A1 or U18666A led to an increase in cell-killing efficacy. Kim et al. (2015) [160] established a strategy to regulate the exocytosis rate of gold nanoparticles via host–guest chemistry. By complexation of the NPs inside cells using cucurbit[7]uril (CB[7]), larger particles were assembled that inhibited exocytosis. While the intracellular amount of gold NPs without CB[7] treatment decreased to 34 % after 24 h, no significant change was observed for cells treated with CB[7] containing media.

3.5. Switchable nanoparticle characteristics

One strategy that is currently widely applied is the development of switchable particle properties. In this case, either intrinsic or extrinsic stimuli are utilized to adapt the properties of nanoparticles to the current requirements in a temporally and spatially coordinated manner. An exemplary application for switchable nanoparticle designs is triggering a charge conversion of the nanoparticle surface (Fig. 6). Higher amounts of positive charges enhance cellular uptake, which was shown in various studies. [162,163] Since cationic particle charges also play a major role regarding endosomal escape mechanisms, the implementation of cationic compounds in NP targeting strategies might be highly advantageous. However, it is critical to take into consideration that positive charges promote increased protein adsorption and thus tend to premature clearance [164], show a higher tendency to interact with the ECM [165], and are known to possess cytotoxic effects. [166] In contrast, particles with a negative surface charge tend to interact less with the ECM and are less susceptible to opsinization, but show lower internalization rates. Triggered charge reversal can be used to obtain the benefits of both surface charges.

Another common application for switchable particle designs is controlled drug release. While stable encapsulation is necessary during blood circulation to prevent adverse drug effects due to premature release, an efficient drug release is required in the target tissue. Thus,

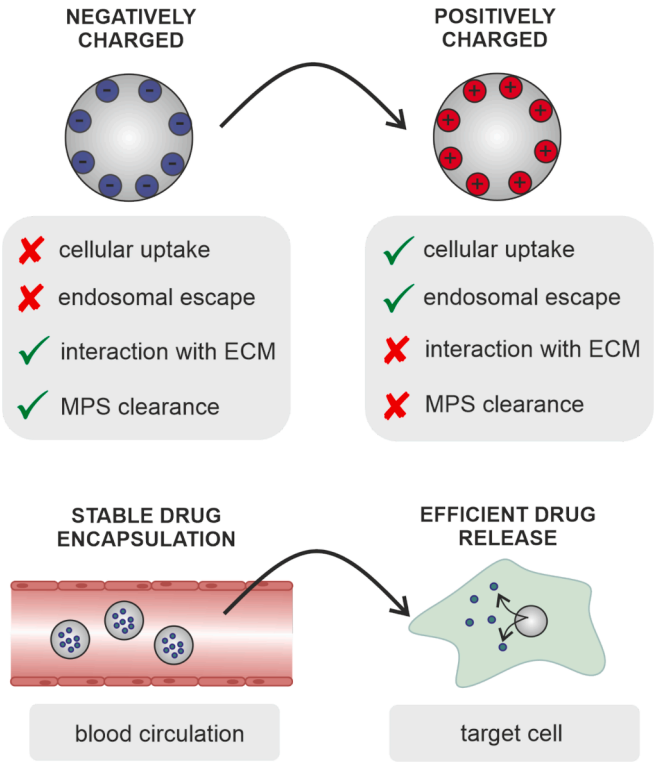


Fig. 6. Applications of switchable nanoparticle designs. Stimuli-controlled charge conversion can switch the initially favorable negative surface with reduced MPS clearance and interaction with the ECM to a positive surface charge with improved NP uptake and endosomal escape. Furthermore, stimuli-responsive compounds can induce sterically and temporally controlled drug release in the target tissue.

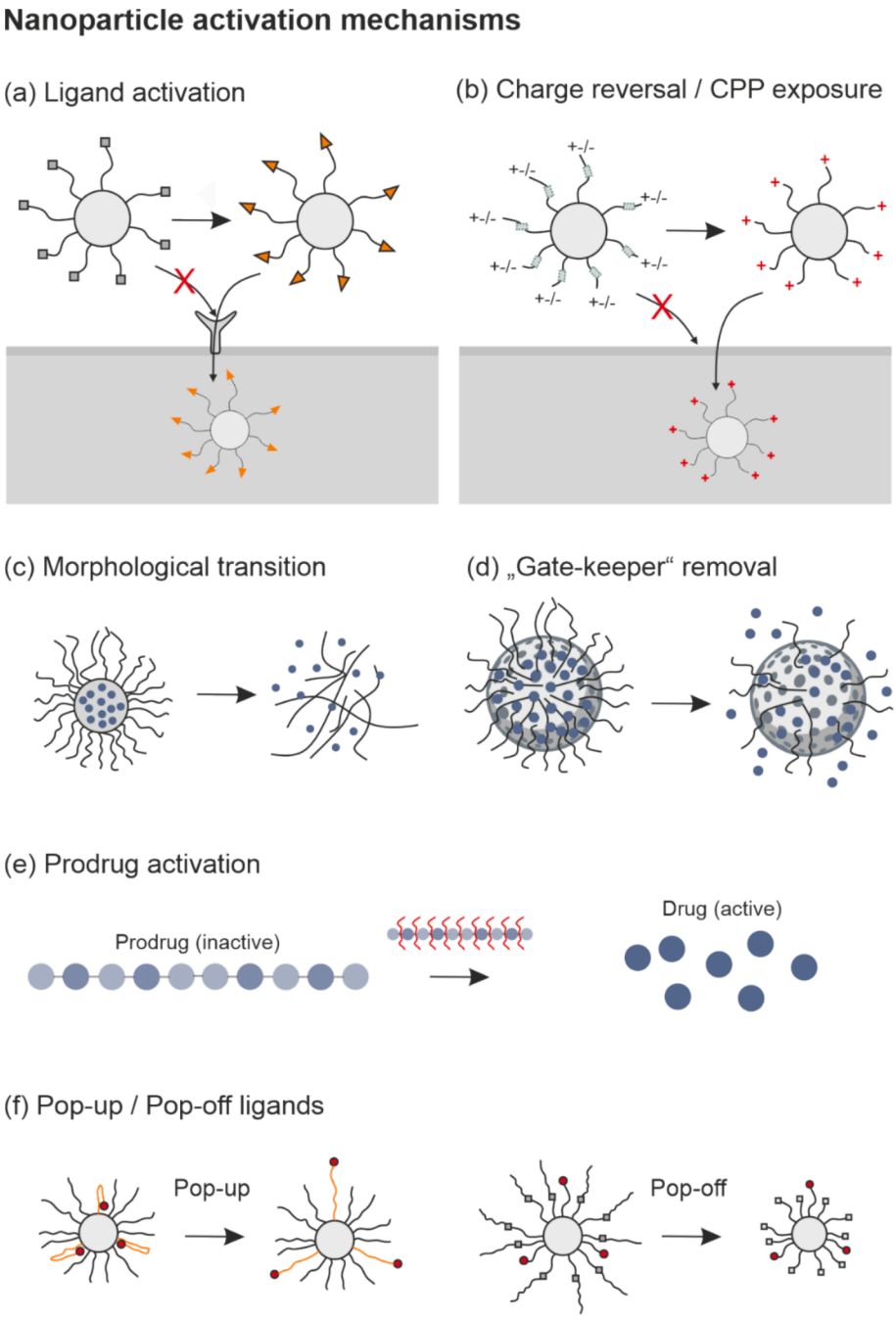


Fig. 7. Nanoparticle activation mechanisms in switchable particle designs. (a) Activation of initially inactive targeting ligands by enzymatic cleavage (e.g. Ang I → Ang II → binding to AT1R). (b) Charge reversal from negative/neutral to positive enables reduced clearance and interaction with the ECM combined with preferential uptake and endosomal escape. (c) Morphological transition such as decomposition in an acidic environment allows spatially and temporally controlled drug release. (d) Gatekeeper removal from mesoporous silica nanoparticles leads to controlled drug release from the nanoparticle pores. (e) Activation of an inactivated poly prodrug by releasing individual drug molecules, e.g. by enzymatic cleavage. (f) Utilization of pop-up ligands that unfold in response to a distinct signal and become visible on the particle surface or pop-off ligands that are cleaved and thus expose sterically shielded compounds of the nanoparticle structure.

releasing the drug due to an intrinsic or extrinsic signal can improve therapy efficacy. [167] Activation of nanoparticles can be achieved by a variety of different mechanisms, as shown in Fig. 7. An overview of different switchable nanoparticle design concepts is shown in Table 1.

3.5.1. *Bioresponsive nanoparticles*

For intrinsically activatable or bioresponsive nanoparticles, physiologically or pathologically occurring conditions in certain tissues or at the subcellular level are used to trigger a specific effect, for example, the activation of a targeting ligand or a prodrug, a morphological transition, or the removal of a gate-keeper which has prevented drug release. (Fig. 7) This is enabled by the incorporation of switching capabilities in the particle structure, which react to changes in the pH value or redox gradients, or can be cleaved by certain enzymes. [185].

As already pointed out, nanoparticles are mainly internalized via endocytic pathways and thus primarily localized inside endosomes. [186] Endosomes possess a pH value of about 5.5–6.3 [187] and are consequently more acidic than other organelles [188] or the cytoplasm, which has a pH value of 7.0 to 7.4. [189] Furthermore, early endosomes undergo a maturation process to late endosomes and ultimately

Table 1
Overview of activatable, smart nanoparticle systems. Abbreviations: ACE, angiotensin-converting enzyme; AMF, altering magnetic fields; CA, cinnamaldehyde; Cys, Cystein; DMA, dimethylmaleic anhydride; DOX, doxorubicin; GGT, γ-glutamyl transpeptidase; GSH, glutathione; HFn, heavy chain ferritin; HAS, human serum albumin; HCPT, 10-hydroxycamptothecin; ICAM1, intracellular adhesion molecule 1; LCST, lower critical solution temperature; MMP, matrix-metalloproteinase; MSN, mesoporous silica nanoparticles; MTO, mitoxantrone; NIR, near infrared; PEG-b-P(TMBPEC-co-AC), poly(ethylene glycol)-b-poly(mono-2,3,6-trimethoxy benzylidene-pentaerythritol carbonate-co-acryloyl carbonate); PAE, poly(β-amino esters); PAEMA, poly(2-azepane ethylmethacrylate); PBA, phenylboronic acid; PDSA, poly (disulfide amide); PEG, polyethylene glycole; PHPMA, N-(2-hydroxypropyl)methacrylamide; PLA, poly lactide acid; PLG, poly (L-glutamic acid); PLGA; poly(lactic-co-glycolic) acid; pLL, poly-L-lysine; p(MEO2MA), poly(2-(2-methoxyethoxy)ethyl methacrylate); PSAR, polysarcosine; PTX, paclitaxel; QDs, Quantum dots; ROS, reactive oxygen species; Ru, Ruthenium; SPION, superparamagnetic iron oxide; TAC, tacrolimus; THPMA, 2-tetrahydropyranyl methacrylate; TMT, ten-tumor metastasis targeting peptide.

Stimulus	NP-system	Responsive Moiety	Target/ Activator	Concept	Objective	Associated Disease	Ref.
pH	PEG-b-P(TMBPEC-co-AC) polymer	Acetal	Endo-/lysosomal compartments	Hydrolytic degradation (morphological transition)	Drug release (Paclitaxel, PTX)	Tumor, not further specified	[168]
	Liposomes modified with pH-sensitive polymer (PEG-PLL-DMA)	Cleavable amide linkage formed between PEG-PLL and DMA	pH 6.5 in tumor microenviron-ment, pH 5.0 in endo- and lysosomes	Charge reversal and NO generation	Endosomal escape and controlled drug release (PTX), overcoming P-gp mediated multi-drug resistance	Cancer, not further specified	[169]
	Poly(β-amino esters) (PAE) as core and PEG-biotin on the particle surface, decorated with anti-ICAM1 antibody via biotin-avidin interaction	PAE ester	Lower pH values in inflammatory tissues	Nanoparticle targeting via anti-ICAM1 antibody + nanoparticle core disassembly (morphological transition) → drug release in inflammatory tissue	Drug (TPCA-1) release from the nanoparticle core	Acute lung inflammation/ injury	[170]
GSH	Poly-HCPT as inner core, lipid-PEG as outer shell, LA as surface layer	Disulfide bond in the poly-HCPT structure	GSH in tumor tissue	Targeting via LA, GSH in cytoplasm, morphological transition, drug (siBcl-2) and HCPT release	Fast release of intact HCPT molecules and encapsulated siBcl-2	Liver cancer	[171]
	PEGylated mesoporous silica core–shell NPs	Disulfide linkers for PEG attachment	GSH in tumor tissue	Shell cleavage (morphological transition) following drug release	PTX release	Breast cancer	[101]
	Polymeric nanoparticles (Cys-8E Cys-PDSA)	Disulfide bond in PDSA polymer	Increased GSH levels in cardiac fibroblasts after myocardial infarction	S-S bond cleavage and thus NP degradation (morphological transition)	Drug release of encapsulated PF543 (sphingosine kinase 1 inhibitor)	Cardiac fibrosis induced by myocardial infarction	[172]
ROS	DSPE-PEG polymer-NPs	Thioketal-bond in polyMTO	Intracellular ROS increased in tumor tissue	Chain-breakage caused release of mitoxantrone (MTO)	Tumor targeting, deep tumor-penetration, on-site drug activation by prodrug cleavage	Cancer therapy, not further specified	[173]
	Polymer-cinnamaldehyde (CA) conjugate NPs	Thioacetal linker of polymer chain and CA	ROS levels increased in inflamed tissues	The functional aldehyde group of CA was protected via chemical conjugation to the polymer via a ROS-responsive thioacetal linker	CA release upon oxidative stress in inflammatory tissue with ROS-scavenging activity (prodrug activation)	Broad range of inflammatory diseases e.g. rheumatoid arthritis or ulcerative colitis	[167]
Enzyme	PLGA/PLA-PEG polymer NP	Angiotensin I	Angiotensin-converting enzyme (ACE)	Ligand Cleavage (Ang I → Ang II) (ligand activation)	NP Uptake	Diabetic nephropathy	[65]
	Quantum dots (QD)	α-Aminobutyric acid	γ-glutamyl transpeptidase (GGT)	Charge Reversal	NP uptake / Deep penetration	Tumor, not further specified	[164]
	PLG-g-LPEG/TAC	MMP9 cleavable peptide sequence (Gly-Pro-Leu-Gly-Leu)	Matrix metalloproteinase 9 (MMP9)	Morphological transition from spherical NPs to microscale aggregate-like scaffolds	Cargo (tacrolimus) release	Rejection after liver transplanta-tion	[174]
	MSN-HSA-PBA-DOX	MMP2 substrate (functional peptide R8-PVGLIG)	Matrix metalloproteinase 2 (MMP2)	Breakdown intracellular linker	Enhanced endocytosis (targeting ligand PBA, exposed CPP)Drug release (DOX)	Tumor, not further specified	[175]
Light-responsive	Self-assembled block copolymer nanoparticles	Ruthenium complex-based photocage	Near-Infrared(NIR) light	Release of Ru complexes (prodrug activation, cleavage photocage)	Combined chemotherapy via drug (tetrahydrocur-cumin, THC) release and photodynamic therapy	Tumor, not further specified	[176]

(*continued on next page*)

Table 1 (*continued*)

Stimulus	NP-system	Responsive Moiety	Target/ Activator	Concept	Objective	Associated Disease	Ref.
Thermo-responsive	Polysarcosine (PSAR)-b-(N-(2-hydroxypropyl) methacrylamide) (PHPMA) NPs	Polysarcosine with 3.5 % of PHPMA	Moderate increase in solution temperature	Changes in particle morphology and shrinkage upon temperature increase	Doxorubicin release in response to subtile thermal stimulation (increase in environmental temperature to 41 °C).	Breast cancer	[177]
Ultrasonic-responsive	Polymer-grafted mesoporous silica nanoparticles	Copolymer p(MeO2MA)–co-THPMA with LCST below 37 °C, upon US irradiation the hydrophobic tetrahydropropyranyl groups in the polymer backbone were cleaved leading to hydrophilic methacrylate and increasing the LCST over 37 °C	US	Drug loading at 4 °C (open conformation), polymer collapses at 37 °C (closed conformation) ultrasound irradiation in cancer → pore opening (gate-keeper removal) and drug release	Controlled drug release in the tumor tissue upon US irradiation; fluorescein was used as model cargo	Cancer, not further specified	[178]
Activation by magnetism	Poly-paclitaxel/cyclodextrin-superparamagnetic iron oxide nanoparticle (SPION)	Iron oxide core	Altering magnetic field (AMF)	Host-guest interaction between ß-cyclodextrin-SPION and poly paclitaxel (pPTX) to form nano-assembly with cluster structures of SPION	Enhanced magnetic guidance for targeted nanotherapy	Anticancer therapy, not further specified	[179]
	Fe_3O_4-NP coated with a silica-PEG shell and loaded with doxorubicin (Dox)	Iron oxide core	AMF	Local heating of the particle core which accelerated Dox release	Controlled drug release in tumor tissue	Anticancer therapy, not further specified	[180]
	Hybrid nanogels composing of thermo-responsive polymers and SPIONS	Iron oxide core	AMF	Local heating which accelerated Dox release	Controlled drug release in tumor tissue	Cancer, not further specified	[181]
Multiple responsive	AUS-PM(PCL-SS-PCL-MPC deblock copolymer) TMT-DOX	TMT (receptor-mediated endocytosis), disulfide (GSH-sensitive), PCL (pH sensitive)gold (sound-sensitive)	TMT receptor, GSH, pH in tumor tissue, gold (ultrasound-responsive)	PCL core breakdown under pH 5.5, disulfide linkage → increased ROS production when exposed to ultrasound stimulation	DOX release, ROS generation, cytotoxicity in cancer cells	Metastatic breast cancer	[182]
	Enzyme/pH dual-responsive NP based on human heavy-chain ferritin (HFn), modified with Anti-PD-L1 peptide CLP002 and MMP-2/9 substrate peptide	MMP-2/9 substrate peptide, pH-mediated disassembly of recombinant ferritin (CMFn)	Matrix metallo-proteinase-2/9 (MMP-2/9) overexpressed within the tumor microenvironment, acidic pH values within lysosomes	MMP-2/9 cleaves linkage of CLP002 → blockade of PD-L1 receptor, release of oxaliplatin in lysosomes after endosomal uptake → synergistic antitumor effect	Tumor-targeted delivery and controlled release of the immune checkpoint inhibitor CLP002 and the chemotherapeutic drug oxaliplatin	Cancer therapy, not further specified	[183]
	pH-responsive polymer, photocatalyst eosin Y, ROS-sensitive prodrug protection group	PAEMA, eosin Y,	Acidic pH value in tumor tissue, light irradiation (460 nm)	protonation PAEMA → morphological transition, exposure of the photocatalyst eosin Y, light irradiation → prodrug activation	Targeted prodrug activation within the acidic tumor micro-environment in combination with photo-dynamic generation of ROS for remediation of cancerous tissue	Cancer therapy, not further specified	[184]

lysosomes, which are even more acidic with pH values between 4.5 and 5. [187] Since the extracellular pH value, under physiological conditions, is in the neutral to slightly alkaline range (pH 7.3–7.4) [188], the entry of nanoparticles into an acidic environment by particle uptake can be used as a trigger for nanoparticle activation. Additionally, there are differences in extracellular pH values, which can be utilized for nanoparticle targeting. The most popular example is the slightly acidic extracellular environment around hypoxic tumor tissue. Here the pH value can drop to 6.4 to 6.8 since cancer cells are metabolizing glucose via lactate-producing pathways. [190] For the development of pH-dependent particles, different strategies have been implemented, e.g. the equipment with acid labile linkers (Table 2), charge-shifting polymers, or particle crosslinking. These features should lead to changes in size, shape, surface chemistry, particle disassembly, and cargo release, respectively. [191] One example is the concept of Zhang et al. (2019). [170] The work group investigated pH-responsive nanoparticles targeting the lungs for the therapy of acute lung inflammation. They implemented pH-responsive polymers in their particle design for a site-specific drug release in the target tissue. After targeting the ICAM-1 receptor via ICAM-1 antibodies tethered to the nanoparticle surface, the previously stable particle core, consisting of poly(ß-amino esters) (PAE), was degraded due to the lower pH values of inflammatory tissues, resulting in the release of the anti-inflammatory model agent TPCA-1. (Fig. 7c) Lee et al. (2008) [192] utilized super pH-sensitive polymers for the design of nanoparticles with a ligand pop-up activation (Fig. 7f). In an acidic environment, the protonation of the previously folded poly (L-lactic acid)-b-poly(ethylene glycol)-b-poly(L-histidine)-TAT block copolymer causes polymer extension and the CPP TAT is revealed on the particle surface, which leads to particle uptake.

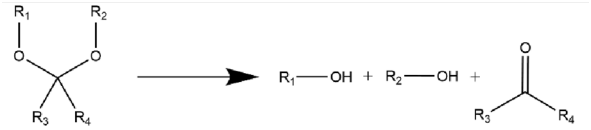
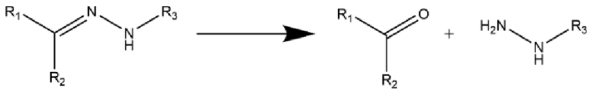
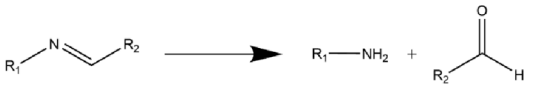
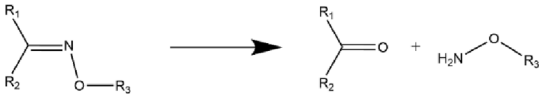
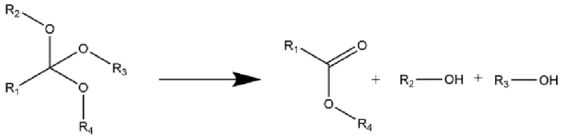
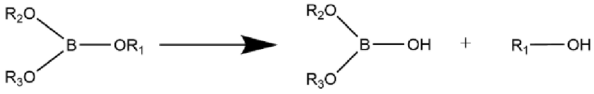
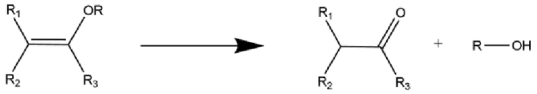
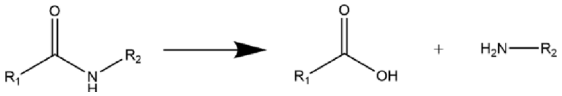
Analogous to particle activation via naturally occurring pH gradients, also redox gradients can be utilized for nanoparticle activation. In this case, instead of acid-cleavable linkers, redox-cleavable linkers are implemented in the particle design. An overview of such oxidizable and reducible linkers is shown in Table 3. Glutathione (GSH), which is a tripeptide cell protective antioxidant [205], is mainly responsible for the activation of reductive-responsive nanoparticles by interacting with for example disulfide bonds (S-S) or diselenide bonds (Se–Se). GSH exists ubiquitously in the human body and participates in various biological functions like gene expression, cell proliferation, or apoptosis. [206] The highest intracellular GSH concentration is found in the cytosol with physiological average values of 2–10 mM. Since the extracellular concentration of GSH is around 100-fold lower (2–20 μM), the particles are stable during blood circulation and cleavage of the linkers occurs after particle uptake. Therefore, GSH-responsiveness is an ideal stimulus to accomplish efficient intracellular, while avoiding unspecific extracellular, drug release. [207] The oxidative cleavage of linkers is usually caused by reactive oxygen species (ROS), like hydrogen peroxide (H_2O_2), hydroxyl radicals (OH·), or singlet oxygen ($^1O_2$). These highly reactive molecules are primarily generated in mitochondria and contribute to human immunity. [208] Prominent examples of oxidative responsive linkers are sulfur- or selenium-containing, or arylboronic ester linkages. [208] Since ROS as well as GSH levels are significantly increased in the tumor microenvironment, redox-responsive on-site activation of nanoparticles is promising in the context of cancer therapy. [171] One example is the investigation of ROS-responsive poly-prodrug nanoparticles with triggered drug release for cancer therapy by Xu et al. (2017) [173], which combined target cell recognition and uptake with on-site prodrug activation. The established NP platform was composed of three components: the poly-prodrug, forming the inner core, which was supposed to respond to increased ROS concentration with a release of the activated drug molecules (Fig. 7e), the outer shell, consisting of polyethylene glycol, and the targeting ligand, internalizing RGD (iRGD), which was supposed to enhance selectivity and tissue penetration. Another application field of ROS-responsive nanoparticles is the treatment of chronically inflammatory diseases such as rheumatoid arthritis or ulcerative colitis. [167] Zhang et al. (2023) [167] established polymeric prodrug nanoparticles, in which the drug, cinnamaldehyde (CA), was protected by an oxidative-cleavable conjugation to a PEG polymer, causing the self-assembly of polymer-drug-conjugate nanoparticles. The functional aldehyde group is only released by ROS activity in inflammatory tissues, where CA acts anti-inflammatory due to its ROS-scavenging activity. (Fig. 7c) Furthermore, Ji et al. (2023) [172] established GSH-responsive polymeric nanoparticles, consisting of poly (disulfide amide) (PDSA) polymers [209], which are disassembled due to the reductive conditions after myocardial infarction by cleavage of the disulfide bonds. (Fig. 7c) In this way, the release of the encapsulated drug, the sphingosine kinase 1 inhibitor PF543, was triggered inside the cardiac fibroblast target cells. The research group has thus provided an efficient strategy for the pharmacological intervention of cardiac fibrosis.

Enzymes can also be used for the bioresponsive activation of nanoparticles. Therefore, substrates of the corresponding enzymes are integrated into the particle design. Compared to pH- or redox-responsive structures, enzyme-responsiveness has the advantage that the application is not limited to certain tissues, such as tumor tissue or inflamed areas, but can be adapted to almost all cell types. Various strategies have been developed, which enable either particle uptake or controlled drug release: Maslanka et al. (2019) [65] designed polymeric core–shell nanoparticles, with the ligand Angiotensin I (Ang I) tethered to the surface. Due to the enzymatic cleavage of the ligand by the angiotensin-converting enzyme (ACE), Ang I was converted to angiotensin II. Thus, the nanoparticle presented a receptor agonist for the AT1 receptor (AT1R), which led to particle binding and uptake. (Fig. 7a) The enzymatic ligand activation increased the target cell selectivity and enabled preferential uptake in mesangial cells that express both ACE and the AT1R. Li et al. (2014) [223] developed nanoparticles, which were activated by cleavage of a PEG-shielding unit by the matrix metalloproteinase 7 (MMP–7). This pop-up activation strategy (Fig. 7f) revealed the targeting ligand folic acid (FA) and thus enabled selective uptake in FA-overexpressing breast cancer cells. Another approach to improve nanoparticle uptake after enzymatic activation is the charge reversal strategy, performed by Dai et al. (2024). [164] (Fig. 7b) The research group implemented a γ-glutamyl-transpeptidase (GGT)-activatable motif into the modular peptide, which was used as a ligand for quantum dots. The initially terminal amino acid, which caused a zwitterionic charge on the QD surface, was removed by cleavage of the peptide bond, releasing a positively charged primary amine on the particle surface. Due to the charge reversal, the QDs showed enhanced cellular uptake and deep tumor penetration. According to this principle, also cell-penetrating peptides may be released. They are not exclusively, but to a large extent, polycationic, and therefore also cause charge reversal. [224] However, enzymatic activation cannot only improve uptake, but also achieve a temporally and spatially stringently coordinated cargo release. One example of this is the work of Luo et al. (2024) [174], which enabled a specific cargo release of tacrolimus in the liver allograft to overcome an acute rejection. The nanoparticles were composed of tacrolimus, which was covalently conjugated to matrix metalloproteinase 9 (MMP9)-cleavable peptide-containing polymers. Since MMP is overexpressed in rejected liver allografts, enzymatic cleavage of the particles in the target tissue caused a morphological transition from spherical micellar nanoparticles to microscale aggregate-like scaffolds and thus a site-specific drug release. (Fig. 7c) A further approach to control drug release by enzymatic responsibility was the cleavage of an end-capping and thus sealing agent for the mesopores of mesoporous silica nanoparticles (MSN), which was attached to the particle surface via a MMP-2 cleavable peptidic substrate. [175] (Fig. 7d).

3.5.2. *Extrinsically-activitable nanoparticle characteristics*

Besides intrinsic signals, also extrinsic stimuli can be utilized for nanoparticle activation. In this case, light of different wavelengths, magnetism, ultrasound, or temperature changes can be applied,

Table 2
pH-labile linkers as pH-activatable NP structures with corresponding activation mechanisms.

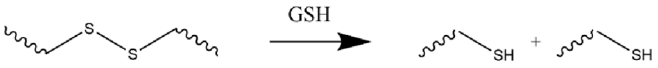
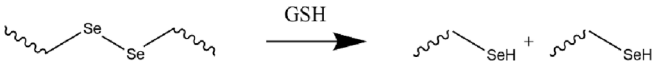
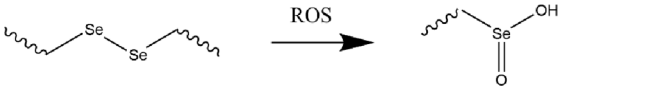
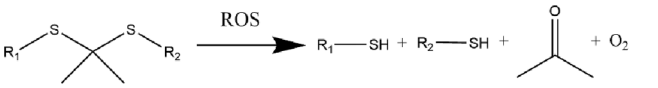
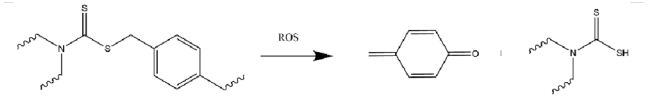
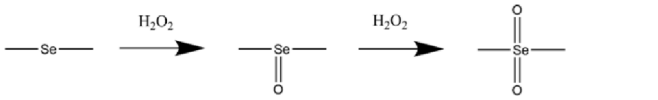
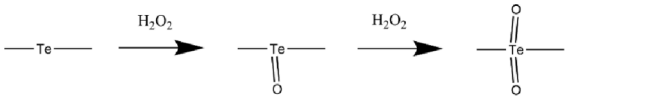
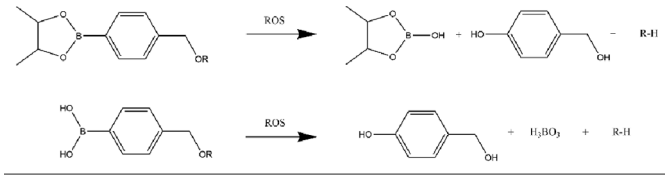
pH-labile linker	Reaction mechanism	Ref.
Acetal/Ketal		[193,194]
Hydrazone		[195,196]
Imine		[197]
Oxime		[198]
Ortho ester		[199]
Borate ester		[200,201]
Vinyl ether		[202,203]
Amide		[204]

depending on the nanoparticle type and its structural features.

Three main groups of photo-activatable compounds are used for the regulation of the distribution, uptake, or cargo release of light-responsive nanoparticles. “Phototriggers” are photolabile protection groups (PPGs) that undergo irreversible photolysis reactions [225], “photosensitizers” are used for the controllable generation of ROS, e.g. singlet oxygen (1O2), hydroxyl radicals or superoxides, also heat, and nitric oxide (NO), that trigger a photo response, while “photoswitches” perform reversible regulation by photoisomerization. [176,226,227] Since light can be regulated very precisely in area, time, and dosage, light-responsive targeting strategies have been widely applied. [226,227] Especially PPGs are frequently used for targeting systems, which allow the controlled release of a variety of caged compounds, such as functional groups, drugs, enzymes, neurotransmitters, or fluorophores. [228] The phototrigger should meet several prerequisites: a highly controllable and predictable photolysis mechanism, low cytotoxicity and a high quantum yield, good solubility, and stability in physiological media. [226] Furthermore, PPGs should provide sufficient absorption of at least 300 nm or higher. and the photolysis products themselves should not absorb in this range, as this would result in a competitive behavior between PPGs and lysis products. [226,229] For the majority of light-responsive moieties an excitation in the UV range is required. This has two fundamental disadvantages: UV light has a higher potential for cell damage and low tissue penetration (< 1 cm) through light scattering and absorption of intrinsic biological chromophores, including hemoglobin, oxyhemoglobin, and melanin. [226,230] Therefore, an increasing number of near-infrared (NIR)-responsive approaches that are activated by light at wavelengths from 700 to 950 nm [176] have been developed in recent years. NIR light is not only safer, but can also penetrate deeper into biological tissue. [176,214,230] A light-responsive approach developed by He et al. (2023) [176] coordinated a ruthenium-based photocage to the anticancer drug tetrahydrocurcumin (THC), which served as a ligand of self-assembled nanoparticles of amphiphilic block copolymers. The photocage primarily inhibited the anticancer properties of THC. Only after cleavage of the photocage by NIR light at 760 nm, the drug was released, resulting in inhibited tumor proliferation. Examples of further commonly used PPGs are shown in Fig. 8.

Thermo-responsiveness describes the ability to respond to changes in temperature with alterations in size, shape, solubility, or the release of an encapsulated drug, and thus can be advantageous in terms of therapy control. [231] Temperature-responsive polymers play an important role in this context. [232] The general idea of thermo-responsive polymers is that by changing the temperature, an encapsulated drug is released due to conformational changes of the polymer structure. They possess either a lower critical solution temperature (LCST) or an upper critical solution temperature (UCST) in aqueous medium. [232,233] For polymers with a LCST, heating leads to polymer shrinkage, and the cargo is ejected from its nanocarrier. The NP size either decreases in terms of colloidally stable particles or increases due to particle aggregation. [231,232] UCST polymers are soluble above a certain temperature. Therefore, after a temperature increase above this value, the encapsulated drug is released by particle disassembly. [234] Consequently, the application of moderate hyperthermia up to 43 °C, obtained by e.g. microwaves [235],

Table 3
Redox-activitable NP structures and activation mechanisms.

Redox response	Redox-responsive linker	Reaction mechanism	Ref.
Reductive cleavage	Disulfide bond		[210,211]
Reductive cleavage	Diselenide bond		[212,213]
Oxidative cleavage	Diselenide bond		[214]
Oxidative cleavage	Thioketal-based linker		[215]
Oxidative cleavage	Thiocarbamat-based linker		[216]
Oxidative structural dissociation	Selenium containing polymers		[217]
Oxidative structural dissociation	Tellurium containing polymers		[218,219]
Oxidative cleavage	Arylboronic ester		[220–222]

radiofrequency [236], NIR [237], ultrasound [238], or magnetic fluid hyperthermia [239], for a prolonged period, enables particle activation. [232] By this principle, Yu et al. (2019) [177] investigated thermo-responsive particles based on polysarcosine-polymers, grafted with 3.5 % of (N-(2-hydroxypropyl)methacrylamide) for the treatment of different kinds of breast cancer. Doxorubicin (Dox) release was strictly controlled by an increase of the environmental temperature to 41 °C. For more detailed information we refer to reviews that give an overview of suitable thermo-responsive polymers and particle structures. [232,240,241].

Ultrasonic response is also mainly concerned with the controlled release of encapsulated compounds from nanoparticles. Ultrasound exposure causes physical disruption, structural changes, or chemical reactions of the drug carrier as a result of thermal or mechanical effects triggered by cavitation or radiation forces. [242] This method can be applied to many different types of nanoparticles, such as polymer NPs, liposomes, gold particles, or carbon nanotubes. [242] An advantage compared to particle stimulation using external light is that low-frequency ultrasound can penetrate deep into soft tissues. [243] Additionally, ultrasonic stimulation can induce a transient increase of blood vessel permeability, which promotes extravasation of the nanoparticles and thus increases cellular uptake in the target tissue. [244] Ultrasound-responsive nanocarriers are being investigated mainly in the context of cancer treatment. [242] An example of an ultrasound-responsive nanoparticle design was presented by Paris et al. (2015). [178] The research group investigated polymer-grafted mesoporous silica nanoparticles with copolymers as pore gatekeepers. The nanoparticles were loaded at 4 °C, where the polymer showed an open conformation. At 37 °C, the copolymer collapsed, resulting in closed pores that could be injected without premature drug release. Only after ultrasound irradiation, the polymer structure changed towards a helical conformation, causing the opening of the mesoporous network and thus drug release. Furthermore, sonopermeation is an explored strategy to promote drug delivery across the blood–brain-barrier (BBB). Hark et al. (2024) [245] used the combination of ultrasound and RGD-coated polymeric microbubbles to induce temporally and spatially controlled opening of the BBB and thus mediate drug delivery by a polymeric drug carrier in an inflamed endothelium-pericyte co-culture model.

Altering magnetic fields (AMF) can be utilized to spatially and temporally control the distribution of NPs to target sites or to promote a magnetothermal drug release by hyperthermic bond-breaking or thermally induced permeability changes. [242,246] One example is the work of Jeon et al. (2016). [179] The work group investigated poly-paclitaxel/cyclodextrin-superparamagnetic iron oxide nanoparticle (SPION) nano-assemblies that were actively guided to the tumor via an externally applied magnetic field. They established a method of NP clustering that additionally provides the possibility of magnetically induced targeting even to cancers deep in the body. Demin et al. (2022) [180] established magnetic-responsive particles with a Fe_3O_4 core and a silica-polyethyleneglycol (SiO_2/PEG) shell, which were loaded with a high level of doxorubicin (Dox) to target different cancer cell lines. The application of an alternating magnetic field led to local heating of the particle core, which accelerated Dox release. A similar drug release mechanism triggered by magnetic hyperthermia was performed in the study of Cazares-Cortes et al. (2017) [181], with hybrid nanogels composed of thermoresponsive polymers and SPIONS.

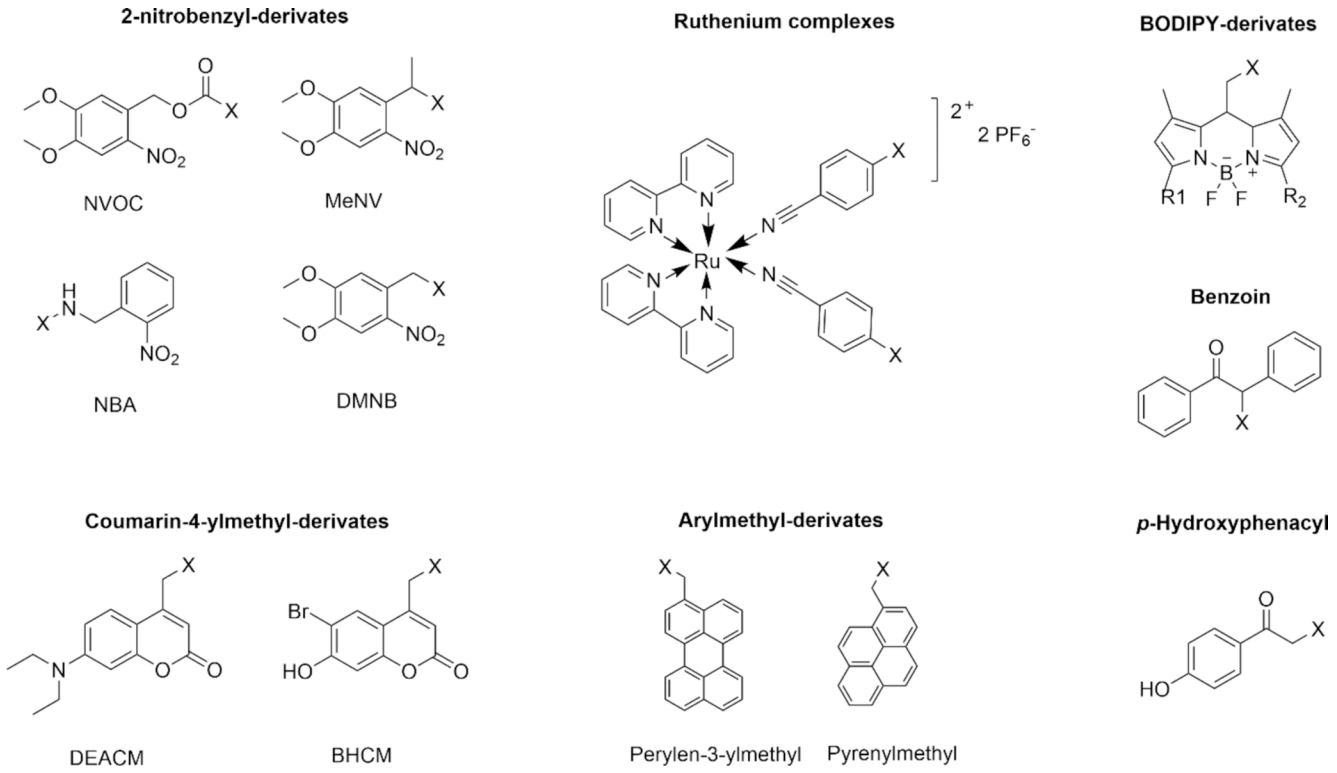


Fig. 8. Structures of representative PPGs.

3.6. *Dual- and multi-responsive particles*

Recently, increasingly complex concepts for targeted drug delivery have been developed. They combine at least two or even more orchestrated steps to enable stringent control of nanoparticle distribution and drug release.

Liu et al. (2024) [183] demonstrated an enzyme/pH dual-responsive particle system for improved tumor immune chemotherapy. The immune checkpoint inhibitor CLP002 was tethered to the surface of ferritin-based particles via a peptidic linkage motif containing the substrate of the matrix metalloproteinase-2/9 (MMP-2/9). Cleavage of the substrate led to the release of the free drug, resulting in the inhibition of its receptor, the PD-L1 receptor. A second drug, oxaliplatin (OXA), was encapsulated into the nanoparticle core. OXA was released due to acidic NP disassembly in lysosomes upon endosomal uptake, which led to a combined immuno-chemotherapy. (Fig. 9A).

Another multi-responsive approach was established by Maghsoudian et al. (2024) [182], who combined pH-, redox-, and ultrasonic-responsiveness. (Fig. 9B) The objective of the study was to develop a biocompatible and stable bioactive zwitterionic micelle for the treatment of metastatic breast cancer. The prepared nanomicelles, which served as drug carrier for doxorubicin, were composed of a zwitterionic polymer of methyl methacrylol phorphoryl cholin, and poly caprolactone (PCL) with a gold core. The integration of gold into the micelle core led to enhanced stability during circulation in the blood stream and served as sound-sensitive agent. The ten-tumor metastasis targeting (TMT) peptide was tethered to the micellar surface and enabled specific target cell recognition and receptor-mediated endocytosis. Additionally, the copolymers were modified to incorporate a disulfide structure. When exposed to ultrasound stimulation, these disulfide linkages led to an increased ROS production and similarly a reduction of the GSH level, which had cell-toxic effects. Furthermore, under a pH of 5.5, which is related to conditions in tumor tissue, the breakdown of PCL increased the release of the encapsulated drug in the target tissue. The findings of this study suggested that the established micellar nanocarriers can induce apoptosis in cancer cells and thus hold great potential for the treatment of metastatic breast cancer.

Li et al. (2024) [184] combined targeted prodrug activation within the acidic tumor microenvironment with the photodynamic generation of ROS. Therefore, a pH-responsive photocatalytic system has been developed that selectively generates ROS and further activates prodrugs in a cascade reaction. At a pH of 7.4, the synthesized switchable poly (ethylene glycol)-b-poly(2-azepane ethylmethacrylate)-b-2-(methacryloyloxy)ethyl 2-(2,4,5,7-tetrabromo-3,6-dihydroxy-9H-xanthen-9-yl)benzoate(PEG113-b-PAEMA50–EYHEMA1) polymer chains self-assembled to form polymeric nanoparticles. Due to the protonation of the PAEMA block, the particles disassembled and exposed the photocatalyst eosin Y. Upon light irradiation, the active eosin Y generated ROS, which led to ROS-induced cleavage of protection groups and thus activation of prodrugs with anticancerous activity. (Fig. 9C).

3.7. *Subsequent particle modification via bioorthogonal click chemistry*

Another innovative strategy to control NP biodistribution is the subsequent particle modification via bioorthogonal reactions taking place in vivo. Bioorthogonal chemistry, which is a further development of copper-based click chemistry, meets requirements such as outstanding selectivity, feasibility in mild aqueous conditions, and high yields with a rapid reaction rate. [247,248] Since the functional groups of the reactant and the product do not interact with functional biomolecules and, as in contrast to the original click-chemistry, no toxic catalysts are necessary, bioorthogonal reactions can take place on cell surfaces or in the cytosol of living cells. [248,249] To influence particle biodistribution, pre-targeting (PT) concepts have been investigated that rely on highly specific covalent interactions between two bioorthogonal entities, of which the nanoparticle carries the first reactive group, while the other one is tagged for example to an antibody, a fluorophore, or a drug. [249,250] Either, the tagged ligand is initially injected, forming a targeting moiety for the subsequently administered nanoparticles, or targeted nanoparticles are injected first and a subsequently injected

drug or label reacts with the NP localized at the site of action. [249] (Fig. 10) The most studied reaction types in this context are the inverse electron-demand Diels-Alder cycloaddition (IEDDA) reaction [250,251] and the strain-promoted alkyne azide cycloaddition (SPAAC) [252,253].

So far, PT has mostly been applied in the context of tumor targeting [33,254,255] and in particular in the positron emission tomography (PET) imaging of tumors. [250,256,257] Nevertheless, this strategy could also be utilized for controlled biodistribution and drug delivery to

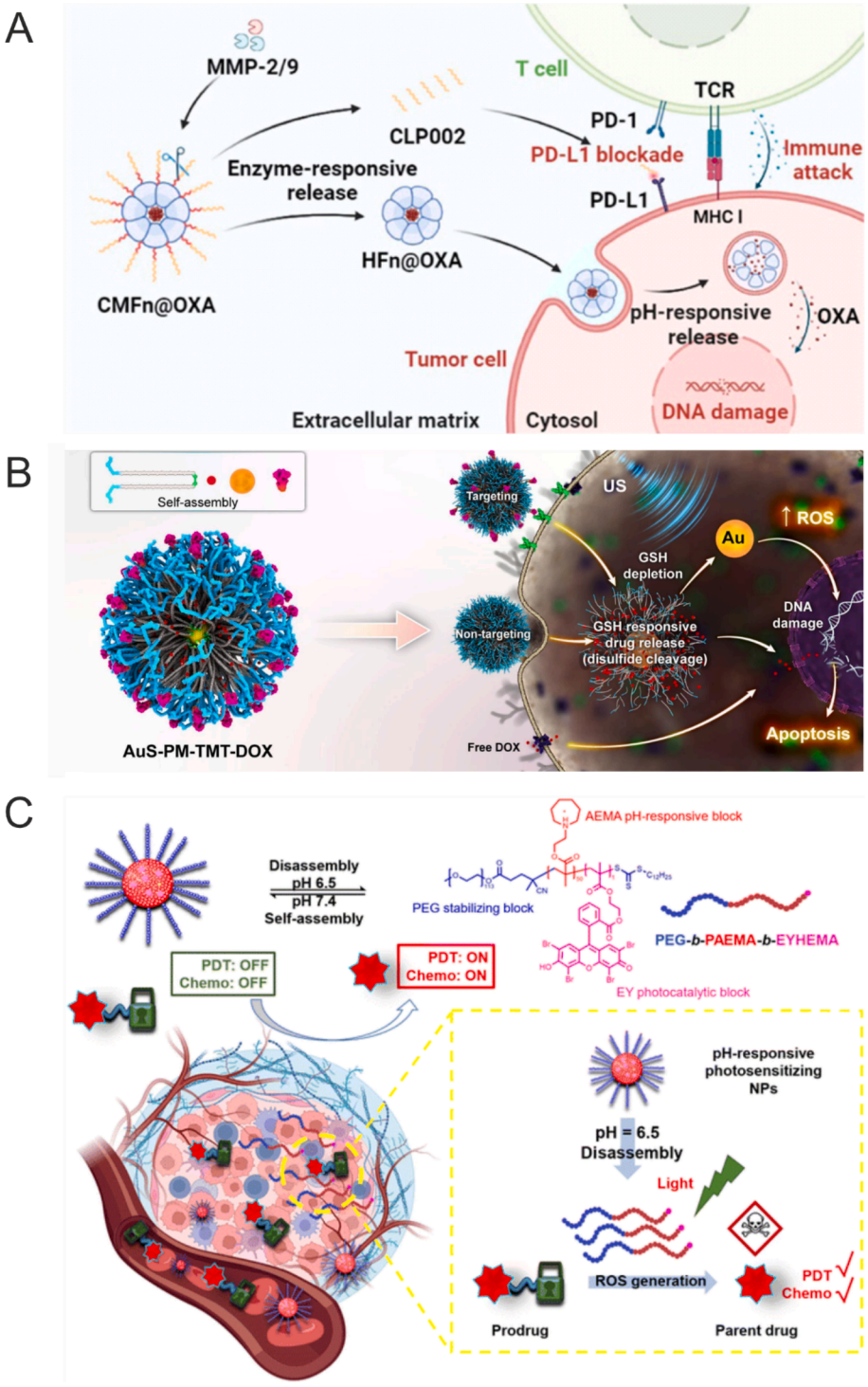


Fig. 9. Concepts of multi-responsive targeting systems. (A) Reprinted with permission from Ref. [222] Copyright (2024) American Chemical Society. Due to the enzymatic cleavage of MMP-2/9 the first active ingredient, CLP002 is released, which inhibits the PD-L1 receptor on the cell surface. Disassembly in the acidic environment of the *endo*-lysosomal compartment leads to the release of the second drug OXA. (B) Reprinted with permission from Ref. [182] Copyright (2024) American Chemical Society. Target cell recognition and endocytosis are mediated by the ten tumor metastasis targeting (TMT) peptide. Ultrasonic stimulation of disulfide linkages increased the ROS production and simultaneously led to a decrease in the GSH level. The disassembly of Polycaprolactone (PCL) under acidic conditions in the tumor microenvironment ultimately triggered the release of the encapsulated drug DOX. (C) Reproduction of material from Polymer Chemistry with permission from the Royal Society of Chemistry. [184] The nanoparticle disassembly in an acidic environment reveals the photocatalyst eosin Y. Upon light irradiation eosin Y then produces ROS, activating prodrugs for cancer therapy.

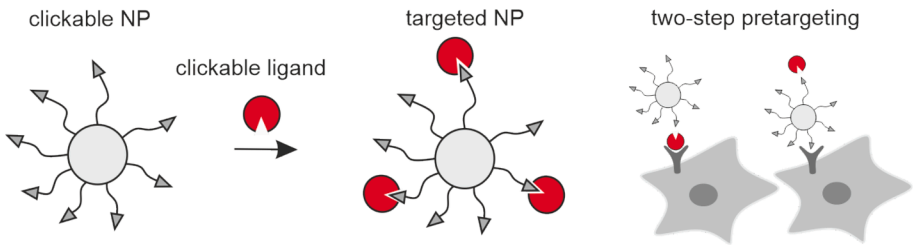


Fig. 10. Nanoparticle targeting using bioorthogonal chemistry. The target cell selectivity of nanoparticles can be increased by pretargeting concepts with a click-reaction between the nanoparticle and a clickable ligand at the site of action. Either a targeting ligand, e.g. an antibody, is administered first, which then serves as an anchor point for the drug-loaded nanoparticle (two-step pretargeting, left), or the nanoparticle itself binds to target cells via targeting ligands, which are attached to the NP surface. In a second step, a drug modified with a click entity can react with the nanoparticle and thus be addressed to the target tissue (two-step pretargeting, right).

other tissues by adapting the targeting moieties accordingly. One advantage of bioorthogonal chemistry-based targeting is that it allows a simple, flexible, and universally applicable NP modification. By tethering one click entity to the NP surface, the NP can easily be modified with a multitude of click partners and is thus suitable for various applications. Many counteracting molecules functionalized with bioorthogonal entities are commercially available and can thus serve as targeting ligands. Furthermore, the attachment of quite small click-entities prevents NP aggregation and cross-linking, which might be problematic for macromolecular ligands such as monoclonal antibodies (mAbs) or avidin. As a result, NP modification and purification are facilitated. [249] Additionally, PT may increase targeting effects by the amplification of available binding sites. One monoclonal antibody (mAb) can be tagged with up to 30 transcyclooctene (TCO) molecules, allowing the binding of several NPs [32], which simplifies detection in tumor imaging, but may also increase therapy efficacy for targeted drug delivery. [32,249] The research group of Yoo et al. (2019) [32] established a pretargeting strategy using TCO-modified trastazumab as targeting moiety and tetrazine-modified, drug-loaded nanoparticles that should be delivered to the site of action. The click-chemistry mediated binding allowed enhanced tumor targeting and thus showed that pretargeting is a promising strategy to maximize the amount of drug reaching the target site. For a more precise description of the reactions and possible biomedical applications of nanoparticles using bioorthogonal chemistry, we would like to refer to reviews focused on this topic. [249,258].

4. Opportunities and limitations of complex nanoparticle design strategies

Due to conflicting requirements and changing demands during the targeting and drug delivery process, the design of targeted nanoparticles is highly challenging. [169] Therefore, a systematic approach that considers the most important aspects of the specific application could improve therapeutic outcomes. However, this inevitably leads to more complex particle designs, complicating nanoparticle preparation, and hampering the reproducibility of results. Additionally, the attachment of a protein corona in biological media can alter the particles' identity, making it difficult to predict if in vitro processes will translate to living organisms. [48,148] Despite these challenges, several research groups have demonstrated that complex nanoparticle design can achieve very promising targeting results in vivo.

Maslanka et al (2020) [259] showed successful targeting of enzyme-responsive, hetero-multivalent particles to renal target tissue. Therefore, in the first step, the nanoparticles bound to the angiotensin II receptor type I of mesangial cells via the AT1R inhibitor EXP3174. Subsequently, the previously inactive second ligand angiotensin I was cleaved by the angiotensin-converting enzyme (ACE), which was expressed on the cell surface. The resulting active ligand, Angiotensin II, attached to the AT1R on the cell surface, promoting receptor-mediated uptake into the target cells. The amount of the dual-modified, enzyme-responsive nanoparticles reaching the target tissue in vivo was considerably higher than the amount of unmodified particles or particles with single-ligand modification. This demonstrated the superiority of the complex, 3-step targeting concept compared to simple nanoparticle targeting. (Fig. 11A).

Li et al. (2024) [260] developed a switchable crosslinked paclitaxel (PTX)-nanoformulation (BPM-PD@PTX) for the precise drug delivery to non-small cell lunger cancer (NSCLC) brain metastases. (Fig. 11B) The formulation incorporated an ultra-pH-sensitive boronate ester linkage and a lipid-like amphiphilic molecule, forming small-sized micelles and nanocomplexes by rapid cross-linking with PTX being loaded. This resulted in excellent biocompatibility and prolongation of the blood circulation time. The ultra-pH-sensitive boronate esters sealed the nanoformulation and effectively prevented premature drug release. Additionally, the external MA groups of BPM-PD@PTX induce glucose transporter 1 (GLUT1)-mediated transcytosis in the blood–brain barrier and blood-tumor barrier. The lower pH value in the extratumoral microenvironment (pH 6.8–6.5) resulted in transformational changes, forming smaller non-crosslinked micelles with enhanced penetrability. As a result, BPTA formed new boronate ester bonds with the sialic acid, which is overexpressed in NSCLC cells, enabling precise PTX delivery. Thus, the research group could achieve highly effective PTX delivery for NSCLC brain metastases with reduced adverse reactions and improved therapeutic efficacy and thus surpass the clinical PTX-nanoformulation (nab-PTX).

Although the in vitro and in vivo evaluations for complex, multi-step nanoparticle targeting systems are frequently highly promising, there are still major hurdles to clinical application. The definition of regulatory requirements and the establishment of GMP-compliant manufacturing processes are essential. This includes the development of standardized production processes and the control of particle size distribution and surface modifications to ensure the scalable, reproducible preparation and the quality control of the nanoparticles. Furthermore, the doses to be applied must be specified in order to reconcile both the safety and efficacy of the drug delivery systems. In particular, the analysis of the long-term toxicity is highly relevant, as nanoparticles might potentially accumulate in tissues and organs. Additionally, the pharmacokinetics of particle distribution and drug release characteristics must be evaluated to define the dosing intervals. In summary, it can be concluded that despite the significant advances in nanoparticular drug delivery with complex targeting and drug release systems, further investigation is required to translate the developed technologies into clinical applications.

5. Conclusion

The previous illustrations emphasize the complexity of nanoparticle targeting and targeted drug delivery. On the one hand, numerous factors must be balanced to develop a particle design that meets all requirements. On the other hand, extremely complex particle structures

impede the reproducible particle manufacturing. Furthermore, the synthesized particle identity may differ significantly from the biological identity in vivo. Nevertheless, there is growing evidence that a moderately complex, multi-step particle activation in situ may be advantageous and holds great potential to address current challenges in targeted nanotherapy. In conclusion, the development of nanoparticle-based drug delivery systems with a controlled time-variant structure, that changes during an application depending on the task the nanoparticle has to master, seems rather advantegeous. Therefore, key factors relevant to each specific application need to be identified and implemented

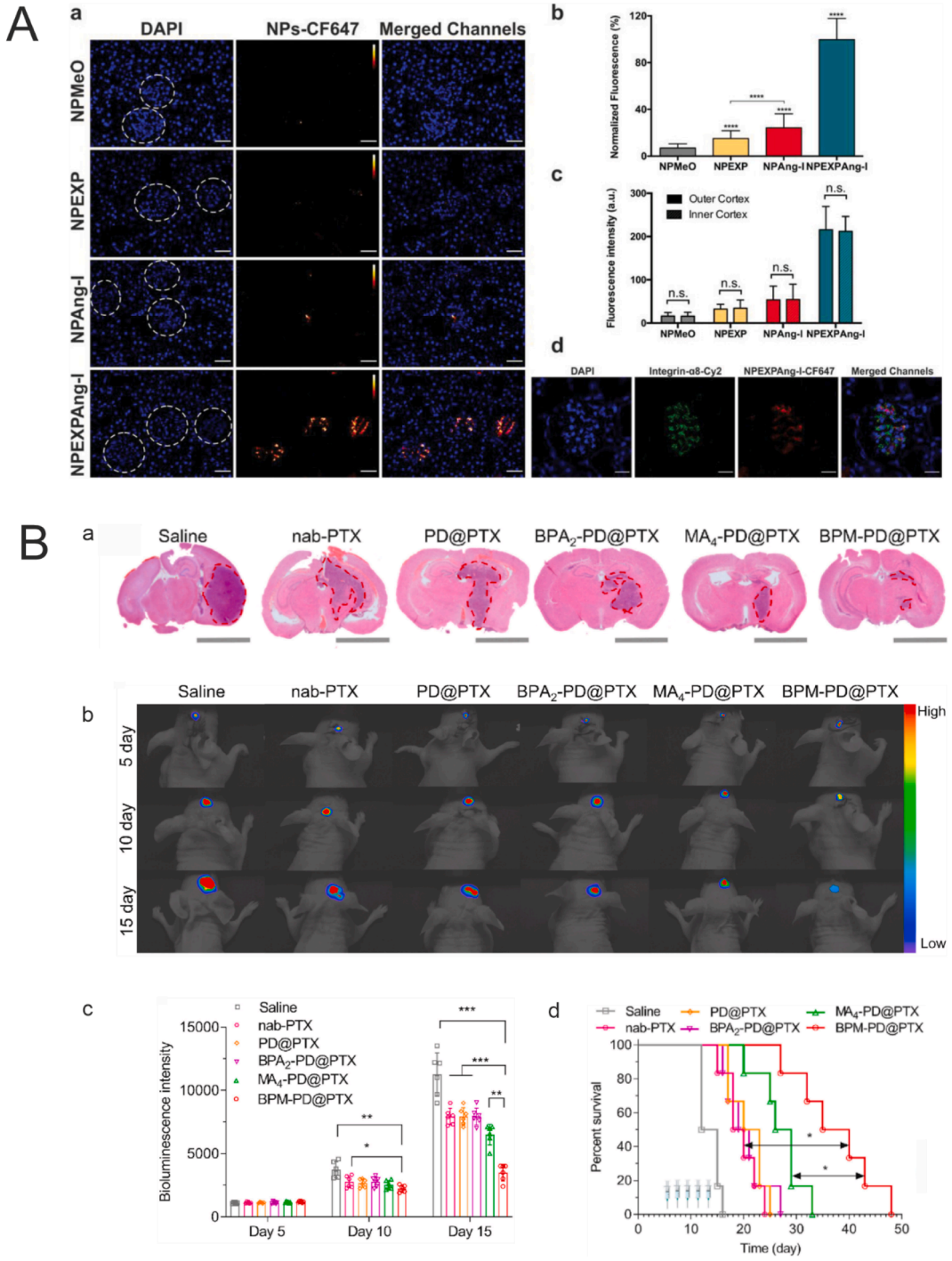


Fig. 11. In vivo investigations of nanoparticle targeting concepts. (A) Reprinted with permission from Ref. [259]. Investigation of the NP-associated fluorescence in kidney glomeruli analyzed via fluorescence microscopy. a) Kidney glomeruli (highlighted with white, dotted circles) treated with different particle formulations (without ligand, single ligand modification, hetero-multivalent particle design with enzyme-responsibility). Scale bar: 40 μm. b) Quantitative analysis of glomerular NP-associated fluorescence. c) Comparison of the NP fluorescence of the inner and outer cortex. d) Localization of NP-EXP-Ang-I via CLSM combined with integrin-α8-staining of mesangial cells. Scale bar: 20 μm (B) Reprinted with permission from Ref. [260] Comparison of nanoparticle albumin-bound PTX (nab-PTX) with nanoformulation where PTX is loaded between two types of dendrimer-modified amphiphilic molecules (BPA2-PD and MA4-PD) and sealed using ultra-pH-sensitive boronate ester linkages (BPM-PD@PTX), preventing premature drug release. Furthermore, the effect was compared to PTX combined with the individual components (PD@PTX, BPA2-PD@PTX, MA4-PD@PTX). a) Hematoxylin-eosin (HE) staining of the brain at day 15 after tumor inoculation. Scale bar = 300 μm.b) Tumor growth evaluation by bioluminescence imaging. c) Quantitative analysis of bioluminescence staining. (n = 6) d) Kaplan-Meier survival curve during treatment. (n = 6).

into the nanoparticle design. Finally, the efficacy of the developed concepts need to be verified in case-by-case studies in vivo to obtain reliable results.

CRediT authorship contribution statement

Melanie Bresinsky: Writing – original draft, Visualization, Validation, Conceptualization. **Achim Goepferich:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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