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LEVERAGING PHYSIOLOGY FOR PRECISION DRUG DELIVERY

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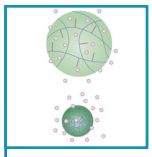

Sun W, Hu Q, Ji W, Wright G, Gu Z. Leveraging Physiology for Precision Drug Delivery. *Physiol Rev* 97: 189–225, 2017. Published November 9, 2016; doi:10.1152/physrev.00015.2016.—Physiological characteristics of diseases bring about both challenges and opportunities for targeted drug delivery. Various drug delivery platforms have been devised ranging from macro- to micro- and further into the nanoscopic scale in the past decades. Recently, the favorable physicochemical properties of nanomaterials, including long circulation, robust tissue and cell penetration attract broad interest, leading to extensive studies for therapeutic benefits. Accumulated knowledge about the physiological barriers that affect the in vivo fate of nanomedicine has led to more rational guidelines for tailoring the nanocarriers, such as size, shape, charge, and surface ligands. Meanwhile, progresses in material chemistry and molecular pharmaceutics generate a panel of physiological stimuli-responsive modules that are equipped into the formulations to prepare "smart" drug delivery systems. The capability of harnessing physiological traits of diseased tissues to control the accumulation of or drug release from nanomedicine has further improved the controlled drug release profiles with a precise manner. Successful clinical translation of a few nano-formulations has excited the collaborative efforts from the research community, pharmaceutical industry, and the public towards a promising future of smart drug delivery.

I. INTRODUCTION

Physiological barriers dwindle the convenience and efficacy of drug administration, demanding the development of drug delivery systems (DDSs) (73, 116, 299, 329, 359, 461). DDSs, including devices and formulations (111, 262, 423, 456), were designed to meet the physiological traits of diseases for improved pharmacokinetic and pharmacodynamic properties of drugs (165, 218, 293, 319). In the meantime, extensive research efforts in DDSs generated a large collection of publications covering multiple disciplines (20, 77, 105, 170, 353, 369, 386, 415, 428).

DDSs have evolved during the last six decades and could be briefly classified into three generations (322, 330). Early systems (since ~1950s) were designed as oral formulations (289) or transdermal patches for delayed drug release (457). Basic principles for drug release were established, such as diffusion, dissolution, osmosis, or ion exchange, during this period (426). The second generation controlled release (since 1980s) mainly refers to the efforts to keep a constant drug concentration in the blood (321). Few second generation DDSs entered the market (370), but the development of bioresponsive polymers during this period paved the way for more controllable DDSs (331). The emerging third generation of DDSs based on nanomaterials (since ~2010) was proposed with modular and tunable physiolochemical properties (110) to facilitate the prospect of "precision medicine" (68, 220, 420), where personalized genomics data would be taken into account for customized drug administration and optimized pharmacokinetics (66, 81, 276, 440).

In this review, we will start with a big picture of the drug delivery field concerning the basic rationale for why, what, and how drugs are delivered for improved therapeutic efficacies. Then we will focus on the latest drug delivery platform, nanocarriers, with cancer as a model disease to describe the physiological barriers and corresponding strategies for target drug delivery. Recent strategies for devising "smart" nanomedicine will also be discussed with the aim of harnessing physiological cues for controlling the targeting and release behaviors of the nanocarriers, such as activated cellular uptake or stimuli-responsive drug release. Lessons learned from FDA-approved nano-formulations or

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formulations undergoing clinical trials will also be discussed.

II. OVERVIEW OF DRUG DELIVERY SYSTEMS

A. Why Deliver?

It is well accepted that pharmaceutical agents administered via different routes **(FIGURE 1)**, especially through systemic administration, often lead to adverse side effects even though pharmaceutically beneficial effects could be achieved. To address this dilemma, DDSs, developed in the form of either formulations or devices (278), work as media between the drugs and the patients. These forms enhance the therapeutic efficacy and safety of the drugs by improving their absorption, distribution, metabolism, and excretion (ADME) profiles (141, 509). An ideal DDS should be able to shield the therapeutics from unwanted physical or physiochemical damages and deliver the right amount of drugs to the right location to act within the body during the right period of time (133). Decades of development enabled DDSs with a wide array of beneficial properties to improve the pharmacokinetic and pharmacodynamic profiles of drugs (101), uncovering a wealth of opportunities for bringing Ehrlich's concept of "magic bullet" to life (155).

1. Absorption

DDSs can help enhance the absorption of drugs, promoting their transportation from the site of administration into blood circulation by *1*) improving the solubility of poorly dissolvable drugs or *2*) changing the route of drug administration (288, 337). Therapeutic efficacies of hydrophobic drugs are often hampered by their low water solubility, which could be mitigated by loading the drugs into amphiphilic material-based formulations (241, 248) or milling the therapeutic compounds into nanocrystalline particles (34, 194, 273). For example, the surfactant-based self-emulsifying DDSs could keep hydrophobic drugs in fine emulsions, making them easier to be absorbed from the gut when administered orally (343). Additionally, the oligosaccharide cyclodextrin (CD), characterized by its hydrophobic internal cavity and hydrophilic external surface, is a popular excipient for improving the solubility of therapeutics, such as the hydrophobic anticancer drugs camptothecin (CPT) (191) and SN-38 (315), by forming host-guest inclusion complexes (80). With the assistance of some nonionic or ionic stabilizers, NanoCrystal Technology applied high shearing forces to mill micron-sized drug crystals into stably dispersed nanoparticles (273), where the subcellular size of nanoparticles enabled them to penetrate the capillary walls. The NanoCrystal Technology has brought about numerous clinically approved formulations, including the immunosuppressant drug Rapamune and the antiemetic drug Emend (509). In contrast to changing the physiochemical properties of the drugs, switching the drug administration route is a straightforward method for enhancing drug absorption. For the noninvasive drug administration routes, such as oral administration (363), absorption of most drugs is mainly a process of passive diffusion across the gastrointestinal (GI) tract, where the concentration gradient of the drug is the main driving force for diffusion, leading to limited absorption rate. In addition, the existence of some efflux mechanisms, such as the P-glycoprotein that can excrete drug from vascular circulation into the intestinal lumen, further limits the absorption of orally administered drugs. Furthermore, metabolism of the administered drugs in the GI tract or the liver before they reach the blood circulation, known as the first pass metabolism, could also reduce the bioavailability of the drugs. To bypass these limitations, parenteral administration routes were explored with numerous types of DDSs being developed. Accurate dosing and rapid absorption by intravenous (IV) or intramuscular (IM) injections are widely used for administering

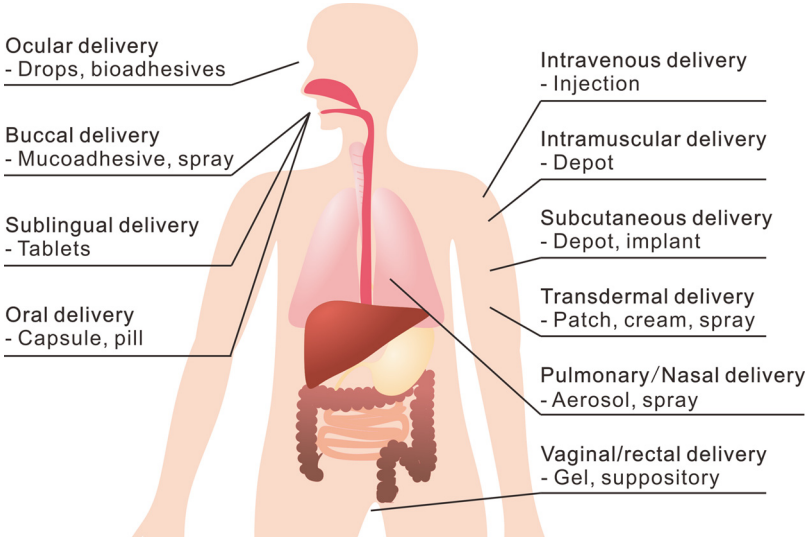

FIGURE 1. Typical routes of drug administration that include ocular, subligual, buccal, oral, intravenous, intramuscular, subcutaneous, transdermal, nasal, pulmonary, vaginal, and rectal routes. Different drug delivery systems were developed to overcome various physiological barriers associated with the routes. The physiochemical properties and therapeutic targets of the drugs determined the choices of drug administration routes.

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drugs. However, the pain associated with these methods elicited people's interest in less invasive surrogates. For examples, microneedle-array has emerged as a great alternative due to its low cost and simplicity for drug administration (200, 477). Recently, a smart insulin patch made of painless microneedle arrays containing glucose-sensitive vesicles was demonstrated for convenient treatment of type 1 diabetes, which held great promise to relieve diabetic patients from the pain of injecting insulin (487).

2. Distribution

DDSs can help control the spatial-temporal distribution of delivered drugs (361). The control of spatial drug distribution, which generally refers to the process involving transporting drugs from blood circulation into the tissues, aims to direct drugs specifically into the site of action; while the temporal control is meant to regulate the timing of drug release or pro-drug activation. DDSs, especially nanocarriers, could be functionalized with specific targeting agents to bind to different types of diseased tissues (8, 328). For example, monoclonal antibody HER2 can target anticancer drugs toward HER2-positive breast tumors, enhancing the therapeutic efficacies by the order of 100–10,000 times (510). Peptides targeting adipocytes are capable of guiding nanoparticles containing small interfering RNA (siRNA) into fat-storing tissues for treating obesity (466). Monosaccharides and their derivatives like galactose and *N*-acetylgalactosamine are able to target transcription factor or siRNA into the hepatocytes (224, 263, 298). To control the timing of drug release or activation, DDSs incorporating stimuli-responsive moieties were designed (247) for different types of physiological factors, such as glucose levels (281, 436, 496), pH gradients (189, 236, 317, 401), redox gradients (121, 171, 266, 335), overexpressed enzymes (23, 161), and ATP gradients (398).

3. Metabolism and excretion

DDSs can alter the metabolism and clearance of delivered drugs through *1*) altering the routes through which drugs are transported within the body, 2) shielding the therapeutic agents from adverse physiochemical environments, *3*) delaying drug release, and *4*) bypassing the active drug efflux transporters (441, 444). The liver and kidney are the major sites for drug clearance. Drugs administered into the body generally undergo metabolic changes, especially in the liver, which is known as "biotransformation" (460). Different types of hepatic enzymes, mainly oxidases and transferases, transform drugs into more clearable derivatives, significantly affecting their half-life, clear rate, and bioavailability. Drugs absorbed by the GI tract will go through the liver via the portal vein before reaching systemic circulation, a circumstance known as the "first-pass effect" that influences the bioavailability or activity of many orally administered drugs (414). Turning to other parenteral drug administration routes, such as transdermal (345), buccal (151), nasal (173), rectal (304), or vaginal (357), could directly bypass the portal venous system. Alternatively, formulations could also help drugs to circumvent hepatic metabolism. For example, the lipid-based nano-formulations could be engineered to make use of the lymphatic system for distribution even after oral administration (6). When drugs enter the blood by different delivery methods, multiple clearance mechanisms exist for eliminating drugs from circulation, such as digestive enzymes, the mononuclear phagocytic system (MPS), and renal clearance (135, 290). Drug delivery formulations encapsulating drugs in a closed compartment could prevent them from enzymatic attacks in numerous types of physiological environments. For example, an in situ polymerized nanogel coating on biomolecular therapeutics could shield proteins from protease digestion (132, 478) as well as protect DNA from DNase (400) or miRNA from RNase (235) degradation. PEGylation, a technique of covalently conjugating poly(ethylene glycol) (PEG) onto therapeutic agents or DDSs, has become a widely adopted strategy for improving the stealth of drugs or DDSs (355). The highly hydrophilic PEG absorbs a large extent of water that can function as a natural barrier to isolate the loaded cargoes from enzymatic degradations, preventing the therapeutic agents from being sequestered into MPS and reducing glomerular filtration by increasing the hydrodynamic size of the formulations.

Compared with adjusting the interaction between drugs and the physiological environments (131), sustained drug release systems provide an effective way for controlling drug clearance (156, 219, 240). Implantable depots capable of continuously releasing drugs for days or even months are convenient systems for delivering fragile drugs, which generally undergo rapid metabolism or clearance, with improved patient compliance (39, 106). After repeated treatment by the same therapeutic agents, in particular with chemotherapeutics, cancer cells would become resistant to that drug or its homologs by overexpressing active efflux transporters of the ATP binding cassette (ABC) containing protein family (374). Nanoparticle-based DDSs can bypass these transmembrane multidrug resistance (MDR) transporters by targeting other receptors on cancer cell membranes (37, 201), co-delivering an inhibitor of the transporters, or incorporating stimuli-responsive drug release that could also significantly block the MDR (85).

B. What to Deliver?

Tailoring a carrier for a drug requires investigation of the chemical composition and target site of the drug (169). Drugs having the same molecular composition and functioning against physiologically proximal targets generally face the same barriers for delivery (279), thus can be delivered by analogous strategies. Deliverable therapeutics include small molecule drugs, proteins, nucleic acids, and

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therapeutic cells. Small molecule therapeutics are classic drugs that make up the majority of drugs on the market (234). They are frequently developed as regulators, mainly inhibitors, of target proteins or other biomolecules (174, 303). Compared with biologics, small molecule drugs can reach targeted sites relatively easily and penetrate through cell membrane effectively. Even though small molecule therapeutics remain the primary type of available drugs, recent years have witnessed a considerable increase in FDA-approved biologics, mainly protein therapeutics, from 7% in 2013 to 27% in 2014 (294). Proteins participate in all life activities, including transporting biomolecules or transducing signals within and between cells, driving biochemical reactions, and supporting cellular or tissue scaffolds (350). Unlike small molecule drugs that are limited to simple functionalities, protein therapeutics perform more diverse yet specific activities that could be typically classified into *1*) replacing or replenishing deficient proteins, *2*) targeting specific molecules, and *3*) vaccination (222). Proteins are usually impermeable to the cell membrane as a result of their relatively large size and electrostatic charges, making extracellular targets more accessible to protein therapeutics. Recently, encouraged by the advances in the intracellular protein delivery systems (133), proteins functioning in intracellular compartments hold great potential for healthcare applications. Nucleic acids represent a broad class of therapeutic molecules with applications in immunotherapy and gene therapy. Pathogen-derived nucleic acids, such as the CpG motif targeting Toll-like receptor 9 (TLR9) in the endosome to stimulate immune cells or viral genomic fragments capable of vaccinating the recipient (439) are efficient alternatives to protein-based immune therapeutics. Gene therapies based on the delivery of nucleic acids are regarded as promising individualized treatments towards various types of life-threatening genetic disorder-associated diseases, such as cancer, AIDS, diabetes, or other hereditary diseases (195, 388). A diverse array of therapeutically active nucleic acids, including antisense nucleotides (16), small interfering RNA (siRNA) (43, 512), microRNA (miRNA) (55, 214), plasmids (375), mRNA (367, 494), or genome editing tools (69, 257) have been discovered. Nucleic acid-based gene therapies must be delivered intracellularly, making the development of efficient vehicles to deliver these drugs extremely important to take advantage of nucleic acid therapeutics (136, 190, 484). In addition to delivering chemically definable molecules, entire cells can also serve as therapeutics either in the context of the natural antigens on the cell membrane or from the perspective of living cells as a functional entity. The antigenicity of exogenous cells could be used to train human immune systems by mimicking natural infections. There has been a long history of using inactivated or suppressed pathogens as vaccines against epidemic diseases (95, 128, 243). Recent development of cell-based vaccines (82) or chimeric antigen receptor modified T-cell therapies (130) even cast light on the treatment of endogenously originated diseases, including cancer. Living cell-based therapies focused on replenishing functional cells to diseased organs, working in an organ replacement manner (310).

C. How to Deliver?

To meet the physiological requirement of various drug targets, numerous types of DDSs were developed ranging from macro-, to micro-, to nanoscale. Macroscale DDSs generally refer to drug delivery devices with at least one dimension greater than 1 mm in size (193, 342). Macroscale devices were developed in varying forms, such as wearable devices (17, 205), mucoadhesives (425), and long-term drug-releasing implants (202, 419). From the perspective of material, polymers are preferred for preparing physiologically compatible DDSs (87, 114, 219, 452). Representative polymers for these devices include natural polymers like dextran, alginate, chitosan, gelatin, or synthetic polymers such as poly(lactic-co-glycolic acid) (PLGA) or poly(β-aminoester) (281). Drugs could be loaded into either a "reservoir," where the drugs are enclosed by a polymeric membrane, or a "matrix," where the drugs are embedded in polymeric networks (393). Release of the drugs could be through diffusion, where the steric hindrance from the polymer scaffold dominates; competitive dissociation, where the drug exhibits specific affinity towards the polymeric carrier; or degradation, where the polymer scaffold could be eroded via dissolution, hydrolysis, or enzymatic digestion (231). Sensitivity to environmental signals could also be incorporated into polymeric systems for smart drug delivery (348). DDSs in the microscale are generally referred as microparticles that are injected locally in the tissue. Microparticles with a large diameter (>1 μm) would get stuck in the capillary bed or get caught by Kupffer cells in the liver, making them unsuitable for systemic injection (287). When administered locally, steric hindrance from the extracellular matrix will limit the movement of microparticles and hold the microparticles in the site of injection. This feature leads to widespread applications of microparticles as drug depots (134).

Unlike microparticles, the nanoscopic size (generally $<$200 nm) enables the nanocarriers to filter through the fenestrations of liver blood vessels as well as penetrate into tumor tissue by EPR effect (252, 260, 344). Of note, EPR effect is not a unique phenomenon limited to solid tumors, but a more prevalent character exhibited by many types of diseases, for example, fungal infections, heart failure, hepatitis A, sclerosis, and renal-associated diseases (18, 216, 261, 499). The size of the nanocarriers needs to be meticulously controlled since lager nanocarriers ($>$500 nm) are susceptible to macrophage uptake while smaller nanocarriers ($<$8 nm) are easily cleared out via renal excretion pathway. Nanocarriers have become a widely investigated DDSs with

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cancer as the most researched target (60). Various types of material have been demonstrated to construct the nanocarriers (125), such as the polymer-based nanogels, micelles, polymersomes, and dendrimers (12, 44); the lipid-based solid lipid nanocarriers, liposomes (327), or lipid-like lipidoids (2); the inorganic nanocarriers, including gold nanoparticles (179, 221), carbon nanotubes, graphene (259), nanodiamonds (285), magnetic particles (120), and liquid metal nanoparticles (244); the macomolecular assembly-based DNA (53, 306, 416) and protein nanocarriers (186).

III. PHYSIOLOGICAL BARRIERS AND DESIGNING CRITERIA FOR DRUG DELIVERY SYSTEMS

The ability to direct therapeutic levels of drugs to the desired site is a prerequisite to achieve efficacious outcomes in treating a variety of diseases. Cancer is the best representative of these diseases, where sufficient accumulation of potent anticancer drugs is the goal for applying nanocarriers. However, physiology poses different barriers to impede nanocarriers from realizing this distant goal (177). For a better concept on how to design cancer-targeting nanocarriers, the sequential barriers from extracellular space to intracellular compartments **(FIGURE 2)** after intravenously administering the nanocarriers will be introduced. Corresponding strategies to overcome these barriers will also be discussed.

A. Extracellular Barriers

1. Nanoparticle-immune system interaction

When the nanocarriers are injected into blood circulation, rapid adsorption of serum protein onto the nanocarrier occurs. Numerous types of protein, such as fibrinogen, globulin, and albumin, will form a corona around the nanocarriers, a process termed as opsonization. This nanoparticle-protein complex is very susceptible for uptake by circulating or residential phagocytes (409, 443). The opsonization-internalization mediated nanocarrier clearance works as the first and major barrier in the blood, causing ~50% loss of the administered dose hours after injection (286). In addition, the opsonization causes collateral damage to the targeting ligands modified on nanocarriers by shielding them from interacting with the targeted receptors (368). Opsonization is affected by surface properties of the nanoparticles, such as particle size, surface charge, shape, hydrophobicity, and biological functionalities (101, 175). Generally, cationic nanoparticles are more susceptible to MPS clearance than neutral or negatively charged ones (338). By far, the most well-established strategy for evading opsonization and MPS is to coat or graft the surface of the nanocarrier with PEG, a process termed as PEGylation (146). As for the mechanism for PEGylation, it is generally thought that the highly hydrophilic PEG could efficiently capture water molecules and form a hydrating layer on the nanocarriers, hindering serum proteins from adsorption. Instead of ascribing the "stealth effect" to protein repellence, a recent report by Wurm and co-workers highlighted

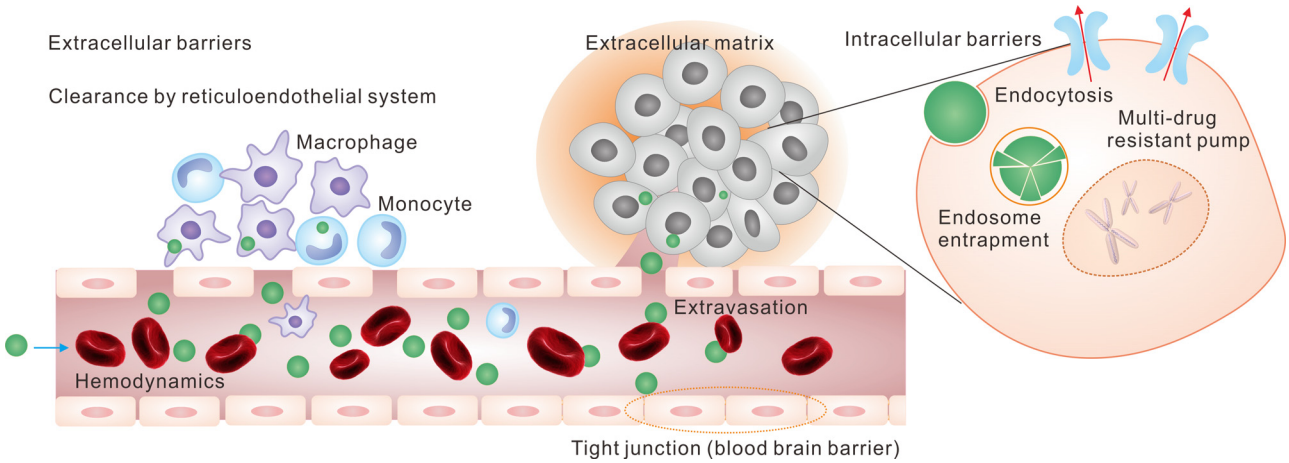

FIGURE 2. Physiological barriers for nanocarrier-based drug delivery system. Nanocarriers enter the systemic circulation by intravenous injection and undergo opsonization by interacting with serum proteins. The opsonization facilitates nanoparticle clearance by reticuloendothelial system, leading to nonspecific accumulation of nanocarriers in organs like liver and spleen. In the blood flow, fluid dynamics of the nanocarrier influences their margination towards vascular walls. The low permeability of vascular endothelium poses another significant hurdle for nanocarriers, especially the tight junctions associated with the blood-brain barrier. After extravasation into tumor microenvironment, the nanocarreir needs to diffuse through the dense extracellular matrix against high interstitial pressure to reach the tumor cells. For drugs that work in intracellular compartments, the nanocarrier needs to be internalized through endocytosis and escape the endosome to reach other organelles. Even after entering in the cells, the cell membrane-associated multidrug resistant pumps could also pump out the delivered chemotherapeutics.

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the role of changed composition of remained protein corona (376). The accumulation of a lipoprotein (clusterin) rather than coagulation-related proteins was shown to be sufficient for reducing nonspecific uptake. Huang et al. (203) pioneered the PEGylation approach for cloaking nanoparticles with PEG and enhancing their circulation time. Conformations of the PEG on the nanocarrier surface are significantly affected by PEG density, from the mushroom conformation (low PEG density) to transition state (intermediate density), and to the brush mode (high density) (479). Grafting sufficient density of PEG chains, preferably high-density PEG, to cover the surface of the nanocarrier is key for enabling full protection of the nanoparticle and preventing opsonization (228). In addition to the classic PEGylation, polymeric PEG substitutes or new "stealth" strategies based on biomimetic components were also demonstrated by different research groups. Zwitterionic polymers pioneered by Jiang and co-workers could induce hydration electrostatically and resist protein adsorption effectively, leading to ultralow fouling on nanocarriers or implatable devices (182, 498). Zhang, Gu, and their co-workers recently demonstrated a strategy harnessing the natural long-circulating capability of human platelets for evading opsonization (160, 162, 164). Polymeric nanoparticles cloaked by platelet membranes exhibited reduced macrophage recognition than the uncoated nanoparticle (11). Using a more direct approach, Discher and co-workers (356) used a peptide derived from CD47 on the cell membrane as a "marker of self." Modifying nanocarriers with the "self" peptide significantly inhibited phagocytosis and prolonged the circulation time.

While it is necessary for cancer cell-targeted nanoparticles to avoid immune system surveillance, efficient interactions with immune cells, such as binding or internalization, are desirable for cancer immune therapy (19, 140). The basic rationale behind cancer immune therapy is to mobilize the immune cells to raid cancer cells, an elegant strategy that has made revolutionary progress towards eradicating existing cancer cells and preventing future recurrence (142). The expression of tumor-associated antigens (TAAs), including neoantigens, proteins expressed from mutated genes, or proteins with altered modification patterns, could tell cancer cells apart from normal cells (380). Nanoparticles deliver TAAs to professional antigen-presenting cells (APCs), like dendritic cells, leading to the presentation of TAA-derived fragments to T-lymphocytes and activating TAA-specific cytotoxic T-cells (107). Additionally, adjuvants capable of magnifying the responses of APCs or T-cell, such as Toll-like receptor agonists, could be incorporated into the nanocarriers (250). Small nanoparticles (ideally 10–40 nm) generally exhibit more efficient infiltration into the immune organs and generate stronger interaction with dendritic cells (384). In this way, nanomedicine serves as "cancer vaccine." In addition to delivering TAAs, blocking the inhibitors of T-cell activation, such as transforming growth factor-β (TGF-β), CTLA4, and PD-L1, also emerged as an effective approach for cancer immune therapy (72, 320, 445). Monoclonal antibodies towards checkpoint inhibitors, including Ipilimumab (target CTLA4), Nivolumab, and Pembrolizumab (target PD-1), were approved by FDA, and the PD-1 antibodies were further designated as "breakthrough therapy."

2. Hemodynamics

In cases where nanocarriers escape MPS internalization, the nanocarriers need to interact with vascular endothelial walls, especially at the tumor site, to extravasate into the tumor tissue. In this process, fluid dynamics of the nanocarriers in blood vessels play an important role for the contact (277). Movements of nanocarriers after administration could be classified as circulation, margination, adhesion, and internalization by endothelial cells (75). Among these movements, margination of nanocarriers towards blood vessel walls is an important contributing factor for promoting the particle-endothelial cell interaction. Generally, red blood cells tend to flow in the center of the blood vessel, forcing platelets to accumulate near the blood vessel walls (74). As for nanocarriers, their distribution would be significantly affected by their size and geometry (278). For the typical spherical nanocarriers, such as small liposomes with a size of 10–100 nm, a small fraction of the administered nanocarriers could marginate to blood vessel walls during circulation (418). Anderson and co-workers (75, 475) demonstrated a synthetic lipid-based nanoformulation that could complex small RNA therapeutics into multi-lamellar liposome-like structure with sizes ranging from 35 to 60 nm. The nanocarrier efficiently avoided the capture by immune cells or hepatocytes and shuttled the RNA cargo into endothelial cells as well as solid tumors in the lung (75, 475). Aside from size, this margination could be enhanced by tuning the geometries of the nanocarriers. For example, discoidal or ellipsoidal nanocarriers could tumble and roll during circulation, and the nanoparticles could oscillate between opposite sides of the blood vessel walls, increasing the chance of contacting endothelial cells (33). It has been reported that the aspect ratio of these particles correlates with their drifting velocities toward the vessel walls, affecting their adhesion and accumulation at tumor sites (413). In a recent report, drug-conjugated poly(L-glutamic acid) released in situ from a micro-size vascular depot could self-assemble into nanoparticles (472). This dynamic strategy improved vascular dynamics of the nanopartilce and enhanced its tumor tropism.

3. Abnormal vasculature: EPR effect and interstitial fluid pressure

While the sealing of endothelial cells by tight junction proteins formed the blood-brain barrier (BBB) (305), the ag-

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gressive angiogenesis of the tumor generates tortuous blood vessels with leaky "gaps" (63, 455). Nanocarriers could extravasate into the tumor microenvironment through the leaky vasculature and remain there due to reduced lymphatic drainage (253). In addition to the traditional concept of "static gaps," recent studies further support the EPR effect with "dynamic vents" that formed spontaneously along the tumor vessels, allowing the extravasation of nanoparticles (70 nm) into the interstitial space (264). EPR effect has become the number one principle for designing nanocarriers in drug delivery as it is highly strong in cancers. Numerous nanocarrier-based anticancer DDSs based on the EPR effect have been approved for clinical use, such as the liposome nanocarrier encapsulating doxorubicin (Doxil) or the paclitaxel-albumin stabilized nanocarrier (21, 91). However, challenges remain for harnessing the EPR effect for anticancer therapy. A tumor is not a homogeneous tissue; both tumors in clinical circumstances and in animal models are highly diverse (126). Vascular densities vary with the stages of the cancer as well as the types of the tumors (153, 251). Tumors with a high-density vasculature, such as renal cell carcinoma or hepatocellular carcinoma, tend to have a high EPR effect, while those with a low-density vasculature, such as prostate or pancreatic cancers, tend to exhibit low EPR effect (108). To conquer the heterogeneity of the EPR effect, methods for increasing blood pressure with angiotensin II (252) or vascular normalization (42) were demonstrated. Rather than increasing vascular pressure, a strategy for improving vascular permeability with TGF-β inhibitor was also proposed by Kataoka and co-workers (40). The uneven vasculature of tumors brings about the EPR effect as a powerful tool for cancer-targeted drug delivery. However, the same mechanism could also cause the extravasation of an excessive volume of fluid into the tumor microenvironment, increasing interstitial fluid pressure (IFP) and viscosity (458). Other tumor-associated factors could also contribute to the IFP, such as the poor lymphatic drainage (421), steric stress from the aggressively proliferating cancer cells, considerable fibrosis, and compact extracellular matrix. The interstitial blood flow is the major force for distributing nanoparticles in the tumors. However, the elevated IFP poses a barrier for the extravasation and diffusion of nanoparticles to different regions of the tumor, especially to the tumor parenchyma, leading to reduced yet heterogeneous drug delivery and compromising therapeutic efficacies (402). To overcome the IFP barrier, strategies targeting the IFP inducing factors were demonstrated, such as reducing angiogenesis by blocking VEGF (188, 417) and reducing collagen density in the extracellular matrix (52). Overall, the EPR effect and IFP constitute contradictory forces in the process of nanoparticle extravasation into tumor; a balance of these two forces needs to be taken into consideration for devising effective solid tumor targeting nanocarriers (394).

4. Extracellular matrix

Nanocarriers that successfully overcome the barrier of vascular endothelial membrane will reach the tumor microenvironment and meet the next obstacle, namely, the extracellular matrix (ECM) (242). The ECM is a complex network composed of various types of networked macromolecules, including polysaccharides, proteoglycans, proteins, and glycoproteins (292). The ECM interacts with the tumor cells in a reciprocal way: the ECM offers a framework affecting tumor morphology and development, the cells are continuously constructing or rearranging the ECM (35, 324, 349). The physical rigidity of the ECM poses significant steric hindrance for nanoparticle diffusion, trapping the nanoparticles or inducing premature drug release before reaching the tumor (49). The ECM could be structurally divided into two parts: the basement membrane and the interstitial matrix. The basement membrane is constructed by stroma, epithelial and endothelial cells together to function as a scaffold for the mural and endothelial cells, while the interstitial matrix is primarily built by the stroma cells (358). The basement membrane is a continuous and compact sheetlike structure mainly composed of type IV collagen, fibronectin, laminins with entactin, and nidogen as linkers (13). Ratios of the constituents vary between different tumors or different sections of the same tumor, contributing to the heterogeneity of tumors. The porous basement membrane does not elevate IFP and the nanocarriers penetrate the basement membrane through passive diffusion. Penetration efficacies of the administered nanocarriers were mainly affected by the collagen fiber densities and pore sizes (4, 226, 403). To overcome the barrier of the basement membrane, a transient window of basement membrane remodeling could be harnessed. The window is created by angiogenesis, which demands the degradation of type IV collagen by matrix metalloproteases (MMP2 or MMP9) (309, 433). Slightly different from the basement membrane, the interstitial matrix is charged and highly hydrophilic with primary constituents including proteoglycans, fibrillar collagens, fibronection, and tenascin C (50, 379). Thick aligned type I collagen fiber is the main composition of the collagen. Combined with the restricted volume of interstitial space, the interstitial matrix is denser than the basement membrane (138). The accumulated tension leads to increased IFP, making it more difficult for nanocarriers to diffuse through. To overcome this barrier, several strategies have been demonstrated. For example, degrading the matrix with co-administered collagenase or hyaluronidase (97, 98, 127, 505), dilating the matrix pores by hypertonic solution (267), or decreasing the crosslinking of collagen fibers (255) could all significantly enhance the diffusion of nanocarriers.

B. Intracellular Barriers

While a small fraction of anticancer therapeutics target specific receptors on cancer cell membranes, such as antibodies

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and cytokines (210, 311), most drugs need to be delivered to intracellular targets to exert effect (453). Therefore, following extravasation into the tumor site, it is desirable that the nanocarriers are capable of shuttling the cargoes into an intracellular compartment. To reach the targeted subcellular compartment, more barriers arise from the subcellular structures of the cells (352).

1. Internalization

Small molecular therapeutics, especially those with high hydrophobicity, are capable of passively diffusing through the lipid bilayer plasma membrane (435). However, for protein or nucleic acid-based therapeutics, nanocarriers are generally needed for transportation into the cells (133, 318). Numerous internalization pathways exist, and the entry is affected by various properties of the nanocarrier, such as particle size, surface charge, physiochemical composition, and the modification with targeting ligands (500). For nanocarriers that are not modified with any specific targeting ligand, the uptake is mainly through endocytosis (387), where vesicles emerge from plasma membrane to encapsulate and internalize the nanoparticles together with extracellular fluids. Size plays a major role in demining the endocytosis pathway. Large particles (up to 1 μm) usually enter the cells by macropinocytosis, and the clathrin-dependent pathway generally takes up nanoparticles smaller than 120 nm (67, 270). Smaller nanoparticles could be internalized through the caveolae-dependent pathway (50–100 nm) or the clathrin- and caveolae-independent pathway (<50 nm) (1). The size cut-off is indefinite, and surface chemistries significantly affect internalization pathways. Also, the internalization pathways are not exclusive; therefore, a specific type of nanocarrier could be internalized through a combination of several pathways (473). In addition to size, extensive research efforts have been devoted to optimizing geometrical properties of nanocarriers for enhanced cellular uptake (152, 280, 334). Due to the negative charge of phospholipids, positively charged nanocarriers generally show stronger interaction with plasma membranes, leading to increased internalization (378). In addition to tuning the physical properties of nanocarriers to increase endocytosis, specific receptors overexpressed on cancer cell membranes could also be exploited for facilitated and selective internalization. For example, epidermal growth factor receptor (EGFR) (364), folate receptor (429), transferrin receptor (491), lectins (339), and low-density lipoprotein receptor (233) are well-characterized receptors to induce efficient cellular uptake. Different types of targeting ligands, including small molecules (480), antibodies (346), peptides (396), and aptamers (470) can be easily functionalized onto the surface of the nanocarriers (27, 390). For example, the folate receptor is a commonly overexpressed receptor by many types of cancers. Modifying high concentrations of the small molecule ligand folic acid onto a DNA nanocarrier was demonstrated to facilitate the intracellular delivery of siRNA (223).

2. Endosome/lysosome escape

After internalization of the nanoparticles through plasma membrane invagination, as in the case of the classic clathrin-mediated endocytosis, the nanocarriers are generally trapped inside the vesicles that help them enter the cells, known as endosomes (124, 366, 464). As the endosome matures, it tends to traffic toward and fuse with the lysosome, where the acidic and enzyme-rich environment would lead to the degradation of the nanocarrier as well as the cargoes (381). Meanwhile, the trafficking of nanocarriers from late endosome to extracellular space through recycling pathways, as in the case for cationic lipid nanocarriers, further limits the cytosolic availability of delivered drugs (366). The endo-lysosome entrapment poses the most critical barrier for the intracellular drug delivery, especially for macromolecular therapeutics. To overcome this barrier, various endosome escape agents derived from viral or bacterial invasion machineries were utilized for nanoparticle escape from the endosome membrane (99, 442, 465). The methods for endosome escape could be further classified into different mechanisms, such as proton-sponge effect (25), nanoparticle-endosome membrane fusion (307, 474), and photochemical disruption (198). Acidification of the endosome plays an important role for cellular uptake of nanoparticles (366, 464), towards which the proton-sponge effect is a widely adopted approach that is generally integrated with polyamine-based polymers with a pK_a range of 5–7 (314). These polymers are able to buffer the acidification of the endosome, increasing the influx of ions into endosomal compartments and causing rupture of the endosome membranes. The most representative example of this type of polymer is polyethylenimine (PEI), a potent transfection reagent for genetic engineering of various types of cell lines (159). For the membrane fusion-based mechanisms, fusogneic lipids or peptides are usually incorporated into the nanocarriers. The popular fusogenic lipid 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (DOPE) is an acid-responsive lipid that undergoes a phase transition from bilayered to hexagonal conformation for fusing with endosome membrane (385). In addition to phase transition, ionizable lipid with optimal pK_a around 6.2–6.5 was proposed to be effective in promoting membrane fusion (124, 464). Endosome acidification would trigger the formation of ion pairs between the lipid and endosome membrane, promoting lipid exchange and drug release into the cytosol. It has been recognized that the pK_a and hydrophobicity of the lipids are crucial properties for preparing efficient intracellular DDSs (3, 302), and the balance between pK_a and hydrophobicity has become a guideline for synthetic lipid and polymeric carriers (144, 180, 506). Fusogenic peptides inspired from the viral capsids, such as KALA or H5WYG, also exhibit structural changes in the acidic environment of the endosome (336). The negatively charged or neutral peptides will transform from random coils into rigid and hydrophobic helixes to insert into the membrane of the endosomes. Another applicable approach for inducing endo-

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some escape in a spatial-temporally controlled manner involves photosensitizer-mediated photochemical therapy (56). Small molecular or polymeric photosensitizers could generate ROS when excited by externally applied photons, leading to drastic destruction of the endosome (323). However, this method is complicated by damaging the delivered cargoes.

In addition to the various methods for disrupting the endosome membrane, an emerging facile strategy is to bypass the endolysosome. Different endocytic pathways lead to distinct intracellular fate of nanoparticles; endosomes generated by the caveolae-mediated endocytosis tend to fuse with caveosomes and bypass the lysosome fusion (365). A representative nanoparticulate system is the spherical nucleic acids, which use highly organized nucleic acid oligos to coat the surface of gold nanoparticles covalently (360). Instead of being internalized through the classic clathrin-mediated endocytosis, this nanoparticle binds the class A scavenger receptor on cell membrane and gets endocytosed through caveolae and lipid raft-mediated pathway, arriving at early endosome (57). Then, through a not yet well-characterized mechanism, possibly associated with the sorting of nanoparticles towards Golgi apparatus or endoplasmic reticulum (354), this nanoparticle could be trafficked to the cytosol without the assistance of endosome escaping agents.

Of note, in spite of all the difficulties of getting nanoparticles out of endosome entrapment, the endosome is not merely a trap. If the timing of endosome escape could be fine-controlled, endosomes could offer a fast ride along the cytoskeleton to move the nanoparticles closer to the interior of the cells (351). Even though most endosome vesicles end up fusing with lysosomes, endosomes are capable of shuttling the cargo to different subcellular organelles, such as the Golgi apparatus, the mitochondria, and the endoplasmic reticulum (172, 459). This feature would be very useful for nuclei-targeted gene delivery, since the endosome-assisted migration towards the nuclei would be more efficient than passively diffusing the nucleic acid through the cytoplasm (469).

3. Nuclear import

The nucleus stores genetic information of the cells, where many therapeutic targets are located (406). In a nondividing cell, the nucleus is wrapped in a double-layered lipid envelope, where the pores on the membrane regulate the traffic in and out of the nucleus. Generally, molecules smaller than 5 nm (approximately the size of a 40-kDa protein) could diffuse through the pores passively, while larger ones (up to 39 nm in diameter) need to be transported actively by the importing machineries (206, 232). The low efficiency of nucleus entry from the cytosol becomes a bottleneck for nucleus-targeted gene therapies (79). To overcome this barrier, nuclear localization sequences (NLS) are often fused with targeted proteins (204), attached to desired plasmids (395) or nanoparticles (316) for facilitating nucleus transport. The NLS interacts with the nuclear pore associated proteins, including importin α and β, and form a protein complex that could be pulled into the nucleus by the nuclear pore complex (178, 450). The most popular NLS was derived from the large T antigen protein of SV40 virus, and it is capable of enhancing nuclear transport efficiency of plasmid by 10- to 1,000-fold (495). Other available NLS include peptides derived from importin β (373) or the NH_2 terminus of yeast transcription factor GAL4 (46). An alternative strategy to NLS for nuclear-targeted plasmid delivery borrows the transportation of endogenous transcription factors (145). By coding a sequence that could bind constitutively expressed transcription factors, such as NF-κB, into the plasmids, transcription factor facilitated nuclear transport could be achieved (213). A general sequence, designated as "nuclear targeting sequence," that can bind various types of transcription factors was derived from SV40 enhancer, which could serve as a universal strategy for facilitated nuclear delivery (123). Furthermore, due to the characteristic expression of transcription factors in different cell lines (404), selective nuclear transport in desired cells could also be achieved by coding the selected transcription binding sequence.

4. Drug efflux pumps

After overcoming the multiple barriers, the administered drugs finally reach the desired intracellular loci of the targeted cell. The delivery task may still fail, especially for chemotherapeutics, due to the potential drug resistance of the cells. Drug resistance develops either intrinsically before administering the therapeutics or externally after extended exposure to chemotherapeutics (48). The chemotherapeutic resistance stems from complex mechanisms that involve defects in the apoptosis machineries, induction of alternative DNA repair pathways, structural changes of the drug targets, and elevated expression of drug efflux pumps (38). Among the different mechanisms, the drug efflux pump is the most significant barrier that could pump out not only the administered drugs but also a wide range of therapeutics with structural similarities, leading to multidrug resistance (MDR) (86, 371, 392). The MDR could remarkably reduce intracellular drug concentrations and compromise the therapeutic efficacies. Classic MDR pumps are comprised of proteins from the superfamily containing ATP-binding cassette (ABC) (100). Representative pump proteins include the P-glycoprotein, where the P stands for permeability (187); the breast cancer resistance protein (BCRP) (54); and the multidrug resistance-associated protein (MRP) (65). The P-glycoprotein mainly pumps cationic and lipophilic drugs, the BCRP mainly transport anions, and the MRP binds substances somewhere in between (208). To overcome the MDR, viable strategies involve optimizing the nanocarrier compositions or co-delivering different agents for bypassing MDR pump recognition, inhibiting transporter activity or its expression (165). For example, nano-

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carriers based on the amphiphilic copolymer Pluronics could abrogate MDR through several well-studied mechanisms: the polymer could be incorporated into cell membranes and alter its viscosity; it could lower the activity of the MDR pumps by reducing intracellular ATP level; it could enhance apoptosis signaling by triggering the release of cytochrome *c* as well as reactie oxygen species (ROS); and it could also avoid intracellular vesicle entrapment of the nanoparticles (24). Many other nanomaterials that could avoid the MDR were also demonstrated, such as DNA origami (181), guanidinium modified polyphosphoester (268). For co-delivering MDR regulating therapeutics, small molecular MDR modulators, such as the P-glycoproteins inhibitors verapamil (446) and tariguidar (325) or the BCRP inhibitor CG918 (467), could significantly reduce the transportation as revealed from the 10- to 100-fold decrease in IC_{50} values. Similarly, co-encapsulating siRNA to target the MDR transporter could also help reduce the MDR (272).

C. Designing Criteria of Nanocarriers for Drug Delivery

The journey of the nanocarriers from the syringe to the targeted site is full of barriers, leaving only a small fraction of those "lucky" nanocarriers reaching the destination. Advances in material science have enabled researchers with the ability to precisely manipulate the properties of nanocarriers in terms of their material composition, size, shape, and surface properties **(FIGURE 3)** (5, 254, 297). To provide a straightforward concept of how to prepare efficient nanocarriers, we have summarized the preferred values for these parameters as below.

1. Size

To prepare nanoparticulate carriers for drug delivery, size is the parameter of top priority that needs to be controlled within the optimal range. To obviate the complication of shape, we will use spherical nanocarrier as a model to discuss the size preferences of nanocarriers for anticancer therapies. Nanocarriers that are too small (<10 nm) are easily cleared from the circulation through glomerular filtration (410), while nanocarriers that are too large (>2 μm) tend to clog the blood vessel due to the limited diameter of the capillaries (~5 μm) (332). For tumor-targeted nanocarriers, the size should be tailored to fit the EPR effect, which limits the particle size within 500 nm (492) and preferentially greater than 200 nm (154). Nanocarriers larger than 200 nm also risk clearance by other organs, such as liver,

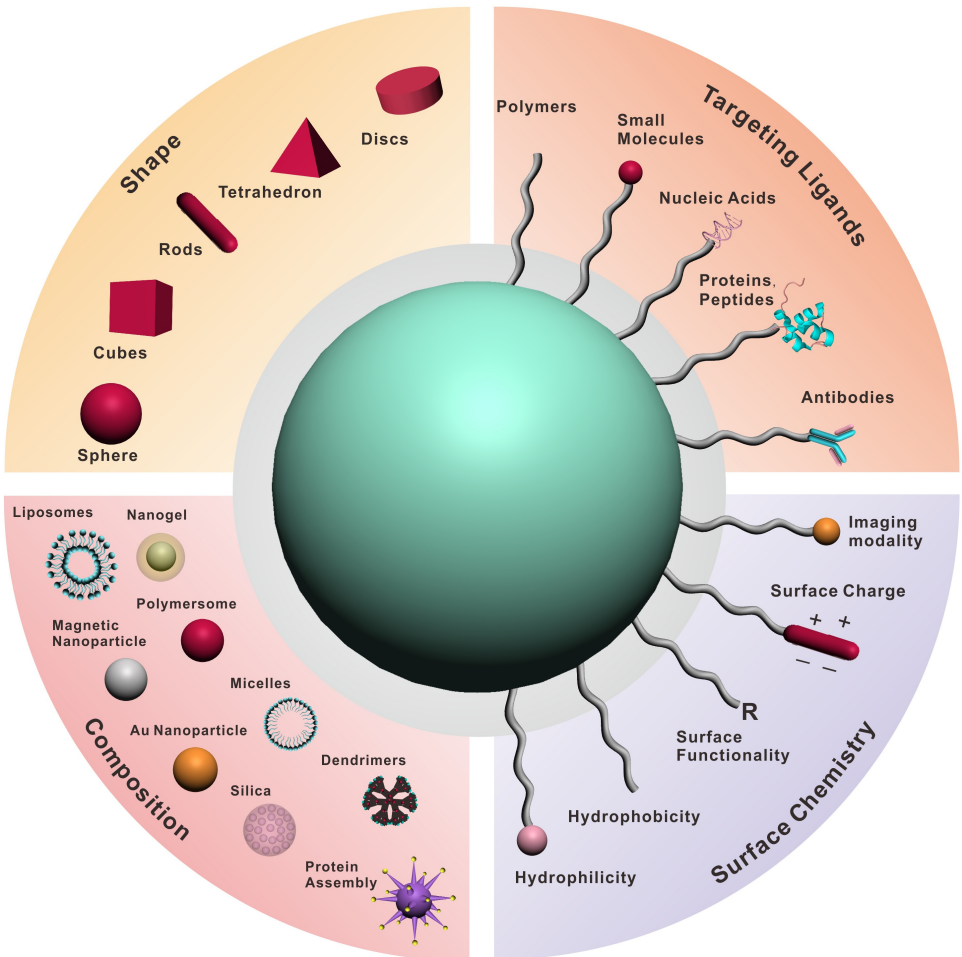

FIGURE 3. Parameters for nanoformulation design. Properties of the nanocarrier could be tailored modularly from the perspective of size, material composition, shape, surface chemistry, and targeting ligand conjugation to overcome the sequential physiological barriers for precise drug delivery.

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spleen, or lung, reducing their circulation half-time. In addition to tumor accumulation, the ability to penetrate dense solid tumors makes nanocarriers within sub-100 nm range more efficient carriers. A systemic investigation of monodispersed silica-based nanocarriers with three different sizes (20, 50, and 200 nm) showed that nanocarriers of 50 nm diameter showed the highest tumor accumulation and penetration efficacies, more efficient than nanocarriers near the lower and higher size limits (407). Overall, nanocarriers within the size range of 10–200 nm, preferentially smaller than 100 nm (51), are typically suitable for tumor targeted drug delivery.

2. Shape

Emerging studies on the effect of nanocarrier shapes revealed that the shape could significantly affect the delivery efficacy from multiple aspects of the delivery process, including circulation, extravasation, and internalization by targeted cells (166, 408, 422). Currently, nanospheres, nanodiscs, nanorods, and nanocylinders are among the most investigated geometries. From the perspective of circulation, nanocarriers with a cylindrical (122) or disclike (296) structure showed distinct hemodynamic patterns versus spherical ones; circulation half-time could be enhanced either by orienting the nanocarrier to follow blood flow or by tumbling in the blood vessels. In addition, the shape of the nanocarriers affects macrophage recognition (45), further affecting the biodistribution patterns. For targeted internalization by cancer cells, nanocarriers with a bacteria-like rod shape, such as gold nanorods (313) and silicon nanorods, generally demonstrate higher intracellular uptake efficiencies than their spherical counterparts possibly due to the evolved machineries in mammalian cells against bacteria. Particularly, nonspherical nanocarriers have shown the potential to exhibit better drug delivery efficacies than spherical nanocarriers, which makes shape an applicable parameter for nanocarrier optimization. To fully utilize the benefits of shapes for optimized drug delivery, emerging strategies that use morphologically transformable nanocarriers were demonstrated (239, 399). For example, a nanocarrier capable of transforming from nanodisks to nanospheres upon environmental triggers, including pH, or chemicals, could take advantage of the elliptical disc shape to avoid macrophages and utilize the spherical shape for internalization (485).

3. Surface charge

Due to the negative charge of cell membranes (482), positively charged nanocarriers typically exhibit superior in vitro internalization efficacy versus negatively charged or neutral ones (148, 197). This phenomenon holds true for numerous types of cell lines, including macrophages or cancer cells (437). Generally, positively charged nanocarriers were endocytosed through the clathrin-dependent pathway while negatively charged nanoparticles tend to be internalized through the caveolae-mediated pathway (147, 365). However, for in vivo administration, the positive charge on nanocarriers could easily attract serum proteins, which are mostly negatively charged, to form protein corona, increasing the risk of being cleared out by immune cells. In addition, the high positive charge also risks disrupting platelets and causing hemolysis (14, 490). In view of this, negatively charged or neutral nanocarriers are better choices for long circulation. To balance the need of long circulation and enhanced cellular uptake, a popular strategy called "charge reversal" was incorporated into many nano-particulate systems (471). For this strategy, the nanocarriers were tailored to maintain a neutral or slightly negative charge while in circulation but shift to a positive charge when reaching the tumor microenvironment. Generally, the acidic extra-tumoral microenvironment is used as a trigger to cause the shedding of the negatively charged shells from the positively charged cores (143); or switching the charge of a synthetic peptide, where the isoelectric point could be tuned (168).

4. Surface composition

Since the surface of nanocarriers is the frontier part that contacts the cells, interaction from the surface components with cells would affect the fate of the delivery process. For example, cellular internalization could be significantly affected by the hydrophobicity or hydrophilicity of the surface and hybrophobic nanocarriers could be easily internalized (301). In this case, the classic PEGylation strategy dramatically increases the hydrophilicity of the surfaces and elongates their circulation time. Complementary strategies to the PEGylation strategy to further reduce the chance of being cleared out by the complement system have been suggested to modify surface of the nanocarriers with self-markers, such as factor H or CD 47 (271) or use naturally derived cell membranes (160, 164). Besides avoiding macrophage recognition, the existence or absence of targeting ligands on nanocarrier surfaces could influence their adhesion and entry into targeted cancer cells. The overexpressed receptors on tumors as well as vascular proximal endothelial cells make targeting ligands a favorable component for targeted delivery with improved precision (405). However, it is necessary to keep in mind that healthy cells also share the receptors of the tumor cells albeit at a lower expression level (88, 245). Significant damage by the targeting ligand still exists.

5. Elasticity and degradation

Elasticity of the nanocarriers is another parameter that could be tuned to optimize the delivery efficacy (10, 90). It has been demonstrated that the energy cost of wrapping up a nanoparticle by the cell membrane decreases as a function of increased stiffness (483), making rigid nanoparticles easier for cellular uptake. However, rigid nanocarriers are eas-

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ily cleared out when administered in vivo. In comparison, elastic nanocarriers exhibit better circulation performances in a way similar to red blood cells (RBC) (70), where the elastic RBC could be easily deformed to squeeze through blood vessels even narrower than their diameter. So, enhancing the elasticity of the nanocarriers is a straightforward option for improving the circulation of the nanoparticles. Biodegradability is another important consideration for designing nanocarriers from the perspective of drug release efficacy as well as biocompatibility. When degradation or dissociation of the nanocarrier is needed to release the encapsulated drug, methods to maintain the drug in the carrier during circulation but release it after arriving at its destination become important for efficient drug delivery (468). In this case, functional moieties that could be degraded by specific signals in the tumor microenvironment could be incorporated into the nanocarriers to control the drug release (502). For the issue of biocompatibility, it is preferable to use nanomaterial that could be degraded into nontoxic products. However, for nondegradable nanocarriers, such as metallic-based nanocarriers, it is desirable that the nanocarriers could be cleared out of the body after finishing the mission of delivery (488). As an example to address the issue, Chan and co-workers (59) have demonstrated a strategy of combining biodegradable DNA into metallic nanocarriers, making the nanoassembly dissociable into smaller nanocarriers for clearance.

Designing nanocarriers for efficient drug delivery is a comprehensive task that needs to take the considerations of multiple criteria associated with physiology into a single formulation. In the next section, we will discuss some exemplary strategies for preparing "smart" formulations that can leverage the physiological signals in the diseased tissue for controlled release of therapeutics.

IV. SMART DRUG DELIVERY SYSTEMS MEDIATED BY PHYSIOLOGICAL SIGNALS

To achieve nanocarrier-mediated drug delivery with higher spatial-temporal precision, bio-inspired strategies that endow the delivery vehicles with the capability of interacting with physiological environment and determining when and where to release the payload are gaining increased interest **(TABLE 1)**. To design these "smart" formulations, stimuli-responsive moieties that translate physiological signals at tumor microenvironment into behaviors of the nanocarriers, such as swelling, degradation, morphological change, and charge reversal, have been developed **(FIGURE 4)**. Nanomedicine responsive to physiological stimuli, including acidic pH, overexpressed enzymes, redox gradient, or elevated metabolite concentrations, holds great promise for improved anticancer efficacy **(FIGURE 5)**. They could exhibit better pharmacokinetic profiles with reduced concern of premature drug leakage during circulation and improved tumor targeting efficacies, where a higher percentage of the administered drug would be accumulated in the targeted cells.

A. Nanomedicine Responsive to Physiological Triggers

1. Acidic environment

Local decrease of pH in different tissues (such as the GI tract and vagina), subcellular compartments (such as the endosome and lysosome), or disease-associated conditions (such as infection, inflammation, and tumor microenvironment) provides a reliable signal to trigger the drug release from the DDSs. For tumors, the abnormal metabolic activities, like the elevated rate of glycolysis, together with poor lymphatic drainage lead to the accumulation of lactic acid. Tumor-targeted nanocarriers will experience subtle pH changes when they extravasate from the blood circulation (pH 7.4) to the extracellular space of tumors (pH 6–7.2) (103). Nanocarriers internalized into intracellular space will undergo a further decrease of pH in endosomes (pH 5.0–6.0) and lysosomes (pH 4.0–5.0) (113). To harness the pH gradient, numerous pH-responsive formulations have been developed based on two mechanisms: *1*) incorporating protonatable polymers (such as polyacids, polybases, or polyamino acids) that could allow solubility or conformational changes upon acid stimulation; *2*) utilizing acid-labile moieties (like bicarbonate salts), or acid-cleavable bonds (such as hydrazine, acetal and ester) to enable disruption of the nanocarrier in acidic environments (317).

The subtle pH difference between blood circulation and extracellular space of tumors is often utilized as a cue to activate the nanocarriers for better tumor penetration or cancer cell internalization, such as shedding the stealth coating, exposing the cell penetrating peptide, or converting the surface charge. For example, Hammond and co-workers (341) demonstrated a sheddable layer coated nanocarrier prepared by a layer-by-layer deposition technique for acidity-triggered internalization in vivo. A stealth layer composed of PEG was coated onto the positively charged inner layer consisting of PLL through the modified linkers: iminobiotin and neutravidin. The iminobiotin-neutravidin bond is stable at alkaline conditions (pH 8–12), but it is easily dissociated at acid pH (4–6). Cloaking the positive charge of PLL by PEG could reduce the incidence of nonspecific uptake during circulation. However, when accumulated in the tumors, interaction between the iminobiotin and neutravidin is compromised upon exposure to the acidic tumor microenvironment, exposing the positively charged PLL layer for facilitated cellular uptake. By incorporating amino acids, including glutamic acid (Glu) and histidine (His), into the polymer backbone composed of PEG, Kempson and co-workers (424) prepared the polymer poly(PEG-His-Glu) with tunable pH-induced charge rever-

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Table 1. *Summary of exemplary physiological stimuli-responsive formulations discussed in this review*

Stimuli	Nanoplatform	Responsive Moiety/Responsive Type	Drugs	Target Type	Referene Nos.
Acidic environment	Polyelectrolyte/DNA complex	Peptide/charge reversal for internalization	Plasmid for gene therapy/phototherapy	Non-small cell lung carcinoma	424
	Peptide-nucleic acid conjugate	Peptide/conformational change for direct membrane penetration	Anti-microRNA-155	Lymphoma	55
	siRNA-conjugated amino-dextrans	Acetal linkage/endsomal cleavage for drug release	siRNA	—	71
	DNA-alkyl conjugate	Acetal linkage/targeting ligand shedding for endosome escape	Transcription factor Nrf2	Hepatocytes	224
	RBC membrane-coated polymeric nanoparticle	Glycerol dimethacrylate/ endsomal degradation for drug release	DOX/TRAIL	Primary and circulating tumor	164
	Polymer-liquid metal conjuate	Liquid metal/fusion and degradation for ligand/ drug release	DOX	HeLa	244
Enzyme activity	Peptide-dendrimer conjugate	Peptide/MMP cleavage for internalization	Plasmid encoding siRNA/DOX	U-87 malignant glioma	167
	PEG-drug conjugate	Peptide/MMP cleavage-mediated PEG shedding for internalization	PTX	Non-small cell lung cancer	508
	Capped MSN	Peptide/MMP cleavage for drug release	Cisplatin	Lung cancer	432
	Modified graphene oxide	Peptide/furin cleavage for sequential drug release and internalization	DOX/TRAIL	Lung cancer A549	185
	Gel-coated liposome	Hyaluronic acid/HAase-mediated drug release and internalization	DOX/TRAIL	Breast cancer MDA-MB-231	183
	Peptide-modified liposome	Peptide/legumain cleavage activated internalization	DOX	Breast and lung cancer	238
	Polymeric nanogel	Peptide/furin cleavage for drug release	Caspase-3	Hela	31
	Polymer/DNA complex	Peptide/kinase-mediated charge reversal for drug release	Plasmid	B16 melanoma	192
	Quinone-modified liposome	Trimethyl quinone/quinone reductase cleavage for drug release	Calcein	—	308
Reducing gradient	Capped MSN	Disulfide/GSH cleavage for drug release	DOX	Hela	249
	PEG-dendrimer conjugate	Disulfide/PEG shedding for internalization	DOX/siRNA	B-cell lymphoma 2	448
	Polymer nucleic acid conjugate	Disulfide/drug release	siRNA	HeLa	94
	Polymeric nanogel	Disulfide/nanoparticle degradation for drug release	P53	Breast cancer	503
	Polymer/DNA complex	Disulfide, diselenide/drug release	DNA	HepG2	150
	Pillararene assembly	Ferrocenium/polarity change for assembly disruption	DOX/siRNA	HeLa	47
ROS	Polymer/nucleic acid complex	Thioketal/drug release	siRNA	Intestinal inflammation	462
	Liposome	Aryl boronic ester/protein activation	RNAse A		449
	Peptide-drug conjugate	Boronic acid/activated internalzation	Imaging agent	Leukemia	454

Continued

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Table 1.—*Continued*

Stimuli	Nanoplatform	Responsive Moiety/Responsive Type	Drugs	Target Type	Referene Nos.
	Polymer-conjugated nanocrystal	Thiolesters/polarity change for assembly disruption	PTX		117
	Ferrocenium-modified polymeric assembly	Ferrocenium/polarity change for assembly disruption	Pyrene		391
Hypoxic condition	Polymer/nucleic acid complex	Azobenzene/PEG shedding for internalization	siRNA	HeLa	333
	Modified dextran nanoparticle	2-Nitroimidazoles/polarity change for drug release	DOX	Squamous carcinoma	411
ATP gradient	HA nanogel-coated DNA duplex	ATP aptamer/drug release	DOX	Breast cancer	282
	Graphene oxide aggregate	ATP aptamer/aggregate disassembly for drug release	DOX	HeLa	284
	Capped MSN	Zn^{2+}-dipicolylamine/drug release	DOX, CPT	HeLa	212
	Polymer/nucleic acid assembly	Phenylboronic acid/drug release	siRNA		300
	Protein assembly	ATP consuming protein/ conformational change for assembly disruption	Imaging agent	HeLa	32
Synergistic multi-stimuli	Polymeric micelle	Ketal+disulfide/pH- and acid-responsive micelle degradation	DOX	HeLa	246
	Polymer-drug conjugate	Aromatic ester + aliphatic ester/redox and esterase facilitated drug release	Aspirin, cisplatin	Prostate and cisplatin-resistant ovarian cancer	326
	Polymer nanoparticle	Thioketal + chitosan/ROS- and acid-triggered conformational change for drug release	Curcumin	Ankle inflammation	347
	Polymer-drug conjugate-based micelle	Thioester + phenol ester/ ROS and redox responsive drug release	SN38	Breast cancer	447
Sequential stimuli	Capped MSN	Peptide + disulfide/MMP and redox sequentially activated internalization and drug release	DOX	Squamous cell carcinoma and human colon cancer	497
	Polymeric nanoparticle	Calcium phosphate + HA/ pH and HAase-triggered sequential release of siRNA and DOX	siRNA/DOX	Ovarian cancer	58
	Liposome	Fusogenic lipid + ATP aptamer/pH and ATP sequentially triggered endosome escape and drug release	DOX	Breast cancer	283
	DNA nanoparticle	Glycerol dimethacrylate + DNA/pH and DNase sequentially triggered drug release	DOX	Ovarian cancer	400
	Polymeric nanoparticle	HA + human serum albumin + glycerol dimethacrylate/HAase, transglutaminase and pH sequentially triggered extracellular aggregation and release of drug	TRAIL/cilengitide	Breast cancer	163
	Polymeric micelle	Glucose oxidase + 2-nitroimidazoles/glucose and hypoxia sequentially triggered drug release	Insulin	Diabetes	487

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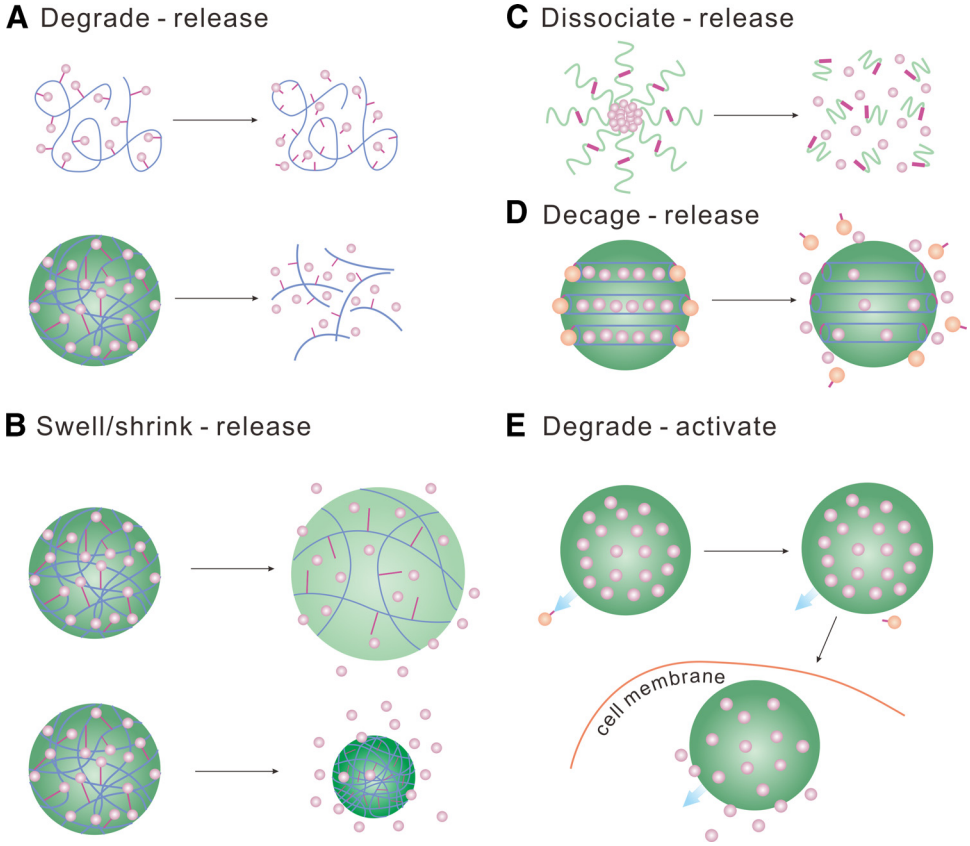

FIGURE 4. Mechanisms of stimuli-responsive nanocarrier for drug delivery. The drugs could be released from the nanocarrier upon physiological signal-triggered degradation (*A*), swell or shrink (*B*), dissociation (*C*), and uncapping the pores of mesoporous silica nanoparticles (*D*). *E*: nanocarrier activation for cell penetration with exposed moieties.

sal properties for enhanced anticancer gene delivery. Charge behavior of the nano-formulation is dictated by the interaction between the three polyelectrolytes: the negatively charged DNA, positively charged PEI, and the charge reversible poly(PEG-His-Glu). The researchers tuned the ratio of the three components and demonstrated that the protonation of amino acids at acid environment (pH 6.8) could reverse the charge of the nanocarrier from negative (pH 7.4) to positive, facilitating intracellular uptake. An acid-dependent uptake profile was observed for the charge reversible nanocarrier, while the "always positively charged" control without the poly(PEG-His-Glu) shell did not show any difference with varying pH. The charge reversal enabled systemic administration of the nanocarriers, and a single injection induced the therapeutic level expression of the anticancer protein in the tumor. Besides activating the electrostatic interactions between nanocarriers and cell membranes, acidity-triggered conformational change of peptide was also proven to be an efficient way for tumor-targeted delivery. Slack and co-workers have demonstrated the application of a peptide that could fold into a rigid α-helix in an acidic environment, named the pH low insertion peptide (pHLIP), for targeted delivery of anti-microRNA (55). During circulation, the random morphology of the peptide made it impermeable to the cell membrane, reducing nonspecific internalization and achieving passive accumulation in tumors. The acidic extracellular space of the tumors induced the folding of pHLIP, which was later inserted into the cancer cell membranes and translocated into the cytosol via an endocytosis-independent way. By appending a neutrally charged peptide nucleic acid (PNA), which was designed to absorb the oncogenic microRNA-155 in cancer cells, the researchers showed that the pHLIP could shuttle the PNA cargo into the cytosol of cancer cells in vivo with high tumor specificity.

In addition to the extracellular acidity-activated cellular uptake, the stronger acidity of intracellular vesicles is generally utilized to activate intracellular trafficking or degrade the nanocarriers for drug release. Davis and co-workers (64) demonstrated a nano-formulation with an intracellularly sheddable targeting ligand to overcome the BBB. The receptor-mediated transcytosis was harnessed for traversing the BBB, and the protein transferrin was modified as targeting ligand onto 80-nm gold nanocarriers via an acid-degradable linker. Binding to the transferrin receptor on the blood side initiated the transcytosis, where the acidification in the vesicles cleaves the acid labile linker and releases the gold nanocarriers to the brain side. Furthermore, it was shown that formulations with the acid-cleavable linker showed much higher transcytosis efficacies than the non-cleavable counterparts. Fréchet and co-workers (71) designed acetal linked amino-dextrans for efficient and acid-cleavable delivery of siRNA, the acetal linker between siRNA and the modified polysaccharide allowed fast release of the siRNA cargo upon endosomal acid degradation. In another intracellular acidity trigger trafficking system, Murthy and co-workers (224) devised a DNA-based nano-

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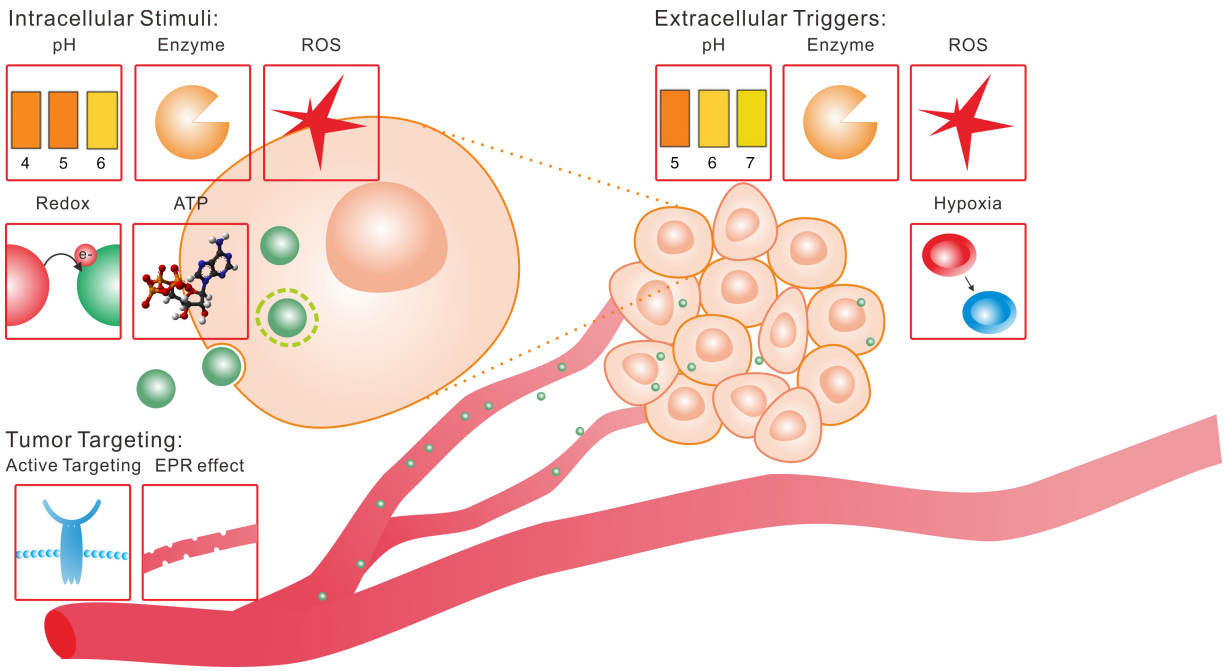

FIGURE 5. Harnessing physiological traits of tumor for precise drug delivery. The nanocarrier could reach the tumor either by actively binding to tumor specific receptors or passively through the EPR effect. Physiological signals in the extracellular space, such as pH gradient, enzyme, ROS, and hypoxic environment, could be utilized to trigger the release of drugs targeting extracellular objectives or activate the nanocarrier for further intracellular penetration. Intracellular environment, such as acidity, enzymes, ROS, reducing potential, ATP gradient, could be used to trigger intracellular nanoparticle transport or drug release.

carrier that could shed the modified targeting ligands after being internalized into endosomes and expose the membrane disruption moieties for endosome escape. Compared with the acidity-assisted intracellular trafficking, endolysosomal acidity-triggered drug release has been explored more prevalently. Unlike conventional nanocarrier degradation through the cleavage of labile linkers, a novel strategy utilizing the acid response of liquid metal was demonstrated recently as a viable approach for mediating acid-triggered drug release as well as clearing metallic nanocarriers from the body (244). In this system, Lu et al. (244) applied a eutectic metal alloy (gallium and indium) that behaves like liquid with low viscosity at room temperature to prepare nanocarriers. The liquid metal was sonicated into nanocarriers and stabilized with thiolated ligands, such as thiolated (2-hydroxypropyl)-b-cyclodextrin for drug loading and thiolated hyaluronic acid for tumor targeting. The ligand-modified liquid metal nanocarrier could target the cancer cells after systemic administration and enter the cells through macropinocytosis. The endosomal acidity will then induce the fusion of the liquid metal, shedding the modified ligands as well as the drug contained in the ligand. The released model drug DOX then diffused into the nucleus of the tumor cells and caused massive remission as evidenced from histological analysis. Unlike Hg, this liquid metal is highly biocompatible. Toxicological analysis of the empty nanocarriers in mice models did not reveal any detectable damage to platelets or tissues (such as liver or kidney) over the period of 3 months. Furthermore, corrosive products of the liquid metal also helped reverse drug resistance of cancer cells.

2. Enzyme activity

Pathological conditions, such as inflammation or cancer, are often associated with elevated expression of certain hydrolytic enzymes (including protease, phospholipase, or glycosidase) when compared with normal states (112, 129, 275). Enzymes secreted into the extracellular matrix of tumors, such as matrix metalloproteinase (MMP), phospholipase, hyaluronidase, and gelatinase, generally contribute to the aggressiveness of cancers. They are among the most intensively investigated triggers for tumor-targeted drug delivery, such as activating cellular internalization moieties or triggering drug release extracellularly. Similarly, characteristic intracellular enzymes of cancer cells, such as furin, kinase, esterase, and cathepsine (258, 434), were also demonstrated as possible cues. Substrates that could be specifically cleaved by these enzymes were incorporated into the nanocarriers as the enzyme-specific sensors and actuators.

For nanocarriers that utilize extracellular enzymes for activation or release, MMP is the most popular target. Tsien and co-workers (184) demonstrated an exemplary MMP-activated cell-penetrating peptide for tumor selective delivery of imaging agents. This activated peptide is constructed by fusing polyarginine (a positively peptide that mediates robust cellular internalization) with a polyanionic domain

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to neutralize the positive charges via a MMP2/9 cleavable linker. With the use of a peptide-dye conjugate, it was demonstrated that the polyanionic moiety inhibited the electrostatic interactions between the polyarginine moiety and cell membrane, reducing cellular uptake during circulation until it was cleaved off by the MMP-2/9. In vivo studies showed that the MMP activatable peptide could enhance tumor-specific accumulation of the imaging agent by approximately threefold. Jiang and co-workers (167) further extended this MMP-activated peptide to modify anticancer-drug delivery nanocarriers. In this system, dendrigraft poly-L-lysine nanocarrier was modified with the peptide, and the larger volume of nanocarriers enabled the co-delivery of two types of anticancer drugs simultaneously: a plasmid encoding siRNA [targeting vascular endothelial growth factor (VEGF)] for inhibiting angiogenesis and small molecule drug DOX for cancer cell killing. MMP activated internalization of the nanoparticle enhanced the specificity of tumor-targeted delivery of the gene and chemotherapies when compared with nanocarriers coated with nonresponsive peptides. This led to significant reduction in blood vessel formation and increased cancer cell apoptosis using a xenograft glioma model in mice. Torchilin and co-workers (508) devised a MMP-2 triggered PEG-sheddable micelle for delivering the hydrophobic drug paclitaxel (PTX). The hydrophobic PTX, hydrophilic PEG was linked through a MMP-2-cleavable peptide to prepare the amphiphilic building block of the micelle (PEG2000-peptide-PTX). A TAT peptide was conjugated to a shorter PEG chain and another hydrophobic moiety phosphoethanolamine to form another cell penetrating building block (TAT-PEG1000-PE), which could be buried under the PEG2000-peptide-PTX during circulation. Cleavage of the peptide in tumor microenvironment shed the PEG2000 shell and exposed the buried TAT peptide for enhanced cellular uptake. In addition to controlled cellular internalization, Meiners and co-workers (432) also demonstrated the application of MMP degradable peptide for controlled drug release from nanocarriers using MSN as a model.

In addition to MMP, other tumor-associated enzymes were also explored for controlled anticancer drug delivery. Furin is an important convertase that processes substrate proteins for secretion; it is distributed both on the cell membrane and in the intracellular compartment (mainly Golgi network) (377, 412). Jiang et al. (185) incorporated the peptide substrate of furin into a graphene-based nanocarrier, where the drug release and nanoparticle internalization are controlled by the overexpressed furin on cancer cell membrane (185). In this system, the model cytokine TRAIL was conjugated to a furin-sensitive peptide, which was further conjugated to the graphene oxide sheet via a PEG linker, and the DOX was loaded into the graphene oxide sheet through π-π stacking. When the nanoparticle arrives at the tumor microenvironment through the EPR effect, cell membrane-associated furin will cleave the peptide linker, releasing TRAIL into extracellular space. Then the remaining part of the nanocarrier will be internalized into the endosomal compartment for DOX delivery. It was demonstrated that the furin cleavable nanocarrier showed significantly higher anticancer efficacy than nondegradable counterparts. Jiang et al. (183) also demonstrated a strategy utilizing the overexpressed hyaluronidase in extracellular environment for the sequential delivery. In this system, a core-shell structured nanocarrier with a liposome as DOX loading core and hyaluronic acid (HA) gel as TRAIL loading shell was prepared. Hyaluronidase degradation of the HA shell released TRAIL in extracellular environment, and it also exposed the cell-penetrating peptide on the liposome surface for facilitated internalization. In addition to long-established enzymes, new enzymes correlated to tumor progression are also under investigation. For example, legumain is a protease overexpressed by tumor associated macrophages (TAM), and it can be trafficked from cytosol to membrane under hypoxia or starvation (76). To utilize this signal, Xiang and co-workers (238) conjugated the tripeptide substrate of legumain (AAN) onto the side chain of the TAT peptide and then appended drug-containing liposomes onto the altered version of TAT peptide (238). The AAN modification reduced TAT-mediated cellular internalization by 72.65%, which could be reversibly recovered by legumain cleavage.

Intracellularly overexpressed enzymes are also attractive triggers for controlling intracellular behaviors of the nanocarriers. Biswas et al. (31) utilized furin in the intracellular compartment for releasing protein therapeutics from the polymeric nanogel. In this acrylamide-based nanogel, positively charged monomer was incorporated for enhanced cellular uptake, and the peptide sensitive to furin was incorporated into the crosslinkers to make this protein-encapsulated nanogel degradable in the presence of furin. Katayama and co-workers utilized intracellular protein kinase to trigger the release of DNA plasmid from DNA/polycationic peptide complexes (192). Cationic polypeptide that could be specifically phosphorylated by protein kinase C-α was screened from a large library and polymerized with acrylamide radically. The polycationic polymer complexed with negatively charged DNA and transported it inside cells, where phosphorylation by the protein kinase will convert the charge of the peptides to negative, releasing the DNA cargo intracellularly. The specific activity of tumor-associated protein kinase C-α made this system a tumor-selective DNA delivery carrier. McCarley and co-workers (308) demonstrated a quinone-modified liposome and utilized quinone reductase as a stimulus for drug release. Trimethyl quinone modified to the NH_2 termimus of the constituent lipid was cleavable upon the reductase activation, releasing the liposomal content. In addition, Amorós and co-workers demonstrated the application of various types of intracellular enzymes, such as caspase-3 (83), β-D-galactosidase (26), and cathepsin B (84) to control the capping of mesoporous

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nanoparticles, realizing enzyme controlled intracellular drug release.

3. Reducing gradient

The reducing gradient between the intracellular compartment and the extracellular environment is a robust physiological stimulus that attracted great interest for controlled drug delivery. Intracellular concentrations of the glutathione tripeptide (GSH) is ~2–10 mM, which is maintained in reducing the state by other reducing factors [such as nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), nicotinamide adenine dinucleotide (NADH), or thioredoxinred] (225). In sharp contrast, extracellular GSH level is only 2–20 μM (372). Furthermore, the GSH level is at least fourfold higher in tumor when compared with normal tissues (102, 209), making the reduction gradient-based nanocarriers more tumor selective.

Nanocarriers are often incorporated with GSH-sensitive bond, typically the disulfide bond, for intracellular activation or degradation. The disulfide bond is stable in the mildly oxidative extracellular space, but after crossing the plasma membrane it will be converted into thiol or undergo thiol-disulfide exchange by interaction with reducing agents. Luo et al. (249) demonstrated the application of disulfide bond to control an α-cyclodextrin and folic acid based capping of MSN nanocarriers. Tang and co-workers (448) used the disulfide bond to link low-generation polyamidoamine (PAMAM) dendrimers with branched PEG shells for enhanced gene and chemotherapeutic delivery. Intracellular degradation of the disulfide bond exposed the siRNA and DOX coloaded PAMAM dendrimer for passive drug release. DeSimone and co-workers (94) devised a siRNA pro-drug by covalently conjugating siRNA onto a hydrogel nanocarrier via a disulfide linker. The nanocarrier was prepared by the particle replication in nonwetting templates (PRINT) method to enable either entrapment or conjugation of the siRNA. The covalent conjugation reduced the risk of burst release compared with the gel entrapment-based loading method. The disulfide linker allowed selective release of siRNA inside targeted cells, while the control conjugate with a noncleavable linker failed to release the drug. Using a disulfide containing crosslinker, Zhao and co-workers prepared a GSH-degradable nanogel for intracellular delivery of various types of anticancer proteins, such as caspase-3 (501), apoptin (502), or p53 (503). Cellular entry could be mediated either by a positively charged monomeric component (501, 502) or by a cancer-specific targeting ligand to target the overexpressed luteinizing hormone releasing hormone (LHRH) receptors (503). After internalization, then the polymeric shell will shed off intracellularly to release the encapsulated payload for inducing apoptosis.

In addition to the classic disulfide bond, other redox-responsive mechanisms were also explored. Selenium is an element that belongs to the same family as sulfur; the higher electron number in selenium makes it a better electron donor than acceptor. He et al. (150) applied the diselenide bond, which is more difficult to be reduced than thiol bond, for constructing a reducing gradient-dependent stepwise unpacking system. In the nanosystem, low-molecular-weight PEI was polymerized through diselenide bond and complexed the DNA cargo through electrostatic interaction. Upon this complex, another layer of disulfide bond modified HA was adsorbed. It was demonstrated that 5 μM GSH was sufficient to degrade the disulfide bond-based shell (mimicking reducing potential the nanoparticle encountered just after cellular uptake), while 5 mM was needed to disassociate the diselenide bond-based core (mimicking the reducing potential of the cytosol). In another study, the charge and hydrophilicity change of ferrocenium cation upon GSH reduction was incorporated into an amphiphilic building block for preparing redox-responsive nanoassembly (47). The hydrophobic pillararene-based building block was sandwiched by two ferrocenium cations, making the conjugate amphiphilic. The cationic amphiphile allowed efficient loading of siRNA through electrostatic interaction during the sonication-mediated assembly process, and it also contributed to efficient cellular uptake. After cellular internalization, reduction of ferrocenium to ferrocene in the cytoplasm shifted the polarity of the building block from amphiphilic to hydrophobic, distabilizing the assembly and releasing the siRNA. When co-delivering siRNA and DOX, it was demonstrated that the nanosystem could efficiently inhibit drug resistance and increase the cytotoxicity of chemotherapeutics.

4. ROS

Intracellular metabolism of oxygen generates ROS, such as singlet oxygen ($^1O_2$), anion radical ($O_2^{-\cdot}$), hydroxyl radical ($^{\cdot}OH$), and hydrogen peroxide (H_2O_2) (511). Aggressive metabolism and damaged ROS scavengers (such as antioxidant enzymes) lead to detrimental accumulation of ROS inside cancer cells (451). The level of ROS in tumor cells could reach 10- to 100-fold that of normal cells, which in return further contributes to DNA damage or mutation, exacerbating tumor malignancy (29). ROS accumulation is a common feature shared by various types of diseases, such as inflammation (109), neurodegenerative disease (22), diabetes (119, 157), and cardiovascular disease (41). To harness the ROS as a physiological cue for controlled drug delivery, nanocarriers were prepared by incorporating labile bonds that could be cleaved [such as thiolketal (462, 493), aryl boronic acid (237, 449), or proline (489)] or undergoing polarity change [such as thiolester (117), or propylene sulfide(7), ferrocene(391)] upon oxidation.

Murthy and co-workers (462) utilized the thioketal based polymer poly-(1,4-phenyleneacetone dimethylene thioketal) for oral delivery of the siRNA (462). The polymer is resistant to acid, alkaline, or proteolytic degradation but

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sensitive to ROS-triggered cleavage, enabling site-specific delivery of nanoparticles to ROS-generating inflamed or cancerous intestines. Xu and co-workers (449) demonstrated a ROS-triggered protein deprotection method for spatial-temporal control of protein activities after delivery. The key lysine residue of the model anticancer protein RNase A was caged by a 4-nitrophenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl carbonate through a ROS labile boronic acid linker. In this proof-of-principle study, cationic lipid was used for intracellular delivery of the modified RNase A for protein-modification based therapy (207). It was shown that only the aryl boronic acid linked cage could be cleaved off after exposure to H_2O_2 while a nondegradable control failed to reactivate the RNase A. The ROS labile boronic acid linker has also been incorporated into an activatable CPP for in vivo agent delivery (454). Similar to the MMP activatible CPP (184), the positively charged CCP (Arg_9) was caged by an anionic moiety (Glu_9) through the ROS-sensitive 4-boronic mandelic acid linker. Exposure to H_2O_2 led to fragmentation of the peptide, activating intracellular penetration.

Using a ROS-mediated polymer polarity change strategy, Leroux and co-workers (117) coated an ROS-sensitive polymeric shell for controlling the aggregation of nanocrystal. Tuning the affinity between the thioester based amphiphilic polymer and the hydrophobic PTX nanocrystals generated stable core-shell nanocarriers in nonoxidative condition. ROS converts the hydrophobic thiolesters to hydrophilic sulfoxide or sulfone, destabilizing the shell for PTX release. Staff et al. (391) utilized the polarity change of ferrocenium/ferrocene upon oxidation for controlling drug release. Polymer containing the ferrocenium was formulated into a nanocapsule that held a drug-loaded liquid core. Oxidation of the polymer changed local polarity of the nanocapsule, releasing the loaded drug.

5. Hypoxic condition

Hypoxia is a hallmark of primary tumors (211), where the disorganized tumor vasculature caused limited oxygen diffusion to regions far away from the capillaries (>200 μm) (463). This hypoxic environment posed a survival pressure to select phenotypic or genetic mutations that favor hypoxia, generating more chemo-resistant, death-resistant, invasive, and metastatic cancer cell variants. The major role of hypoxia in tumor progression and drug resistance made hypoxia an attractive target for cancer therapy. Huge amounts of efforts have been devoted to target the hypoxic area, such as developing hypoxia-activated chemotherapeutics (397), engineering anaerobic bacteria to express tumor suppressing protein (486). Due to the severe hypoxia in tumor but not normal tissues, there is an emerging trend for harnessing hypoxia for designing tumor-targeted nanocarriers for theranostics (92, 504).

To utilize the hypoxia as a cue, hypoxia labile bonds were generally incorporated into polymeric nanoparticles. Torchilin and co-workers (333) used azobenzene as a hypoxia cleavable linker to prepare a PEG sheddable nanocarrier for hypoxia-targeted delivery of siRNA. Building block consisted of PEG, azobenzene, and PEI, and the lipid DOPE was prepared to form micelles, where the siRNA payload was complexed into the nanocarrier through electrostatic interaction. When the siRNA-loaded micelle diffuses to the hypoxic tumor region, the PEG shell will be cleaved off and expose the cationic PEI layer for cancer cell uptake. Thambi et al. (411) incorporated the hypoxia-sensitive group 2-nitroimidazoles (NI) into the side chain of the hydrophilic polymer carboxymethyl dextran. Due to the hydrophobicity of NI, the amphiphilic polymer could self-assemble into nanocarriers and load a hydrophobic drug inside. When the nanocarrier was exposed to hypoxic environment, the NI group got reduced to a hydrophilic derivative, destabilizing the self-assembly for drug release. It was demonstrated that the hypoxia-responsive nanoparticle showed hypoxic cancer cell/tumor selectivity both in vitro and in vivo. In spite of the progresses made in harnessing hypoxia for triggering nanocarrier activation or drug release, diffusing the nanocarriers to tumor regions distant from the blood vessels could be very challenging.

6. ATP gradient

The aggressive proliferation of tumors leads to the upregulation of various types of metabolites. As the "molecular unit of currency," ATP plays a central role in metabolic energy transfer. There is a sharp ATP concentration difference between extracellular (<5 μM) and intracellular environments (1–10 mM). Increased intracellular ATP has been observed for cancerous tissues (507). Thus ATP has emerged as a new physiological trigger investigated for controlled intracellular drug delivery.

To construct ATP-responsive nanosystem, the ATP binding aptamer (a short single-stranded DNA) is the most widely used ATP-sensitive moiety (398). Mo et al. (282) applied the ATP aptamer as the ATP sensor as well as drug release actuator for DOX delivery. In this formulation, the ATP aptamer with its complementary strand was hybridized into a DNA duplex, which provides a "GC" pair for loading the DOX. The DOX-loaded DNA duplex was condensed with a positively charge peptide protamine and then coated with a polymer shell composed of HA. Systemic administration of the nanoparticle led to targeted accumulation in the tumor tissue, where the HA shell got degraded by the HAase-rich tumor environment and shuttled the DOX-loaded DNA duplex intracellularly. When exposed to the high ATP level of the intracellular compartment, ATP competitively bound with the ATP aptamer and dissociated the DNA duplex for DOX release. Compared with a nonresponsive DNA core, the ATP aptamer-based

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nanocarrier showed significantly enhanced tumor growth inhibition. The relatively short length of the ATP aptamer made it easy to be adapted to different types of nanosystems (149, 229, 284).

In addition to the classic ATP aptamer, other ATP binding molecules were also explored for constructing ATP-responsive DDSs. Lee and co-workers (212) utilized the strong affinity between ATP and Zn^{2+}-dipicolylamine to prepare an ATP-responsive theranostic system. In this three-layered nanocarrier, an upconversion nanoparticle core was coated with MSN, where the pores of MSN could be used to load the anticancer drugs (DOX or CPT) capable of absorbing fluorescence emission from the core. The MSN was further modified with Zn^{2+}-dipicolylamine, upon which a layer of polypeptide-containing aspartate was coated for capping the pore. Exposing the nanocarrier to intracellular level of ATP will dissociate the polypeptide coating due to the competitive binding between ATP and Zn^{2+}-dipicolylamine, releasing the loaded drug and recovering the fluorescence of the upconversion nanocarrier core. Inspired by the application of phenylboronic acid in RNA choromatography, Naito et al. (300) exploited the reversible interaction between phenylboronic acid and the ribose ring present in nucleic acids for ATP-responsive siRNA delivery. In this PEG-polylysine-based polyion complex, phenylboronic acid was conjugated to the cationic polylysine segment. SiRNA was loaded into the nanocomplex through both polylysine-mediated electrostatic interaction and phenylboronic acid generated reversible covalent bonds. ATP sensitivity could be controlled by tuning the ratio between phenylboronic acid and siRNA.

In spite of the efforts devoted to designing ATP-responsive nanosystems, these strategies all face the common challenge of ATP resolution. The ATP aptamer is adenosine specific, making ATP and ADP equivalent triggers. ATP binding polymers are based on phosphate (Zn^{2+}-dipicolylamine) or ribose (phenylboronic acid) competition, making any phosphate or ribose containing molecules viable alternatives to ATP. Currently, the chemical moiety with the highest ATP fidelity involves the use of proteins that utilize ATP as substrate. Aida and co-workers (32) harnessed the specific ATP-consuming capability of a protein chaperon GroEL for designing ATP-responsive DDSs. Naturally, GroEL grabs incorrectly folded proteins into its cavity for refolding and then releases it through conformational changes powered by ATP hydrolysis. In the engineered version of GroEL, GroEL monomer was polymerized into a tube through a Mg^{2+} coordination-based mechanism. Payload could be conjugated to a guest "wrongly folded" protein for loading into the cavity of GroEL. Further modification of the protein assembly with boronic acid derivative made the nanosystem permeable to the cell membrane, where intracellular ATP triggered conformational change of the monomers for nanotube disassembly and drug release.

B. Programmed Multi-Stimuli-Responsive Delivery Systems

To further enhance treatment precision and efficacy, two or multiple physiological trigger-relevant designs can be integrated into the formulations to achieve programmed performance. Nanocarrier activation or drug release could be controlled by physiological triggers in boolean logic ways. The triggers could either work synergistically (where any one of the cues could activate drug activation/release alone, but combined cues will lead to more effective drug release) or sequentially (where the multiple trigger function in tandem and all the triggers are essential) (312).

1. Synergistic stimuli-responsive systems

Synergistic stimuli-responsive nanocarriers have been extensively explored to incorporate a combination of distinct physiological triggers (such as pH/redox, redox/enzyme, pH/ROS, oxidation/redox) for controlled drug delivery. The "either trigger A or trigger B" logic could help achieve a more specific drug targeting (where the target region is characterized by both A and B) or overcoming the heterogeneity of tumors (where A and B are distributed in different regions of the same tumor).

The synergistic effect of pH and redox on drug release has been broadly studied for facilitated drug release. Lu et al. (246) incorporated the pH-sensitive ketal group and the GSH cleavable disulfide bond into a PEG and polyserine based graft co-polymer. The polymer with a disulfide-linked PEG backbone (hydrophilic) and ketal-modified polyserine pendents (hydrophobic) self-assemble into core-shell nanoparticle that encapsulated the hydrophobic drug DOX in the core. It was demonstrated that the dual-responsive nanocarrier could be disrupted after exposure to GSH (10 mM) and acid condition (pH 5.0) either separately or in combination. The delivered DOX could be observed in the nuclei of targeted cells after incubation for 4 h, inducing high levels of apoptosis. Dhar and co-workers (326) demonstrated a redox/esterase dual-responsive nanocarrier for simultaneous delivery of two drugs. Aspirin and cisplatin were co-delivered in the same nanocarrier for their anti-inflammatory and anticancer effects, an efficient combination therapy against prostate cancer resistant to castration. In this nano-formulation, aspirin and cisplatin were conjugated to second-generation dendrons through aromatic ester and aliphatic ester bonds, respectively. Then the dendrons were linked to a PLA backbone for incorporation into a PLGA-PEG-based self-assembly. Facilitated release of aspirin was observed in the presence of esterase while cisplatin was released much faster by sodium ascorbate-mediated reduction. The co-delivery system enabled stringent control of drug dosages and exhibited improved anticancer efficacy in cisplatin-resistant cancer cell lines. Analysis of the empty carrier showed high biocompatibility with

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low cytotoxicity or immunogenicity using a model RAW 264.7 cell line. Pu et al. (347) demonstrated a ROS/pH-responsive nanosystem for targeted delivery of a model anti-inflammatory drug curcumin. This nanocarrier is mainly composed of *N*-palmitoyl and Cy3 modified chitosan and a thioketal-based polymer. Protonation of amine groups in chitosan would affect their charge-mediated repulsion and cause conformational change. ROS would shift the polarity of the polymer from hydrophobic to hydrophilic, destabilizing its association with the nanocarrier. The hydrophobic curcumin assembled into the hydrophobic core of the nanoassembly. The nanocarrier exhibited high stability in physiological pH and efficiently accumulated at inflamed tissue. Rapid cellular internalization was observed within 15 min after reaching the targeted tissue. ROS scavenging effects occurred either extracellularly or intracellularly to exert therapeutic effects.

In addition to responding to two orthogonal stimuli, Wang et al. (447) demonstrated a nanocapsule that could be degraded by two opposite stimuli: GSH and ROS. In this system, the labile phenol ester of the model anticancer drug SN38 was found sensitive to hydrophilic neighboring group mediated electron withdrawing as well as GSH-mediated thiolysis; both of these conditions could trigger the degradation of the phenol ester bond and release the drug. The hydrophilicity-based electron withdrawing was further controlled by a hydrophobic thioester that could be oxidized by ROS to become hydrophilic. The amphiphilic building block constitutes of the hydrophilic PEG and the hydrophobic SN38 self-assembled into a nanocapsule. Exposure to either ROS or GSH could cleave off SN38 and disrupt the nanoassembly. The GSH/ROS dual responsive system holds the promise to overcome the heterogeneous oxidative states at different regions or stages of a tumor.

2. Sequential stimuli-responsive systems

Sequentially triggered DDSs were typically designed for enhancing subcellular specificity. The "trigger A then trigger B" strategy encodes the stimuli-responsive components in different layers of a nanosystem and then exhibits a stepwise activation along the pathway to destination. Trigger A is often an endogenous physiological stimulus, but trigger B could be either from the physiological environment or from predesigned components in the nanocarriers.

Zhang et al. (497) devised an enveloped MSN to harness extracellular MMP and intracellular GSH in tandem for programmed nanoparticle internalization and drug release. A disulfide bond was used to anchor MSN surfaces with β-CD, upon which adamantane linked with a multifunctional peptide was docked. The peptide is composed of a RGD targeting ligand, MMP-sensitive region, and anionic poly(aspartic acid). DOX was loaded into MSN pores as a model drug. After systemic administration, the anionic poly(aspartic acid) augments the circulation efficacy of the nanoparticle by avoiding unspecific uptake. MMP in extracellular environment then cleaves the poly(aspartic acid) shell and exposes the RGD peptide for inducing cancer cell specific uptake. The β-CD will be removed by intracellular GSH to liberate the loaded DOX. Choi et al. (58) devised a pH/HAase co-responsive carrier for stepwise degradation of a core-shell structured nanocarrier for siRNA and DOX delivery. For the core, HA modified with the hydrophobic 5β-cholanic acid self-assembled into nanoparticles, entrapping the DOX inside. To load the anionic siRNA onto the anionic HA nanoparticle, Zn^{2+}-dipicolylamine based RNA receptor was conjugated to the HA core for binding siRNA through ZN(II)-phosphate interaction. To reduce the perturbance of siRNA loading by physiological phosphates, a layer of calcium phosphate-based shell was further coated. After systemic administration, the calcium phosphate shell would be dissolved by extra-tumoral pH and partially expose the HA core for CD-44-mediated targeting and internalization. Further removal of the calcium phosphate shell occurred in the endosome-lysosome, releasing the siRNA together with phosphate and calcium ion for proton-sponge-mediated endosome escape. The encapsulated DOX would then be released after HAase degradation of the HA core.

In contrast to using sequential endogenous triggers, incorporating autonomous responsive components into the nanocarrier enables the design of more sophisticated systems for executing predesigned sequential reactions. The artificially created/potentiated second trigger could complement the absence or low intensity of the second signal for more robust nanocarrier activation or drug release.

Mo et al. (283) demonstrated a pH/ATP sequential responsive system for DOX delivery, where endogenous endolysosomal pH was the first trigger. The second ATP trigger and ATP-responsive moieties were all incorporated in the nanosystem that was programmed to take effect after pH activation. This two liposome-based ATP delivery and ATP-responsive release system was designed for supplementing external ATP to trigger drug release intracellularly. In one liposome modified with pH-responsive fusogenic peptide, the DOX-loaded ATP aptamer duplex was encapsulated, while another unmodified liposome was designed for delivering ATP. After co-administering the two liposomes, they accumulated at the tumor by the EPR effect. Internalization of the liposome in acidic endolysosome activates the fusogenic peptide for lipsome and endosome membrane fusion, exposing the ATP aptamer to ATP for triggering DOX release. In the study by Sun et al. (400), a pH/DNase-based sequential stimuli-responsive system was demonstrated. The endogenous pH was used to activate the second trigger DNase for nanocarrier degradation and intracellular drug release. In this strategy, a DNA-based nanocarrier was prepared by rolling circle amplification for loading DOX through DNA intercalation. The DNase trigger was locked

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by an acid-degradable nanocapsule. The positively charged nanocapsule was adsorped onto the DNA nanoparticle through electrostatic interaction to form stable nanoassemblies. Internalization of the nanoassembly by cancer cells led to acid triggered shedding the polymeric capsule, leading to DNase activation in the endosome. The liberated DNase then chop up the DNA carrier and release the loaded DOX.

Hu et al. (164) demonstrated a biomimetic core-shell nanoparticulate system, in which an acid-degradable polymeric nanocarrier was used as the core for loading the small molecule drug DOX and a membrane derived from platelets for anchoring an anticancer protein TRAIL (164). The "self marker" rich membrane could reduce immunogenicity and prolong circulation time of the nanocarriers. The P-selectin on the coated platelet membrane could also enhance the cancer targeting efficacies by binding to the overexpressed CD44 on solid tumors or circulating tumor cells, augmenting the interaction between the loaded TRAIL and tumor cells. Surface interaction between the core-shell nanocarrier and cancer cells facilitated internalization of the nanocarrier, transporting the nanocarrier to the endosome. The polymeric core will undergo gradual degradation in the acidic endosome due to the incorporation of an acid-labile cross-linker, glycerol dimethacrylate, in the polymeric network. The degradation expedited the release of DOX into the endosomal compartment, which further diffused into the nucleus to exert a synergistic anticancer effect with the membrane targeted TRAIL protein. In another study, a HAase/transglutaminase/pH triple stimuli-responsive system was conceived for co-delivering the TRAIL protein and an antiangiogenic peptide (cilengitide) into the extracellular environment of tumors (163). Endogenous HAase and pH triggers and an exogenous transglutaminase (96) cue provided by the carrier were harnessed to construct a drug containing depot in vivo for sustained release. In this core-shell nanocarrier, the transglutaminase was encapsulated into nanogels composed of HA and the HA nanogel constitutesd the outer layer of the formulation. The drugs TRAIL and cilengitide were encapsulated into a polymeric gel-based core, which was crosslinked by an acid-sensitive crosslinker. The core particle was further modified with human serum albumin (HSA) for enhanced stability. Meanwhile, the HSA also provides acryl and amine groups for controlling the aggregation of core. Once administered systemically, the nanoformulation will accumulate in tumor microenvironment, where the rich HAase will liberate transglutaminase from the HA nanogel. The transglutaminase then catalyzed the crosslinking of the HSA on the surface of the core-nanocarrier, aggregating the nanocores into micro-scaled particles. The micro-aggregation inhibited size-dependent endocytosis of nanocarriers and remained in the extracellular environment, where the mildly acidic condition triggered gradual degradation of the TRAIL/cilengitide containing particle for drug release.

In addition to pH or HAase initiated sequential reactions, endogenous metabolites are also investigated for initiating sequential autonomous responses. Yu et al. (487) designed a multifunctional micelle containing enzymes to convert glucose signal to regional hypoxia, which later triggered the innate reduction of the hypoxia-sensitive moieties in the nanocarrier for disassembly and drug release. Ye et al. (481) harnessed the natural response of pancreatic cells to glucose for controlled insulin secretion. Pingarroń and co-workers (89) demonstrated a Janus nanoparticle that converts glucose or ethyl butyrate into acidic signals through preimmobilized enzymes. Then the acidity would automatically trigger drug release from another part of the nanosystem, pH-responsive MSN, for drug release (89).

V. CLINICAL IMPACT OF DRUG DELIVERY SYSTEM

The confluence of emerging development of materials and biomedical science provides tremendous translational opportunities of innovative DDSs. Whereas the number of commercialized products is still small, compared with the traditional medications. The total number of nanoformulations that are clinically approved or under clinical trials is on the order of ~250 (104). From the perspective of the nanoparticulate platform, nanomedicine under clinical investigation could be classified into liposomes, protein-bound nanoparticles, antibody-drug conjugates (61), polymer-drug conjugates (93), polymeric micelles, and inorganic nanocarriers. Typical issues involving manufacturing scale, homogeneity, and reproducibility need to be addressed for enhancing the success rate in translation (217). Here, we summarized the clinical translation of nanomedicine for anticancer therapies and highlight recent progresses of stimuli-responsive nanoformulations **(TABLE 2)**.

Doxil, DOX-loaded liposome, was the first approved nanomedicine for cancer treatment in 1995. Dramatic increase in DOX delivery efficiency was observed (4- to 16-fold) using the liposome carrier rather than free DOX (118). Decades of development generated dozens more liposome-based formulations for delivering small molecule drugs (daunorubicin, cytarabine, vincristine, etc.) or macromolecular therapeutics (vaccines, nucleic acids) (9, 176). Liposome has become a canonical DDS with typical merits for a robust DDS: *1*) stable loading and protection of either hydrophilic drugs (in the aqueous core) or hydrophobic drugs (in the lipid bilayer); *2*) long circulation, especially after PEG modification; and *3*) efficient EPR effect and improved distribution.

Protein nanoparticle-based nanomedicine has been demonstrated as a robust platform for drug delivery. Abraxane, albumin bound (Nab) paclitaxel nanoparticle, was approved in 2005 for treating a variety of cancers, including breast, pancreatic, lung, ovarian, gastrointestinal, and head neck carcinomas (274, 362). Albumin is an abundant pro-

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Table 2. *Representative clinical translations of nanomedicine delivering anticancer therapeutics*

Name	Formulation	Drug	Status*	Indications
Doxil	Liposome	Doxorubicin	First approved in 1995	Ovarian cancer, AIDS-related Kaposi's sarcoma, multiple myeloma
Marqibo	Liposome	Vincristine	Approved in 2012	Acute lymphoblastic leukemia
Onivyde	Liposome	Irinotecan	Approved in 2015	Metastatic adenocarcinoma
Promitil	Liposome	Mitomycin-C	Phase I (NCT01705002)	Metastatic colorectal cancer (mCRC)
IHL-305	Liposome	Irinotecan	Phase I (NCT02631733)	Solid tumors
DCR-MYC	Liposome	siRNA	Phase I (NCT02110563)	Multiple myeloma, Non-Hodgkins lymphoma, pancreatic neuroendocrine tumors
Anti-EGFR immunoliposomes	Liposome	Anti-EGFR + doxorubicin	Phase I (NCT01702129)	Solid tumors
TKM 080301	Liposome	siRNA	Phase II (NCT01262235)	Neuroendocrine tumors, adrenocortical carcinoma
MM-302	Liposome	Doxorubicin	Phase II/III (NCT02213744)	Breast cancer
Thermodox	Liposome	Doxorubicin	Phase III (NCT00617981)	Hepatocellular carcinoma
CPX-351	Liposome	Daunorubicin + cytarabine	Phase III (NCT01696084)	High-risk acute myeloid leukemia
MM-398	Liposome	Irinotecan	Phase III (NCT01494506)	Metastatic pancreatic cancer
Abraxane	Protein-bound nanoparticle	Paclitaxel	First approved in 2005	Metastatic breast cancer, locally advanced or metastatic non-small cell lung cancer, metastatic adenocarcinoma of the pancreas
Ontak	Fusion protein	Diphtheria toxin	Approved in 1999	Cutaneous T-cell lymphoma
Kadcyla	Antibody-drug conjugate	Emtansine	Approved in 2013	HER2-positive, metastatic breast cancer
Brentuximab vedotin^{+}	Antibody-drug conjugate	Monomethyl auristan E	Approved in 2011	Hodgkin lymphoma and systemic anaplastic large cell lymphoma
Albumin-bound rapamycin	Protein-bound nanoparticle	Rapamycin	Phase II (NCT02646319)	Advanced cancer with mTOR mutations
CRLX-101	Polymeric conjugated	Camptothecin	Phase I/II (NCT02769962)	Small cell lung carcinoma, non-small-cell lung
Eligard	Polymeric nanoparticle	Leuprolide	Approved in 2002	Prostate cancer
Oncospar	Polymeric conjugate	Asparaginase	Approved in 1994	Acute lymphoblastic leukemia
NC-4016	Polymeric micelle	DACH-platin	Phase I (NCT01999491)	Advanced cancers, lymphoma
NC-6004	Polymeric micelle	Cisplatin	Phase I/II (NCT00910741)	Locally advanced and metastatic pancreatic cancer
NK-012	Polymeric micelle	SN-38 (irinotecan metabolite)	Phase II (NCT00951054)	Triple negative breast cancer
PK1^{+}	Polymer-drug conjugate	Doxorubicin	Phase II (NCT00003165)	Breast cancer
Genexol-PM	Polymeric micelle	Paclitaxel	Phase III (NCT00876486)	Breast cancer
Paclical	Polymeric micelle	Paclitaxel	Phase III (NCT00989131)	Epithelial ovarian cancer, primary peritoneal cancer, fallopian tube cancer
Xyotax^{+}	Polymeric conjugate	Paclitaxel	Phase III (NCT00108745)	Ovarian carcinoma, peritoneal cancer
CYT-6091	Gold nanoparticle	TNF-α	Phase I (NCT00356980)	Adult solid tumor

*ClinicalTrials.gov identifier is given for ongoing trials. $^{+}$Drug release that could be triggered by physiological signals.

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tein with a hydrodynamic size of 3.5 nm; it tends to bind hydrophobic agents reversibly within plasma. The protein nanoparticle was used to replace the toxic solvent Cremophor and solve the issue of low solubility of paclitaxel. The 130 nm Abraxane nanoparticles dissociate into smaller paclitaxel-albumin complexes (8 nm) upon administration and enter the cells through an albumin-mediated internalization. Success of Abraxane also inspired clinical translation of other chemotherapeutics suffering from poor solubility, such as rapamycin (62). In addition to protein-bound nanoparticles, protein conjugates and fusion proteins were also successfully translated (115, 295). Trastuzumab emtansine, HER2 antibody conjugated with emtansine via a stable linker, was approved in 2013 for treating breast cancer (438). This nanoformulation significantly improved the survival rate of HER2-positive breast cancer patients. Ontak, a fusion protein of interleukin-2 and diphtheria toxin, was approved in 1999 for targeting cutaneous T-cell lymphoma (115).

Many polymeric based nanoformulations, including polymer-drug conjugate (382) and micelles, are marketed or in the pipeline for translation. Genexol-PM, a paclitaxel-loaded polymeric micelle (199), has been commercialized in many countries, such as South Korea, for treating breast or lung cancer. It is currently under the 505(b)(2) regulatory pathway for accelerated United States FDA approval with Abraxane as a reference. The amphiphilic property of micelles makes them suitable for delivering either hydrophilic or hydrophobic therapeutics, generating various micelle-based formulations under clinical investigation (78, 139, 158, 265, 340, 476).

Inorganic nanocarriers based on different metals have made their way for clinical imaging (137, 269), cancer thermal therapy (196, 256), or therapeutic delivery. CYT-6091, a gold nanoparticle bound with both TNF-α and PEG, has finished phase I clinical trials in patients with advanced stage cancer (230). Improved safety profiles were observed by the gold nanoparticle-based nanomedicine versus free TNF-α.

Several successful translations of physiological stimuli-responsive nanomedicine have been demonstrated. Brentuximab vedotin, a CD30 antibody conjugated with monomethyl auristan E through a cathepsin degradable linker (36), was approved in 2011 for treating refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma. The CD30 antibody reduced undesired internalization by normal cells, and the degradable linker could facilitate drug release inside the tumor microenvironment. The poly(L-glutamic acid)-based nanoparticle with paclitaxel conjugated to the side chain was demonstrated to enhance the solubility of paclitaxel for in vivo administration (227, 389). Endosomal enzymes could trigger the degradation of the carrier for drug release. Meanwhile, the degraded glutamate could further enhance paclitaxel tolerance, enabling higher dosage. The poly(L-glutamic acid)-paclitaxel formulation with the trade name Xyotax is currently undergoing phase III clinical trials. Similarly, PK1, a polymer conjugated DOX formulation releasing DOX in response to endosomal pH or enzymes, is also undergoing clinical investigation (383, 427).

VI. SUMMARY AND OUTLOOK

In summary, nanocarriers have contributed to the promising future of "precision medicine" by improving the ADME profiles of various drugs. Increased understanding of the physiology-material interaction has engendered rational guidelines for designing nanoformulations to overcome extracellular and intracellular barriers. Further "evolution" of nanomedine has shown emerging "intelligence" to sense the physiological environment and act accordingly. Although the list of FDA-approved nanomedicine sheds light on the encouraging future of nanomedicine, more efficient and "smarter" nanoformulations are needed to meet the demands of the market.

To facilitate clinical translation of novel formulations, actions from different perspectives must be taken.

1) Further understanding of the physiology behind diseases is needed (30). Theoretically, diseases are caused by a combination of perturbances to the complex molecular system of patients. The same disease might be caused through different pathways in different patients, and the genetic variations among patients further complicate the outcome of a therapy. In 2015, the federal government announced the Precision Medicine Initiative for optimized therapies based on the genetic and molecular analysis of a patient (15). In this context, a more rational match between the patient and the tested therapy holds the promise to improving translational rates. Moreover, individual patient-responsive medications can be expected when taking into account systematic data analysis associated with the patient's physiological conditions.

2) Generation of more accurate animal models is needed. Animal model-based studies are used to see drugs or formulations with promising animal study data failed in human tests (28, 431). Apart from the flaws in design of animal or human study, larger error could be introduced due to the incapability of animal models to accurately reflect the disease in humans (430). For example, the expressway for tumor-targeted drug delivery, the EPR effect, is not as robust in human subjects as in preclinical animal models (215). Overexpression of receptors could be transient, and the fluctuating receptor density would significantly compromise targeted nanomedicine.

3) Engineering of smart but simple formulations is needed. Structurally simplified formulations are more competitive

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than complicated ones from the perspective of quality control. The pursuit of multifunctional nanomedicine often results in the appendage of extrafunctional modules. One more component in the nanoformulation not only raises the total cost but also increases the challenge in characterization, scalability, and reproducibility.

4) Interdisciplinary collaboration (291) is needed. The field of nanomedicine is multidisciplinary in that it requires knowledge and skills from different areas (such as life science, material science, chemical engineering, mechanical engineering). It is impossible for any researcher with a single background to realize the process from conception to market. A team composed of experts from different areas is necessary for nanomedicine development. Collaboration between academia and pharmaceutical companies is also an important link for connecting frontier technologies with commercialization channels.

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