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REVIEW

Current research trends of nanomedicines

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Clinical translation

Abstract Owing to the inherent shortcomings of traditional therapeutic drugs in terms of inadequate therapeutic efficacy and toxicity in clinical treatment, nanomedicine designs have received widespread attention with significantly improved efficacy and reduced non-target side effects. Nanomedicines hold tremendous theranostic potential for treating, monitoring, diagnosing, and controlling various diseases and are attracting an unfathomable amount of input of research resources. Against the backdrop of an exponentially growing number of publications, it is imperative to help the audience get a panorama image of the research activities in the field of nanomedicines. Herein, this review elaborates on the development trends of nanomedicines, emerging nanocarriers, *in vivo* fate and safety of nanomedicines, and their extensive applications. Moreover, the potential challenges and the obstacles hindering the clinical translation of nanomedicines are also discussed. The elaboration on various aspects of the research trends of nanomedicines may help enlighten the readers and set the route for future endeavors.

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1. Introduction

Nanomedicines are generally defined as medicines that apply nanotechnology and are intended for therapeutic or diagnostic applications with dimensions controlled within the nanoscale range (1−1000 nm)[1]. In pharmaceutical sciences, nanomedicines refer to the use of nanotechnologies in producing active pharmaceutical ingredients (APIs) as nanoscale particles or combining APIs with suitable nanomaterials to produce nanoscale particles further formulated into versatile dosage forms. The nanomedicine market is dominated by applications based on drug delivery, surpassing regenerative medicine, diagnosis both *in vitro* and *in vivo*, and vaccine-oriented applications. For cancers and infectious, cardiac, and orthopedic disorders, almost 40% of phase II clinical trials are based on nanomedicines[2]. Searching the database of ClinicalTrials.gov using the keyword "nanomedicine", over 500 active clinical trials involving nanoparticles are found by the end of 2022. So far, the US Food and Drug Administration (FDA) of the United States has approved more than 60 nanomedicines[3]. Fig. 1 illustrates the milestones in the development of nanomedicines.

Against the backdrop of tremendous input into the development of nanomedicine products, basic, translational, and product-oriented research is flourishing too. A huge number of nanocarrier drug delivery systems (NDDSs) prepared from various materials, including lipids, polymers, proteins, metals, and inorganic materials, have been reported over the past decades[4−10]. NDDSs work through versatile mechanisms in effectuating transporting across biobarriers; however, targeted delivery is always the top quest. Passive targeting is frequently combined with active targeting to optimize drug delivery to diseased sites such as tumors and minimize non-target drug distribution. Active targeting is commonly attained by surface modification of nanocarriers with ligands recognizing and binding with receptors expressed on membranes of target cells[11−16]. Actively and passively targeted nanomedicines have been exploited as imaging tools, in addition to therapeutics, in recent years with impressive preclinical and clinical potentials[14,17−22].

Albeit prosperous in research, most NDDSs under investigation get lost in translation owing to one or more issues of polymer/carrier toxicity, poor manufacturability, instability, and difficulties in quality control. Even though problems have been actively addressed, little is known about the *in vivo* fate and underlying mechanisms, which hampers the successful translation of NDDSs into commercial products. It is crucial to unveil the biological (*in vivo* and subcellular) fate by exploring where, when, and how the fundamental components of NDDSs interact with the body and with each other[23−27].

This review aims to update the research trends of nanomedicines. In addition to pinpointing the development trends by data analysis and introducing emerging nanocarriers and trigger-responsive mechanisms, we also discuss the *in vivo* fate and safety issues of nanomedicines, as well as their potential in treating various diseases. This review aims to provoke discussion which may benefit the translation of notions into clinical products.

2. Bibliographic analysis

Increasingly attention has been paid to nanomedicines, and the number of products under clinical investigations is growing rapidly. A search of the database "Web of Science" using the keyword "nanomedicine*" from Jan 1999 to Dec 2022 gives a total number of 100,192 publications with 80% published from 2015 to April 13, 2023 (Fig. 2). Meanwhile, more and more efforts in developing advanced nanomedicines to further enhance therapeutic efficacy and reduce side effects is still in full swing.

To date, more than 60 nanomedicines have been marketed. Over 500 nanomedicine-related products are in the stages of clinical trials (Data records are retrieved from ClinicalTrials.gov and the Cortellis Drug Discovery Intelligence database). Most of them are in phase I (33%) or II (21%) clinical trials for the treatment of cancer (53%), infectious diseases (14%) (Fig. 3), and other diseases (Fig. 4), such as inflammation and those inflicting the circulatory, immunological, nervous, cardiovascular, mental, endocrine and metabolic systems. Liposomes/lipid nanoparticles comprise the biggest fraction of carriers (33%), antibody-drug conjugates the second with 15%, polymeric nanoparticles, polymer-drug/protein conjugates, and viral vectors the third with 9%−10% each, and each of other carriers with less than 5% (Fig. 5). The success of lipid-based ones, such as liposomes and lipid nanoparticles, is mainly attributed to the superior biocompatibility and biodegradability conferred by their endogenous compositions or derivatives. Other drug carriers, such as polymeric micelles, are hot in earlier research but have a low translation rate, owing to issues of safety, stability, mass production, and quality control. The most successful nanomedicines target cancer and infectious disease treatment. For the treatment of the COVID-19 pandemic, nanomedicines were considered promising

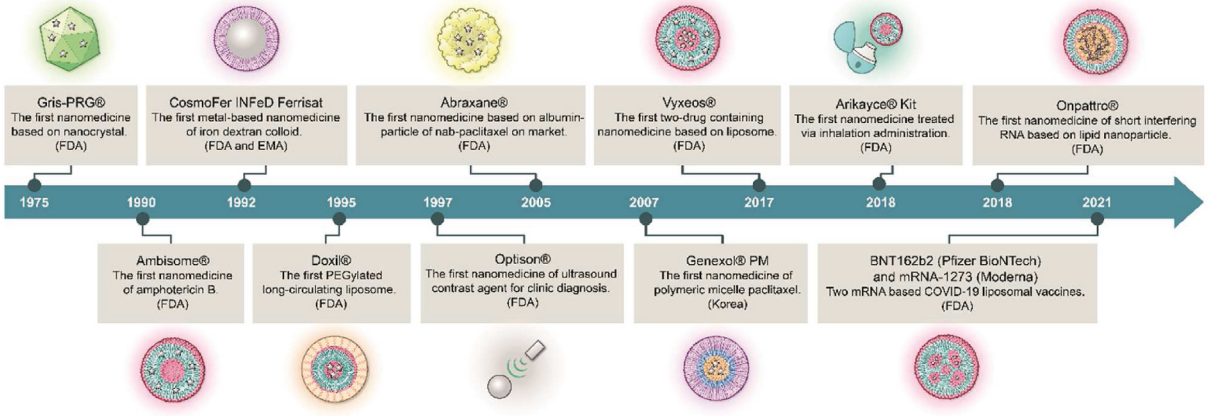

Figure 1 Historical timeline of major nanomedicine development.

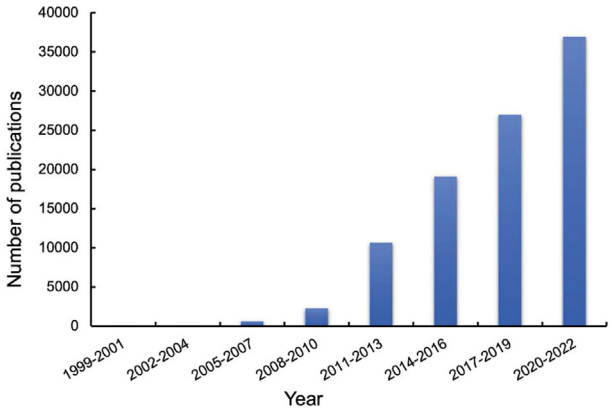

Figure 2 The trend of publications related to nanomedicines over the past decades. Data are derived from the Web of Science utilizing the keyword "nanomedicine*".

strategies for developing new vaccines against coronavirus. For instance, to meet the urgent need in 2020, two types of lipid-based messenger RNA (mRNA) vaccines (Pfizer BioNTech Vaccine and Moderna COVID-19 Vaccine) were launched because they could effectively deliver antigens, mimic the structure of the coronavirus, and serve as adjuvant ideally[28,29].

3. Emerging nanocarriers

Nanomedicines with special biological effects have been widely applied in various diseases for treatment[30], monitoring[31], diagnosis[32], and controlled drug release[33], as conventional chemical drugs present prevalent defects, including insufficient accumulation in specific lesion sites,[34] rapid metabolic clearance in circulation[35], and extensive systemic toxicity[36] Owing to the unique properties of a specific nanostructure or nanomaterial[37], such as nanoscale particle size[38] and particular surface modifications[39], nanocarriers have been endowed with a legion of advantages, for example, increasing the selectivity of drug delivery[40], improving drug solubility and stability[41], synergizing delivery of multiple drugs[42], reforming bioavailability,[43] mediating sustained or controlled drug release[44], enhancing therapeutic efficiency, and reducing side effects[45]

Over the past decades, nanocarriers of diverse structures and constituents such as liposomes[46,47], nanocrystals,[48–52] carrier-free nanoassemblies,[53] albumin nanoparticles[54], polymeric micelles[55], and nanoemulsions[56] have been intensively investigated both in basic research and commercial translation[57] Liposomes (Doxil®, 1995) are the first nanocarriers approved by FDA. The treatment spectra of liposomes have expanded into various diseases with drug payloads covering a range of small molecules and biomacromolecules (*e.g.*, peptides, genes, monoclonal antibodies, etc.)[58–60].

In company with continuing advances in nanotechnology and a rapidly growing nanomedicine market, more and more nanomedicines with enhanced therapeutic efficacy have been approved[57] In addition, the emergence of advanced natural/synthetic materials[61] and novel nanocarriers such as lipid-based nanoparticles[62], extracellular vesicles[63], bioinspired and biomimetic nanocarriers[64], metal–organic framework (MOF)[65] and so on broaden the horizon of nanomedicine research and development. Herein, examples are given to illustrate the current applications of emerging nanocarriers (Fig. 6).

3.1. *Lipid nanoparticles*

In recent years, lipid nanoparticles (LNPs) have reinvigorated interests and redeveloped to tackle unmet needs in the delivery of more challengeable entities, notably mRNA and deoxyribonucleic acid (DNA) antigens[66], oligonucleotides[67], and CRISPR[68] LNPs integrate the advantages of conventional colloidal nanocarriers while negating some related drawbacks. Conventional LNPs are generally suitable for encapsulating and delivering lipophilic drugs and well adapted for administration *via* different routes, including transdermal, dermal, intramuscular, mucosal, and ocular routes. Through optimization of constituting lipids and preparative techniques, as well as functional surface modifications, LNPs could be engineered with appealing characteristics[69]: 1) improved biocompatibility; 2) optimized drug encapsulation capacity; 3) harmonized co-encapsulation of both hydrophilic and hydrophobic drugs; 4) reduced toxicity; 5) controlled or targeted delivery of therapeutic agents.

LNPs-based drug delivery has been used to treat various diseases, including cancer[70], infections[71], and those inflicting the cardiovascular[72], neural[73], and dermal systems[74] *via* different routes (*e.g.*, oral, parenteral, ocular, topical, brain, and pulmonary routes). Some of them, exemplified by Onpattro®, have been approved for clinical use as systemic delivery platforms[75] A recent study reported a novel LNP-based mRNA delivery system rationally constructed by mitigating surface charge from neutral to anionic, illustrating the potential to selectively target hepatic reticuloendothelial system (RES) *via* the comprehensive *in vivo* biodistribution and clearance mechanism of LNPs[76] Also, LNPs can target the spleen and lungs by replacing standard helper lipids with anionic (phosphatidylserine, phosphatidylglycerol, and phosphatidic acid) or cationic (1,2-

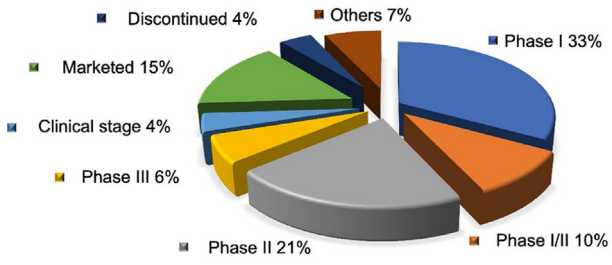

Figure 3 Statistics of nanomedicines marketed and in different stages of clinical trials.

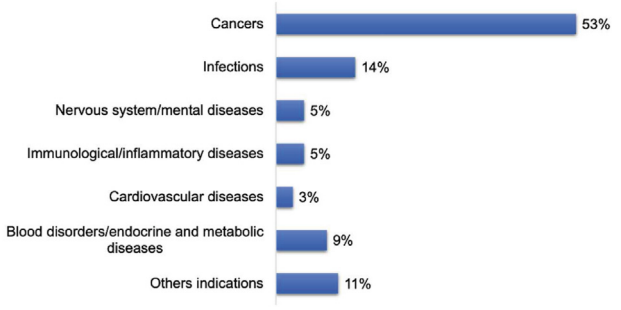

Figure 4 Indications of nanomedicines on the market or in clinical trials.

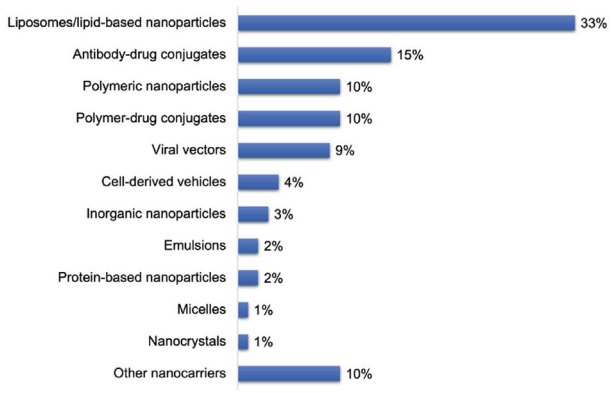

Figure 5 The percent (%) of nanomedicine types on the market or in clinical trials.

dioleoyl-3-trimethylammonium propane (DOTAP) and ethyl phosphatidylcholine) lipids[77]

Furthermore, LNPs played a vital role in developing vaccines against COVID-19, highlighting the powerful potential of delivering nucleic acid-based drugs and vacciness[78] The keys to this success rest with the tremendous impact of LNP components, including structure, size, apparent pKa, stability, encapsulation efficiency, cellular uptake, and endosomal escape[79] Despite the numerous advantages of LNPs in drug delivery, the translation from preclinical concepts to industrial scale-up production still lags behind[80] Stable, reliable, and reproducible scale-up methods are in urgent need for LNP production.

3.2. *Extracellular vesicles*

Extracellular vesicles (EVs) are heterogeneous submicron cell-derived nanoparticles that function as critical mediators in intercellular communication and many (patho)physiological processes[81,82] EVs are generally nanosized (40−1000 nm) and comprised primarily of lipid membranes, with various specific molecules embedded, including proteins, nucleic acids, metabolites, and enzymes[83] Engineered EVs function to deliver their payloads to nearby and distant recipient cells[84] Defined by their endosomal origin and size, EVs are typically categorized into three subpopulations: 1) apoptotic bodies (50−5000 nm), which are generated by fragmentation from cells undergoing programmed death[85], 2) microvesicles (100−1000 nm) which are derived from specific types of endosomes and can fuse with the plasma membranes to release their content in the extracellular spaces[85], and 3) exosomes (40−150 nm) which are derived from multivesicular bodies[86]. As phospholipid membrane vesicles derived from various cells that play a key role in antigen presentation and cell−cell communication, EVs are often utilized to encapsulate and deliver biopharmaceuticals, such as proteins, antigens, microRNAs (miRNAs) and mRNAs[8].

EVs have drawn considerable attention and emerged as potential drug delivery carriers, owing to their bestowed biocompatibility and ability to circumvent biobarriers[8]. For instance, EVs show the potential to cross the blood−brain barrier (BBB) and blood−brain tumor barrier (BBTB), one of the most intriguing and challenging obstacles in brain delivery. Niu et al.[86] fabricated natural EVs-based nanoparticles decorated with doxorubicin (DOX)-loaded heparin-based nanoparticles (EV-DNs). Through EVs-mediated receptor-dependent transcytosis and membrane fusion, EV-DNs could bypass BBB/BBTB and penetrate tumor tissues, significantly promoting tumor accumulation, cellular internalization, and antiproliferation efficiency[86]. In addition, various functionalized modifications have been engineered on EVs to reinforce their natural features[87].

So far, several clinical trials of EVs-based therapeutic agents have been completed or are underway to investigate their *in vivo* therapeutic efficacy and safety[88]. Some exosomes loaded with tumor peptides/drugs were involved in Phase I clinical trials to treat advanced non-small cell lung cancer, metastatic melanoma, colorectal cancer, etc[89]. However, even though extensive studies have demonstrated the promise of EVs-based drug delivery systems, clinical translation of EVs-based therapeutics remains challenging, owing to obstacles such as low drug loading, low isolation yield, potential safety concerns, and considerable complexity[90]. Meanwhile, insights into the mechanisms that endow EVs with effective immune escape, intracellular uptake, and targeted delivery are needed to unlock their full potential[63,91].

3.3. *Bioinspired and biomimetic nanocarriers*

Biomimetic drug delivery systems (BDDSs), inspired by “natural camouflage" strategies, recently emerged to overcome defects of conventional synthetic nanocarriers, such as insufficient targeting selectivity[92], easy recognition and clearance by the RES[93], inadequate biocompatibility[94], poor tumor penetration and intracellular internalization[6], and excessive systemic toxicity[95]. BDDSs can mimic natural cells and viruses by regulating size, surface charge, shape, and material consistency[64]. Various mammalian cell-, virus- and bacteria/fungus-inspired drug delivery systems are increasingly employed in biomedicine and targeted drug delivery[96]. To date, bioinspired and biomimetic carriers have been developed as promising tools for drug delivery because they can mimic features of biological constituents and systems[97]. Through the novel strategy of “articles used as homing systems” that takes inspiration from biological molecules, organisms, and cells, these carriers can deliver the therapeutic agents to the targeted site more specifically than conventional nanocarriers[98].

Biomimetic or bioinspired nanocarriers are constructed by integrating biomimetic surface functionalization of synthetic nanocarriers and natural cell-derived or bioinspired artificial membranes. They inherit the plasticity and flexibility of synthetic materials and the diverse biological functionalities of biomimetic materials[99]. Many endogenous materials, including erythrocytes[100], leukocytes, tumor cells, macrophages, and neutrophils, are used as “self-camouflage" modifications in constructing biomimetic nanocarriers. Biomimicking endows conventional nanocarriers with significantly enhanced biocompatibility, prolonged *in vivo* circulation, and the ability to target specific pathological sites[101−103]. Song et al.[103] fused platelet membranes onto poly(-lactic-*co*-glycolic acid) (PLGA) nanoparticles to treat atherosclerosis. The membrane-coated nanoparticles demonstrated higher affinity to the plaques and significantly enhanced targeting efficiency in lesions than the naked nanoparticles. Given the simplified endogenous functions of vectors limited by a single cell type, multiple cell-membrane fusing is always used. Bu et al.[104] modified iron oxide magnetic nanoparticles using hybridized cancer stem cell and platelet membranes for dual-targeting tumors highly expressing CD44.

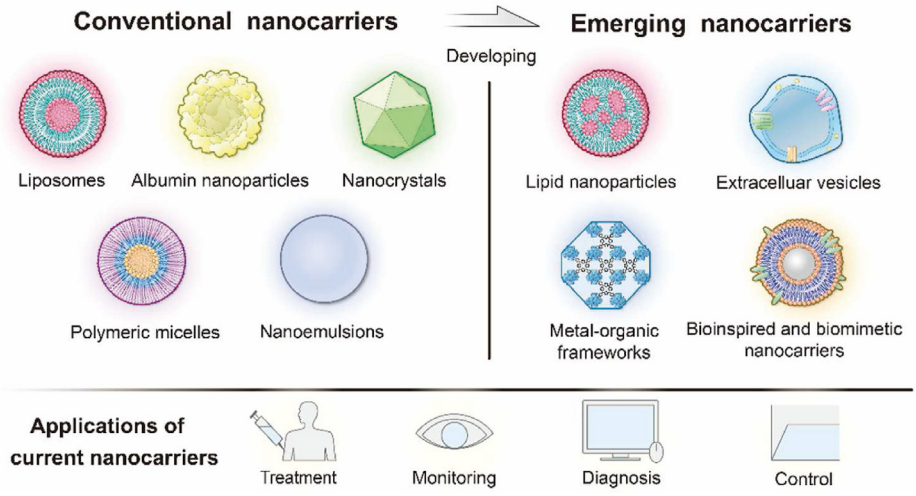

Figure 6 Overview of development from conventional nanocarriers to new nanocarriers and their applications.

Increasing BDDSs focus on targeted drug delivery, aiming at transporting drugs into the cytoplasm and reducing toxicity to circulation, organs, and tissues[105]. In particular, the emergence of biomimetic or bioinspired nanocarriers promotes the application of drug delivery because they are promising to solve the problems regarding biological drugs, insoluble drugs, and those with high toxicity[106]. However, their translation remains challenging[107]. For instance, the clinical trial of biomimetic nanocarriers always suffers from tough checks compared to traditional small molecular drugs[108]. Furthermore, continuous scale-up production presents another obstacle to translation[109].

3.4. Metal-organic framework

MOFs, advanced hybrid porous structures constructed by metal ions/clusters and organic linkers, have received broad attention as emerging nanocarriers in the past decade[65,110]. MOFs have become promising drug delivery platforms owing to their advantages, including well-defined composition and structure, ultra-high surface area and porosity, adjustable pore size, biocompatibility, low toxicity, and versatile functionality[111]. MOF has flexible variable and adjustable properties and thus can be used as nanocarriers to load various types of drugs[112]. The MOFs with hydrophobic pores, such as the first MOF carrier-MIL (Materials of Institut Lavoisier), are suitable for encapsulating drug molecules with poor aqueous solubility[113]. Conversely, MOFs with hydrophilic pores can carry either positive or negative charges and can be applied to load the charged-active compounds[114]. For instance, Zhao et al.[115] constructed MOF nanoparticles (ZIF-8) for miRNA delivery. The nanoparticles significantly enhanced miRNA stability, released miRNA responsively in lysosomes, and induced apoptosis of tumor cells *via* the generation of reactive oxygen species triggered by Zn^{2+} [115]. Hitherto, the porous structures impart MOF-based nanocarriers a superior capacity to load small molecular, macromolecular, or biomolecular cargoes and realize controlled drug release.

In addition, various surface chemical modifications have been utilized to enhance suspending stability, protect against degradation, and improve the delivery efficiency of MOF-based nanocarriers[116]. Zhuang et al.[117] coated MOFs with the platelet membranes by physical co-extrusion to develop platelet membrane-cloaked porous MOFs, aiming to load a small-interfering RNA (siRNA) (P-MOF-siRNA) for specific gene slicing therapy. The results indicated that P-MOF-siRNA had natural tumor-homing characteristics and biocompatibility and significantly enhanced the delivery efficiency and siRNA stability[117].

Collectively, MOFs exhibit the huge potential to act as drug carriers and MOF−synergistic drug systems[118]. The porous structure makes MOFs candidates for drug loading and flexible modification due to the multi-selectivity of metal ions and ligands[119]. However, several challenges remain for their clinical translation. For instance, drug molecules incorporated by ordinary pore encapsulation or surface adsorption suffer from gradual leakage due to insufficient interaction forces. The covalent binding provides stronger interactions; however, the complex synthetical procedures may compromise the efficacy of functional molecules[120]. Moreover, their fundamental understanding is yet to be discovered, *e.g.*, metabolism, excretion, and toxicity[121].

4. Trigger-responsive designs in nanomedicines

Nanomedicines hold tremendous potential for the selective delivery of therapeutic agents and efficient treatment of various diseases[2,122]. Surface modification is widely used to elevate nanoparticle selectivity. Incorporating trigger-responsive materials is always utilized to improve delivery and tackle systemic and intracellular drug delivery barriers[123]. The triggers can be classified as exogenous (*e.g.*, light, radiation, ultrasound, and magnet)[124] and physiological/pathological triggers (*e.g.*, pH, temperature, enzyme, redox, and hypoxia)[125], as summarized in Fig. 7.

4.1. Exogenous triggers

4.1.1. Light

Light has been extensively investigated as an attractive trigger for responsive nanomedicines, whose strength could be adjusted by modulating specific areas, wavelengths, and irradiation power. Various nanocarriers (*e.g.*, liposomes[126], polymeric micelles[127], poly-ion complex vesicles[128], and nanorods[129]) have been

designed with light- or photo-responsiveness to simultaneously improve the treatment efficiency and minimize the potential damage to normal tissues. In general, nanomedicines could respond to light triggers *via* several mechanisms: 1) disassemble nanocarriers or reversibly assemble nanoparticles by breaking light-sensitive chemical bonds[130]; 2) induce responsive drug release at target sites[131]; 3) activate temperature changes in photothermal therapy (PTT)[132]; 4) generate reactive oxygen species (ROS) in photodynamic therapy (PDT)[133]; 5) mediate light-activated imaging for multi-mode theranostics[134].

Light-triggering is promising in controlling drug delivery and precise treatment[135]. In a recent study, a near-infrared (NIR) photo-controlled spherical nucleic acid (PSNA) was reported for delivery of siRNA and antisense oligonucleotide (ASO)[136]. Upon irradiation by NIR light, singlet oxygen ($^1O_2$) was produced by the inner photosensitizer in tumor cells, disassembling PSNA by breaking the $^1O_2$-cleavable linker between siRNA and ASO[136]. In addition, light can also promote drug delivery by intervening in primitive biological functions. For example, Vickerman et al.[137] developed light-triggered-engineered red blood cells (RBC) for targeted delivery of proteins, using light-induced RBC hemolysis and subsequent drug release. The surface modification with a dormant hemolytic peptide enabled the RBCs to have prolonged circulation time and selectively deliver coagulating enzymes under spatiotemporal control[137]. However, using light-responsive nanomedicines is always limited by insufficient sensitivity and poor tissue penetration of common light[138].

4.1.2. *Magnet*

Nanocarriers constructed by magnet-responsive materials can respond to magnetic triggers non-invasively under an external magnetic field[139]. Magnet-triggering could mediate targeted drug delivery and generate local hyperthermia for responsive drug release or PTT[140]. So far, various magnet-responsive NDDSs have been investigated, such as liposomes[141], polymeric micelles[142], polymer nanoparticles[143], superparamagnetic iron-oxide nanoparticles (SPIO)[144], magnetic nanogels[145], and magnetic nanoclusters[146]. Recently, Chung et al.[147] developed magnet-responsive nitrogen oxide (NO)-releasing materials conjugated with MOF-derived porous Fe_3O_4 nanocomposites for selective activation of NO and treatment of bacteria-infected cutaneous wounds. The results demonstrated burst or intermittent NO-releasing using continuous or pulsatile magnet stimulation[147].

Magnet-responsive nanomedicines are often designed for local therapy. Conventional magnet-responsive nanoparticles could be endowed with drug delivery by surface functional modifications[141]. For example, Schleich et al.[148] developed a dual tumor targeting (active/passive) PLGA nanomedicine loading paclitaxel and SPIO. The integrated nanoparticles exhibited enhanced tumor targeting and effective tumor ablation, owing to magnet-mediated guidance and bifunctional arginine-glycine-aspartic acid (RGD) modification.[148]

4.1.3. *Ultrasound*

Ultrasound by frequency-switchable sound waves is a widely used exogenous trigger[149]. Ultrasound-responsive nanomedicines are always used in bioimaging[150], diagnosis[151], triggered drug delivery, and therapy[152]. An ultrasound-responsive nanoemulsion was developed for intratracheal and intravenous delivery for lung cancer therapy, using low-intensity focused ultrasound (LIFU)

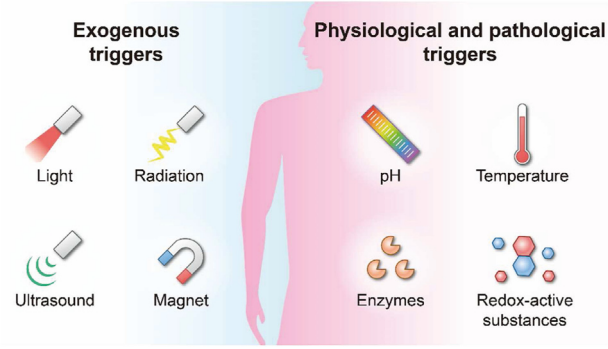

Figure 7 Mechanisms involved in responsive nanomedicines. Physiological and pathological triggers include pH, temperature, enzymes, redox, etc. Exogenous triggers include light, radiation, ultrasound, magnet, etc.

guided by ^{19}F magnetic resonance imaging[153]. The nanoemulsion could rapidly distribute in the lungs and tumor tissues after intravenous injection. In particular, LIFU triggered burst drug release and increased the permeability of tumor tissues[153]. In another study, air-trapped poly(butyl cyanoacrylate) nanocarriers loaded with cyclodextrin were reported for multimodal imaging and therapy of atherosclerosis[154]. The results indicated that the ultrasound treatment allowed increased uptake and elevated anti-atherosclerotic efficacy in an *ApoE*$^{-/-}$ mouse model.

In addition, ultrasound can provide some special biological effects for developing the desirable ultrasound-responsive nanomedicine[155]. Lammers et al.[156] used poly(butyl cyanoacrylate)-based microbubbles (MB) to load ultrasmall superparamagnetic iron oxide (USPIO) nanoparticles on the shell for mediating and monitoring BBB permeation. The USPIO-MB can be destroyed by exposure to transcranial ultrasound pulses, resulting in acoustic forces inducing vessel permeability and promoting the accumulation of USPIOs in extravascular brain tissue. However, the use of ultrasound-sensitive nanomedicines is limited to untoward biodistribution[157] and trans-vascular transport due to large size[158].

4.2. *Physiological and pathological triggers*

4.2.1. *pH*

The pH conditions *in vivo* differ significantly because of the differences in compositions and microenvironment of organs and tissues. Generally, the pH values are around 7.0−7.4 in normal blood and tissues[159], 4−6 in intracellular lysosomal/endosomal organelles[160], and 6−8 in the lesions (*e.g.*, tumor microenvironment)[161]. The pH-responsive approach can be used for precise delivery, using the pH gradients between normal and diseased tissues[162]. Pujara et al.[163] prepared pH-responsive nanoparticles using bovine β-lactoglobulin (BLG) and succinylated BLG crosslinked with epsilon poly-L-lysine to improve oral delivery of curcumin. As succinylated BLG dissolved readily at pH 7.4, the constructed nano colloids respond to the pH trigger for sustained release[163]. Conversely, curcumin was not released in acidic conditions and was protected from degradation[163]. In addition, the pH-responsive mechanism can be applied to regulate cellular ion homeostasis. Ploetz et al.[164] reported lipid-coated iron-based MOF nanocarriers (Lipid@MOF) for delivering iron ions into cells. The constructed Lipid@MOF nanoparticles were absorbed into cells,

followed by the release of iron ions due to degradation in response to acidic pHs in the lysosomes[164]. The authors concluded that Lipid@MOF could control the release of iron ions into cells to promote distinct ferroptosis- and pyroptosis-mediated programmed cell death and reduce off-target side effects[164].

4.2.2. *Temperature*

Temperature is another trigger attracting extensive attention in drug delivery. Various smart temperature-responsive NDDSs, initiated by external temperature and stimulating the body temperature, have been designed for precision medicine[165–167]. Prawatborisut et al.[168] developed a nanoparticle coated with poly(*n*-isopropyl acrylamide). The results indicated that the hydrophobicity and protein binding on nanoparticles could be altered by adjusting the temperature during incubation with human plasma[168]. The temperature-dependent protein binding significantly affected the nanoparticle uptake by RAW264.7 and HeLa cells, and nanoparticles primarily associated with apolipoprotein A1 and E at 37 °C, while bonded with apolipoprotein J at 25 °C[168]. Inoue et al.[169] synthesized amphiphilic side-chain liquid crystalline polymers (LCPs) having nematic−isotropic phase transition at physiological temperature and size of ∼130 nm in aqueous media. The formed LCPs demonstrated enhanced drug release at temperatures higher than the nematic-isotropic phase transition temperature (T_{NI}) but reduced drug release at temperatures lower than T_{NI}[169].

4.2.3. *Enzymes*

Enzymes, such as lipases, matrix metalloproteinases (MMPs), cathepsins, glycosidases, and oxidoreductase enzymes, play vital roles in biological reactions and homeostasis. They act as plausible triggers upon abnormal expression in specific tissues/organs for enzyme-responsive drug delivery. The enzyme-triggered mechanisms applied to accelerate chemical reactions include: 1) directly breaking the bond/conjugation between drugs and carriers for enhanced drug release[170], 2) disassociating or degrading the carrier structures *via* enzyme-induced hydrolysis[171], and 3) cleaving the enzyme-sensitive chemical bonds for activating prodrugs, biological probes, ligands, and so on[172]. Enzymes-sensitive nanomedicines provide great opportunities in diagnosis, monitoring, tissue prevention, and disease treatment[173].

For instance, an enzyme-sensitive paclitaxel-loaded hyaluronic acid nanogel modified with CD44 and biotin was constructed for targeted delivery to breast cancers[174]. Rapid release of paclitaxel was demonstrated, caused by the catalysis of hyaluronidases and/or lipases after dual bio-specific receptor-mediated tumor-targeting[174]. To improve the sensitivity, multiple responsive mechanisms could be involved[175]. He et al.[176] developed enzyme-responsive nanoparticles, using mitochondria-targeting triphenylphosphonium derivative as cores loaded with lonidamine dimers and CD44-targeting hyaluronic acid (HA) as shells. The results demonstrated that the system could sensitively respond to hyaluronidases for degradation of HA-DOX shells and accelerate DOX release in cascade[176].

4.2.4. *Redox*

Inspired by different reduction capacities in specific pathophysiological conditions, redox-sensitive nanomedicines have been extensively studied[177]. Many engineered nanocarriers, such as liposomes, polymersomes, polymeric micelles, gold nanoparticles, and polymer−drug conjugates, are integrated with a redox-responsive strategy for targeted therapy[178]. Lou et al.[179] reported redox-responsive paclitaxel-maleimide prodrug nanoassemblies. By conjugating with paclitaxel and albumin-binding maleimide, the paclitaxel prodrugs could self-assemble into nanoparticles without excipients and immediately bind to albumin in circulation following intravenous administration and readily disintegrate into prodrug/albumin nanoaggregates, facilitating targeted accumulation in tumors *via* albumin receptor-mediated active targeting[179]. Furthermore, through controllable redox-responsive reactions, the *in vivo* fate of nanocarriers can be effectively regulated to improve delivery efficiency while reducing unwanted side effects. For instance, redox-responsive hyperbranched polyprodrug micelles by Zhong et al.[180] displayed on-demand and accurate control of gemcitabine release in the tumor acidic microenvironment with minimized systemic toxicity.

Abundant trigger-responsive nanomedicines have been extensively investigated in drug delivery; however, few formulations have been translated[181]. The following challenges often limit the translation: 1) the differences between human and animal models; 2) inadequacy *in vivo* validation of the triggering mechanisms; 3) systemic toxicity, side effects, biodegradability, biocompatibility, and biosafety pending improvement.

5. *In vivo* behaviors of nanomedicines

The leading trait that endows nanomedicine with promising drug delivery capabilities is its small size which generally falls within the nanoscale range with greatly reduced size-dependent untoward interactions. Nevertheless, the extraordinarily small size poses a big challenge in tracking and unraveling the *in vivo* behaviors of nanomedicines. Ignorance or negligence of the *in vivo* fate presents as one of the bottlenecks to translation of preclinical nanodelivery designs to clinical therapeutic products[25,26]. Unraveling the *in vivo* and subcellular fate of nanomedicines is gaining interest from various disciplines recently[23,25–27,182]. It is believed that a good understanding of the *in vivo* behaviors of nanomedicines helps optimize the designs of delivery systems and accelerate the process of product development.

5.1. *The general consideration on in vivo fate of nanomedicines*

The *in vivo* process of nanomedicines begins when they make a contact with the body. Fig. 8 describes the sequential steps that may take place to nanomedicines after entry into the body[183].

5.1.1. *Biobarriers restraining the migration of nanocarriers*

The biological barriers present as the first and outmost impediment to the entry of nanomedicines into the body. These physiological barriers made up of densely packed cells prevent both paracellular and trans-cellular transport of nanocarriers, hence restricting the gross circulatory exposure of nanomedicines[184]. Tight junctions formed from multiprotein complexes serve as gatekeepers for paracellular trafficking across closely packed epithelial cells. Nanocarriers with sizes bigger than a few tens of nanometers (*e.g.*, micelles) cannot go across membrane pores less than one nanometer in diameter. However, nanocarriers could be taken up by epithelial cells *via* endocytosis pathways, whereas the "easy endocytosis, hard exocytosis" conundrum prevents nanocarriers from crossing multilayers of cellular barriers[185–187]. Except for the intravenous route, nanomedicines administered *via*

different routes (*e.g.*, ocular, transdermal, oral, pulmonary, nasal, etc.) are hampered by the epithelial barriers and tight junctions[184,188]. In addition to the epithelial barriers, the endothelial barriers block the back door to the blood circulation[184,189]. Even for the intramuscular and subdermal routes, nanomedicines are unable to be delivered to the blood circulation directly, and there are complicated biobarriers that restrain the migration of nanocarriers.

5.1.2. *Uptake by the mononuclear phagocyte system*

Nanocarriers are generally recognized as foreign objects with nanoscale sizes. The first thing the body will do is to "fight" and clear them out. The immune systems keep alert at the forefront of the battlefield, ready to tame the nanovehicles. When nanomedicines enter the body, the sentinels, especially the MPS, proactively interact with the nanoparticles by a mechanism of phagocytosis which dramatically clears the particles from the blood circulation and accumulates them in the MPS. The eventual fate of the captured particles involves intracellular trafficking, lysosomal disintegration, polymer degradation, drug release, and sometimes translocation of non-degraded particle remnants. The MPS is comprised primarily of blood monocytes, tissue macrophages, dendritic cells, and bone marrow progenitor cells which reside mainly in the vital organs (*e.g.*, lungs, liver, kidneys, and spleen). The design of long circulation evades opsonization and diverts a fraction of nanocarriers to organs and tissues beyond the MPS[93,190].

The sequestration of nanocarriers from blood involves sequential steps, including blood circulation, marginalization, firm attachment, and cell internalization[191]. Serum albumin complements, immunoglobulins, and apolipoproteins, among other plasma proteins, bind to nanocarrier surfaces and form “protein corona (PC)”. Depending on surface hydrophobicity/hydrophilicity and functionalization (*e.g.*, with ligands), as well as size, shape, and zeta potential, the “PC” defines the physiological features of nanomedicines. Following internalization and binding to specific phagocyte receptors, protein-coated nanocarriers are delivered to the phagosomes before lysosomal fusion. The spleen, liver, and lymph nodes contain macrophages responsible for this process. Opsonization is a crucial step that determines the pharmacological and toxicological effects of nanomedicines. As reported, opsonization can also influence the functionality of targeting ligands, resulting in a lack of selectivity. Salvati et al.[192] found that transferrin (Tf)-decorated silica nanoparticles did not bind to Tf receptors (TfR) on A549 cells or soluble TfR, demonstrating how opsonization prevents ligand/receptor binding and results in a loss of specificity. In-depth analysis has connected the physicochemical properties of particles such as size and surface charge with PC formation[193,194]. Smaller particles favor protein attachment due to a higher surface area-to-volume ratio[195,196]. Regarding surface charge, positively charged nanocarriers are rapidly cleared from the blood, whereas neutral and negatively charged ones circulate longer in the blood and could attain enhanced accumulation in peripheral tissues such as tumors[197,198].

On the other hand, the sequestration mechanisms of the MPS can be targeted as well when diseases inflict the MPS themselves. For instance, macrophages play a significant role in inflammation, resulting in diseases like atherosclerosis and cancers. As a result, macrophages may be regarded as prospective therapeutic targets[199]. For example, aquaporin 3, a membrane protein channel highly expressed by monocytes/macrophages, can be utilized for macrophage targeting.[200] Hara-Chikuma et al.[201] developed an anti-aquaporin 3 monoclonal antibody that successfully prevented liver fibrosis in a carbon tetrachloride (CCl_4)-induced mouse model.

5.1.3. *Impact of hemorheology and hemodynamics*

Site-specific distribution can be achieved by long-circulating engineered nanocarriers. To engage target cells, nanocarriers must maintain prolonged circulation and drift laterally through the core layer of blood cells before adhering to the vessel walls. The size and position of the vasculature affect the hemodynamics and flow of circulatory blood cells[202,203]. As reported, hemodynamic factors (*e.g.*, velocity, rheology, flow pattern, and shear stress) effectuate in starting and strengthening platelet adhesion to arterial walls[204]. Platelet or leukocyte adhesion is higher in steady-state conditions with high shear stress than in pulsatile conditions[204−206]. To adjust the physicochemical properties of nanocarriers and achieve better adhesion to the endothelial walls, it is necessary to understand the vasculatures and the hemodynamics related to disease pathology. Nanocarriers with spherical geometry have less lateral drift, a lower propensity to marginalize towards the arterial walls, and a lower affinity for endothelial cells, and therefore do not frequently contact or attach to the endothelial walls. They stay in the cell-free layers between the RBC core and artery walls, inhibiting site-specific delivery[207,208]. To reach the endothelial cells and relevant receptors, optimum nanocarriers are required to dissociate from the erythrocyte cores, aggregate in the cell-free layers, and travel toward the vessel walls. The non-spherical analogs can make highly complex motions like rolling and tossing. Without assistance from outside factors, they are capable of marginalization. Furthermore, it has been established that the aspect ratio of the nanocarriers directly influences the lateral drift velocity. Rod-shaped particles are more straightforward to the edge than spherical particles because of their rotating and oscillating motion from one wall to the next[191].

Another factor affecting adhering to vessel walls is the equilibrium among the ligand density on carrier surfaces, the number of receptors on cell surfaces, and the shear stress at the vessel walls. Particle adhesion is also influenced by particle size and shape. Submicron particles have weak hydrodynamic forces. Few ligand/receptor interactions can survive the shear stress because of the limited particle/cell contact area. Although the hydrodynamic force also increases with larger particles, the number of ligand/acceptor links increases too[209]. Utilizing parallel plate flow experiments, Chareonphol et al[210]. revealed that spherical particles with a size of 2−5 μm demonstrated better wall edges than submicron particles at a relatively high shear rate and channel height.

5.1.4. *Site-specific extravasation and tissue accumulation*

Although site-specific extravasation and accumulation of nanocarriers are seen in the treatment of many diseases, the notion is best understood in the context of cancer. Nanocarriers are discovered to accumulate in various tumor regions following continuous circulation and selective yet robust adherence to the vessel walls. Before being absorbed by the cancer cells, they cross the endothelia and travel further into the interstitial spaces of tumors. The tumor vascular system is distinguished from normal blood vessels by complicated, heterogeneous leaky vessels with heterogeneous blood flow[211,212], which can promote passive tumor targeting and accumulation of nanocarriers based on the EPR effect[213,214].

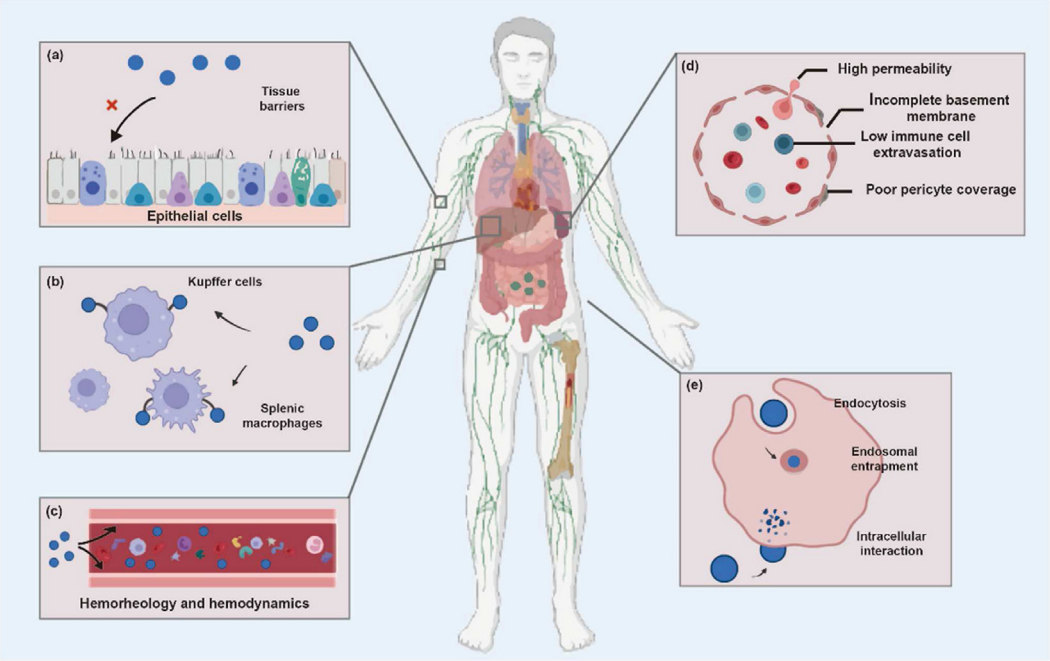

Figure 8 Sequential *in vivo* processes that nanomedicines may go through: (a) interactions with the tissue barriers that prevent nanomedicines from entering into the body; (b) uptake of nanomedicines by the mononuclear phagocyte system (MPS); (c) hemorheological and hemodynamic disposition of nanomedicines which alters the integrity, kinetics, and interaction with hematic components; (d) post-MPS distribution and disposition of nanomedicines by specialized physiological mechanisms such as passive tumor targeting owing to the EPR effect; (e) endosomal compartmentalization and cell membrane trafficking of nanomedicines. Adapted with permission from Ref. 183. Copyright©2022 Elsevier.

Receptors like VEGF, $\alpha_v\beta_3$, and so on are overexpressed on the endothelial surfaces of the neointimal tumor systems. For targeted adhesion and internalization, ligands unique to these receptors are typically used to functionalize nanocarriers[215]. It should be aware that the physiological characteristics of tumor vasculatures can affect the penetration ability of nanoparticles. The tumor heterogeneity impacts nanocarriers' vascular permeability, which in turn impacts the accumulation rate in tumors. Studies also reveal that the tumor microenvironment impacts nanocarriers' tumor accumulation and vascular permeability. According to a study, EPR is influenced by the tumor's type and the tissue where it is located. The accumulation of liposomes was evaluated in multiple tumor xenografts at various original and metastatic sites, including breast cancer (T1), lung cancer (LL), and colon cancer (CT26) cells[216]. This is correlated with the ratio of tissue inhibitor of metalloproteinase one to matrix metalloproteinase 9 (MMP-9), indicating that elevated MMP-9 levels are indicative of higher vascular permeability[217,218].

The interstitial compartment of tumor tissues has a very different makeup from normal tissues[218]. Due to unregulated cancer cell development, extensive fibrosis, dense extracellular matrix, and a lack of anatomically well-defined working lymphatic networks, interstitial fluid pressure (IFP) is raised in tumors[219]. While vascular permeability and tumoral accumulation could be enhanced owing to EPR, raising IFP makes it harder for extravasation to reach the area of interest. This could have a meaningful impact on how nanocarriers are used to diagnose and treat tumor development and metastasis[219].

5.1.5. *Subcellular fate of nanocarriers*

NDDS should be delivered directly to subcellular organelles when intracellular drug release is demanded. Understanding the processes of internalization and the subcellular fate of nanocarriers conveys important information to unravel the underlying mechanisms. "Big" as their size is, nanocarriers could not permeate across cell membranes through passive diffusion as small molecules do. Drug nanocarriers are generally endocytosed and processed within cells before breaking down to release drugs at target organelles. The physicochemical and surface properties such as size, shape, surface charge, surface morphology, elasticity, surface chemical decorations, and so on affect the subcellular behaviors of nanocarriers[220–225]. Fig. 9 delineates the common pathways for endocytosis. During endocytosis, nanocarriers will form membrane invagination and fuse with highly acidic lysosomes to create intracellular vesicles (phagosomes or endosomes)[226]. Although phagocytosis-mediated endocytosis is frequently seen in MPS cells, clathrin-mediated endocytosis is the conventional mechanism for nearly all nanocarriers. When endocytosis is mediated by clathrin or receptors, ligand-functionalized nanocarriers are attached to cell surface receptors. Following the creation of clathrin-coated pits, the ligand−receptor complexes separate from the membrane to create clathrin-coated vesicles, which thereafter combine with the early endosomes and loop back to the plasma membrane or enter the lysosomes. Many nanocarriers, together with drug payloads, end up in lysosomes, raising concerns about the functionality and activity of the delivery systems. Caveolae-mediated endocytosis is an alternative pathway. Membrane invaginations with a size of 50−60 nm, known as caveolae, are created in this instance by intact membrane proteins called caveolins and peripheral membrane proteins called cavins. The caveolae separate from the membrane and combine with caveolae having a neutral pH. Caveolae, unlike phagosomes or endosomes, occasionally skip the lysosomes (Fig. 9)[220].

5.2. Pharmacokinetics of drugs vs. nanomedicines

Contrary to conventional medications, the pharmacokinetics (PK) of nanomedicines involves a complicated web of interactions between free drugs, encapsulated drugs, and empty nanocarriers. The equilibrium dynamics in between are crucial for proper PK modeling. To acquire a pertinent PK model, it is important to mind that conventional PK models cannot be directly applied to describe the PK of particles. Conventional PK is primarily based on the equilibrium between blood and target drug levels, which in turn depends on the distribution of drug molecules between blood and tissues by a mechanism of diffusion. Nevertheless, nanomedicines present as particles during the *in vivo* disposition processes and there are no such mechanisms as those of small molecules. The level of nanomedicines in tissues may be more informative than that in the blood. Currently, multiple (two- or three-) compartment models have been attempted in PK modeling of nanoparticles[190,227], but the prospect of application is yet to be assessed. One thing is for sure, the non-compartmental models such as statistical moment is a practical approach to obtaining fundamental PK parameters of particulates[190,227].

The area under the curve (AUC) following oral administration is a crucial parameter in conventional PK models to calculate the absorption rate. However, in the case of nanomedicines, calculating plasma drug concentration by time alone may be irrelevant because of ignorance of the stability of nanomedicines. Groo et al.[228] found in a subcutaneous tumor model that the most potent paclitaxel nanoformulation was not the one with the largest AUC following oral delivery. Notably, the tumors are not resistant to encapsulated but free paclitaxel. The unstable formulation produced the maximum AUC during absorption; however, the released paclitaxel was ineffective against the tumor. Despite less paclitaxel being absorbed (smaller AUC), it worked better when enclosed in stable nanocarriers[228].

The goal of the development of nanomedicines is to optimize their biodistribution to increase activity and/or decrease toxicity. Due to the interaction of particles with tissues and body fluids throughout the distribution process, conventional PK models cannot accurately describe the dynamics of distribution. The physicochemical properties of nanomedicines determine the *in vivo* fate of nanocarriers. Environment-responsive fluorophores have been employed to label and track nanocarriers *in vivo* based on rationales of Förster resonance energy transfer (FRET) and aggregation-caused quenching (ACQ)[229–233]. FRET is currently one of the primary methods for assessing the biodistribution of nanomedicines. Laine et al.[234] employed FRET to assess the behavior of several lipid nanocarriers, including lipid nanocrystals (LNCs), polyethylene glycosylated LNCs, and lipid nanoemulsions (LNEs). The findings revealed various release kinetic patterns, with extended circulation duration and strong structural stability for several hours following intravenous injection for PEGylated LNCs and LNEs[234]. Gravier et al.[235] utilized macroscopic and microscopic bioimaging to assess the stability of LNEs and LNCs in the biological environment. According to the findings, LNCs were more stable than LNEs in the presence of serum or cancer cells[235]. These investigations deepen our understanding of what happens to nanocarriers *in vivo*, but FRET fails to accommodate precise quantification of nanocarriers.

5.3. The influence of protein corona on nanomedicines in vivo

After entering the bloodstream, nanomedicines quickly bind with different plasma proteins and generate a protein coat known as PC[123,236,237]. PC often arises from a complicated and dynamic mechanism. Typically, "hard corona" is formed by proteins with a greater affinity and a longer residence time, whereas "soft corona" is made up of proteins with a lower affinity and a shorter residence time[238–240]. The features of the nanomedicines, such as size, shape, and surface qualities significantly impact the compositions of PC[241,242]. The larger ones with more surface area and less surface curvature often result in better protein coverage[243–245]. Additionally, more plasma proteins are drawn to charged or hydrophobic interfaces[246–248]. The physicochemical properties of nanomedicines are altered as a result of the dynamic interactions between nanocarriers and proteins, endowing them with new biological features and altering their *in vivo* fate.

5.3.1. Stability

Nanoformulations are typically more stable *in vitro* than *in vivo* owing to the adsorption of body proteins, which may alter the *in vivo* behaviors of nanocarriers before reaching their targets[249]. Ho et al.[250] investigated the effect of PC [IgG, fibrinogen, ApoA1, and human serum albumin (HSA)] on the aggregation of gold nanoparticles with low protein/nanoparticle ratio and physiological pH associated with increased aggregation. On the other hand, thorough coating with PC at a higher ratio decreases the attraction between nearby nanoparticles and limits aggregation. PCs are more effective in preventing nanoparticles from aggregation than bare nanoparticles[250]. Similarly, despite the medium being supplemented with NaCl, which has been demonstrated to enhance silver nanoparticle aggregation in a concentration-dependent manner[251], PC formation *in vitro* after incubation of silver nanoparticles with Fetal Bovine Serum (FBS)+/Dulbecco's modified Eagle's medium (DMEM) decreased their aggregation. Additionally, PC development in the gastrointestinal tract may severely impact the stability of nanoparticles taken orally. Cao et al.[252]. examined the relationship between casein and titanium dioxide nanoparticles. Notably, the electrostatic attraction between the particles diminished by neutralizing the positive charge of the nanoparticles, increasing the aggregation of protein complexes[252]. Additionally, PC may change the release of nanoparticles. The release of DOX from magnetic mesoporous silica nanoparticles was retarded by PC, as reported by Pourjavadi et al.[253]. Coating the nanoparticles with polyethylene glycol (PEG) decreases PC formation[253].

5.3.2. Cellular uptake

PC alters the way that nanomedicines interact with non-phagocytic cells, changing how they are taken up by cells and endocytic pathways. Cheng et al.[254] examined the impact of PC on the cellular entrance of gold nanoparticles of three distinct sizes (5, 20, and 50 nm) and found that the cellular absorption of gold nanoparticles decreased significantly with the formation of PC. Aliyandi et al.[255] demonstrated that cellular uptake of PC-precoated silica nanoparticles into endothelial cells was affected by the size and compositions of PC. Notably, pre-coating with histidine-rich glycoprotein decreased the endothelial absorption of nanoparticles[255]. As a result of the selective binding of ApoE to low-density lipoprotein (LDL) receptors, PC was discovered to

increase endothelial internalization of magnetosomes *via* LDL receptor-mediated endocytosis. Additionally, nanoparticles can alter the integrity of the endothelium layer by interacting with intercellular linker proteins such as vascular endothelial calmodulin[256].

5.3.3. *Targeting capability*

PC may reduce the effectiveness of targeting, whether actively or passively[257–259]. It has been commonly observed that PC interferes with ligand/receptor interactions, impairing the targeting efficiency of many targeted nanomedicines. For instance, the active targeting ability of polystyrene nanoparticles modified with transferrin is reconciled by cerebrospinal fluid proteins in a way similar to the uptake of polyethylene glycolyzed polystyrene nanoparticles with the same size and surface charge[260]. Similar findings were made by Varnamkhasti et al.[261] who discovered that mucin receptors loaded on chitosan nanoparticles for targeting colon cancer cells are missing after protein adsorption. Nemati et al.[262] reported that PC significantly reduced the targeting abilities of folate-modified chitosan nanoparticles and hindered uptake by tumor cells. *In vivo* adsorption of proteins, particularly IgM, conceals the specific identification of folate receptors on tumor cells[263].

The targeting ability of nanomedicines does not always suffer from PC formation. Suchanova et al.[264] reported that the targeting capacity of Tf-modified virus-like nanoparticles was not impacted by serum proteins. PC can also direct nanocarriers to intended therapeutic targets. For instance, PC coating does not influence the targeting specificity of Tf-modified PEGylated nanoparticles to brain malignant cells[258]. However, proteins that adsorbed on nanoparticles, primarily ApoA-I, made it easier for them to cross the BBB[258]. Therefore, while constructing targeted nanoparticles based on disease type, nanoparticle system, and targeting fraction, it is crucial to thoroughly investigate the effect of PC on targeting efficiency.

5.3.4. *Pharmacokinetics*

The plasma proteins encapsulated on nanomedicines' surfaces give them a "new face" which alters their pharmacokinetics. Firstly, the nanomedicines' surface-bound biomolecules impact the circulation time and interaction with the body. Complement

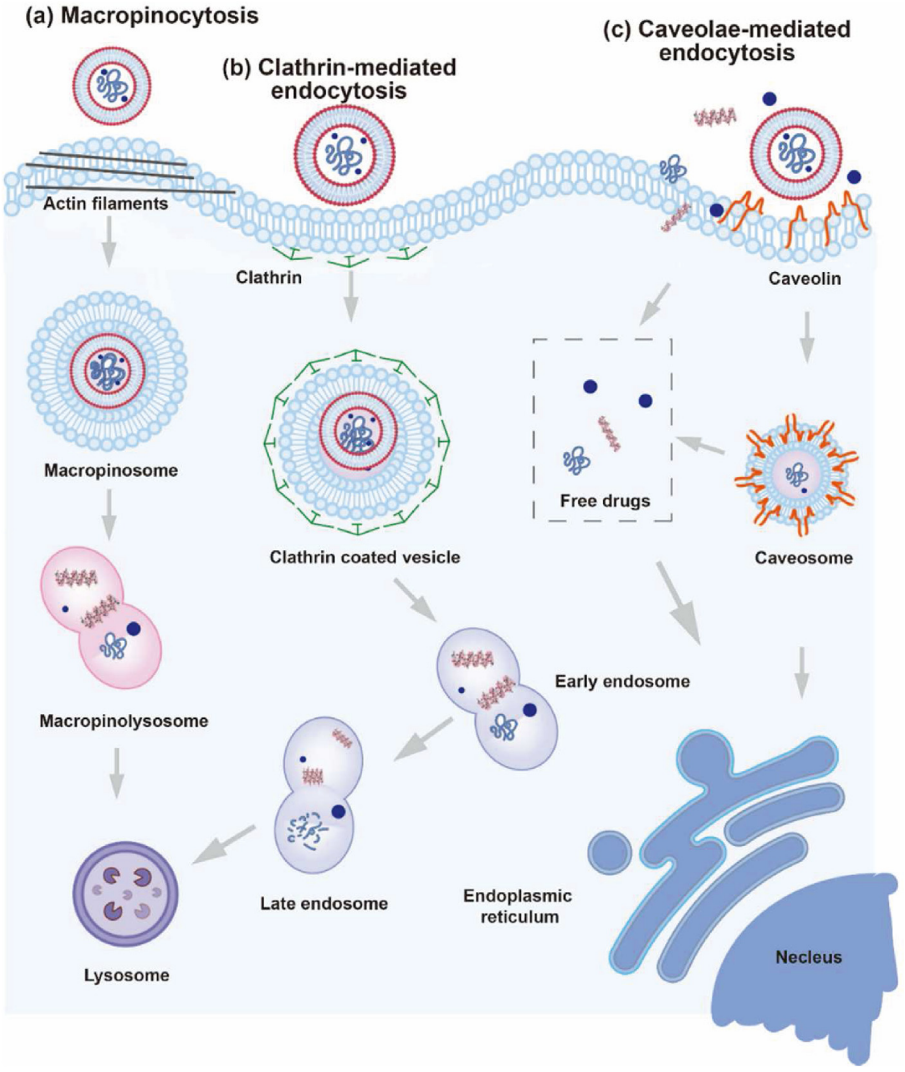

Figure 9 Summary of cellular endocytosis routes for nanomedicines. (a) Micropinocytosis. (b) Clathrin-mediated endocytosis. (c) Caveolae-mediated endocytosis. (d) Phagocytosis. Adapted with permission from Ref. 220. Copyright©2019 Elsevier.

proteins can attach to nanomedicines' PC and be exchanged *in vivo* when nanomedicines are introduced into the blood[265]. Thus, PC improves cellular absorption and phagocytosis of nanomedicines by the MPS, decreases cell membrane adherence, and attenuates cell membrane disruption induced by naked nanomedicines[266–269]. Particularly, nanomedicines' internalization and biodistribution can be significantly influenced by binding proteins[270]. IgG adsorption, complement factors, and fibrinogen, for instance, facilitate the phagocytosis of nanomedicines, while troponins like albumin are hypothesized to increase the circulation of nanomedicines in the blood[271]. Spherical nucleic acids are internalized by macrophage complement receptors, where they are then distributed throughout the liver and spleen[272]. By tuning the corona compositions (*e.g.*, Apos, protein C, and hemoglobin subunits), nano-polyelectrolyte complexes could be imparted with extended circulation duration[273]. When PC was enriched with HSA, dendritic cells' ability to phagocytose nanomedicines was decreased[274]. The prevalence of clusters in PC was shown to limit macrophage absorption of non-specific cells[275]. Complements, immunoglobulins, and immunological antibodies are modulators that cause macrophage absorption and hasten nanomedicine clearance[276]. Therefore, the lifespan of nanoparticles and the mechanisms and effects of PC production must be considered when designing drug delivery systems.

Nanomedicines must be delivered to specific cell targets to work effectively. Combined passive and active targeting strategies are used to improve the accumulation of nanomedicines in disease sites. However, PCs may misguide nanocarriers to off-track destinations. For instance, when loaded with biological substances such as human albumins[277], PC formation dramatically lowers the hepatic retention of gold nanoparticles. The plasma protein ApoE can bind preferentially to nanoparticles coated with polysorbate 80, promoting nanoparticle accumulation in the brain[199]. Bionic liposomes with a peptide tag are associated with exchangeable apolipoproteins and absorb significant amounts of ApoA1, E, and J, improving the bionic liposomes' ability to target the brain[278]. Therefore, understanding the relationship between PC and nanomedicine biodistribution may help work more effectively in therapeutic applications.

In addition to cellular uptake and disposition, PC affects the biodegradation of nanomedicines as well. For instance, induced myeloperoxidase release and hypochlorite production in neutrophils cause single-walled carbon nanotubes (SWCNT) precoated with HSA to degrade at a greater rate[279].

5.3.5. *Cytotoxicity*

PC can increase the safety of nanomedicines against normal cells[280], but it can also cause immunotoxicity. Cationic nanocarriers may associate with negatively charged cell surfaces, disrupting the plasma membrane and ultimately causing cellular damage[281]. However, the presence of PC protects the positive charges, raising the nanomedicine level of safety. For instance, compared to uncoated carbon nanotubes, bioprotein-coated ones considerably reduced the cytotoxicity of human monocytes and endothelial cells[281]. Additionally, the hemolysis of nanomedicines can be successfully avoided by the quick formation of human PC[282].

5.3.6. *Immunotoxicity*

Ingested nanocarriers are recognized as exogenous particles that could cause immunological reactions. PC coatings on the surface of nanomedicines may provide an efficient biological interface for nanomedicines engaging with the immune system. PC increases adaptive immune responses, the complement system, and innate immune cell (*e.g.*, monocyte) differentiation.

PC mediates the recognition and differentiation of immune cells (*e.g.*, monocytes, macrophages, and neutrophils). For example, Mo et al.[283] found that PC coating of black phosphorus nanocarriers elicits immunotoxicity and activates macrophages. Yan et al.[284] discovered that in immune cells like monocytes and other macrophage-like cells, PC formation is necessary for nanomedicine internalization. Additionally, it has been demonstrated that poly(acrylic acid)-modified gold nanocarriers promote the unfolding of ingested fibrinogen, resulting in inflammatory responses[285].

It is believed that activation of the complement system by nanomedicine-PC complexes initiates the opsonization processes[286]. Evidence shows nanomedicines bind quickly to a third complement component after exposure to human serum or blood[265]. Adhesion of IgM to liposome surfaces, whether naked or surface-modified, negatively impacts complement activation[263,286,287]. Vu et al.[288] noted that PC accelerates the binding of immunoglobulin with all nanocarriers. Pattern-recognition molecules such as collection, mannose-binding lectin, and ficolin recognize structural fingerprints on nanocarrier surfaces to activate the complement system[289]. PCs on nanomedicines also cause both adaptive and innate immune reactions. Conformational changes in corona proteins adsorbed on nanocarriers exposed immunogenic epitopes, resulting in opsonization and adaptive immune responses[290].

It is concluded that PC has a two-sided effect on both *in vitro* and *in vivo* performance of nanomedicines. The topic of PC emerges as a critical issue in nanomedicine research. Stealthy coating with hydrophilic polymers such as PEGs repels the adsorption of proteins and therefore mitigates the effect of PC. A fresh perspective on PC is that targeting of nanocarriers is somehow mediated by the proteomes of PC and the protein compositions of PC could be actively modulated for specific targeting purposes. Overall, PC exhibits considerable promise in offering fresh design concepts and thought-out viewpoints for drug delivery involving nanocarrier systems[291].

5.4. *Nanotoxicity*

Although various nanomaterials have been tested in preclinical and clinical trials, we still do not fully understand the safety hazards of new nanomedicines[292–294], especially inorganic ones. Due to structural instability and subsequent cadmium ion leakage, CdSe quantum dots, a bioimaging agent, demonstrated considerable hepatotoxicity in earlier *in vitro* investigations[295]. Studies also demonstrated that carbon nanotubes could cause adverse physiological reactions such as inflammation, genetic damage in different cells, and even synergistic toxicity when combined with other pollutants like zinc ions. Despite therapeutic efficacy, the unfavorable toxicity of nanomedicines to normal tissues may have undesirable biological repercussions. It is crucial to develop nanomedicines with maximized efficacy but minimized toxicity (Fig. 10).

5.4.1. *Direct physical deterioration of DNA and biological membranes*

Nanostructures with rigid surfaces and sharp edges, particularly inorganic and carbon-based nanomaterials, can be physically associated with biological systems and damage biological

activities[296] in an irreversible and/or concentration-dependent manner. Carbon nanotubes (CNTs) that are thin, stiff, and have needle-like features can pierce the plasma and nuclear membranes of mesothelial cells, resulting in pathogenicity similar to asbestos[297]. Recent studies have proven that inorganic nanoparticles can rupture the membranes of *Escherichia coli*, causing macropores[298]. Similarly, Gram-positive *Staphylococcus aureus* and Gram-negative *E. coli* can interact with the highly sharp edges of graphene oxide, directly damaging their membranes[298]. The findings suggest that strong hydrophobic interactions between graphene and lipid molecules allow graphene nanosheets to penetrate the membrane and absorb significant amounts of phospholipids, affecting the integrity and stability of the membrane and even creating nanoscale gaps[299−301]. Additionally, nanomaterials smaller than 10 nm in one dimension have the potential to directly enter the nucleus, damage DNA structure, and have genotoxic consequences such as chromosome breakage. This would result in DNA strand breaks[302−304]. It has been documented that centrosomes can incorporate SWCNTs with diameters of 1−4 nm, disrupting the mitotic spindle, breaking DNA, and resulting in cellular aneuploidy[305].

5.4.2. *Physical obstruction*

SiO_2 and quantum dot-induced epigenetic effects and CNTs' ability to inhibit ion channels[306] are examples of physical disturbances that may be brought by nanomaterials whose dimensions and shapes are similar to the essential cellular machinery[304,307]. Physical disturbance typically results in functional rather than structural damage, in contrast to the direct physical damages mentioned above. Both iron oxide nanoparticles[308] and CNTs[309] can associate with actin myofilaments and induce aberrant cellular activity, including unchecked growth linked to cancer. Another study demonstrated that CNTs[310] could interfere spatially with DNA, causing substantial chromatin reconfiguration or heritable gene changes. Notably, physical interference rather than direct DNA damage produces altered gene expression predominantly through point mutations or translational suppression[284].

5.4.3. *Physical contact with cells*

Nanomaterials interact with cells and may activate specific physiological processes that can be harmful[311,312]. For instance, immune cells like platelets, neutrophils, and macrophages interact with nanomaterials such as CNTs. A large number of cytokines like interleukins and tumor necrosis factor may be produced as a result, potentiating a chain of immunological reactions that lead to fibrosis and bronchial granulomas[313−316]. Instead, nanoparticles like SiO_2, TiO_2, and hydroxyapatite increase cellular contractility by severely disrupting intracellular microtubule assembly without appearing toxic, which eventually facilitates strong substrate adherence and limits cell mobility[317,318]. Nanomaterials may be broken down in an acidic environment and/or by hydrolases in lysosomes when endocytosed and subsequently transferred to endosomes by fusion of lysosomes with late endosomes, releasing toxic components and resulting in lysosomal dysfunction[319,320]. The released nanomaterials progressively induce inflammation and ROS or associate with cytoplasmic biomolecules such as glutathione and organelles (*e.g.,* mitochondria and endoplasmic reticulum), causing additional malfunction and even cell death[321,322]. Additionally, autophagic malfunction brought by nanomaterials may result in apoptosis or autophagic cell death[323,324].

5.4.4. *Production of ROS*

Oxidative stress and subsequent mitochondrial damage, lipid peroxidation, and DNA damage may result from excessive ROS production by a metal oxide or carbon-based nanomaterials[325]. Numerous studies have demonstrated that iron oxide nanoparticles promote the conversion of intracellular hydrogen peroxide (H_2O_2) to hydroxyl radical (HO•) *via* Fenton, Fenton-like, or Haber−Weiss cycle reactions, resulting in oxidative damage and even cell death[326]. It is also demonstrated that graphene oxide nanosheets could lead to oxidative stress-induced cytotoxicity by catalyzing the conversion of H_2O_2 to HO· and NDUFB9-mediated biological pathways to generate ROS[327,328]. Setyawati et al.[329,330] discovered that raising intracellular ROS and Ca^{2+}, nanodiamonds, and gold nanoparticles could cause loss of interendothelial cell connections and quasi-stable cytoskeletal remodeling of the vascular barriers.

To date, much work has gone into identifying the causes of nanotoxicity and using that information to create safe nanomedicines. Various nanomaterials, including liposomes, polymers, mesoporous silica, carbon nanotubes, and graphene, have been investigated to build efficient and secure nanosystems for drug delivery, bioimaging, tissue engineering, and biosensing. It is crucial to comprehend the connection between the design of nanomaterials and their biological effects to extract information that can be utilized to develop safer medical nanosystems.

6. Therapeutic landscape of nanomedicines

6.1. *Chemotherapy*

Emerging intelligent nanomedicines offer great promise for effective cancer chemotherapy (Fig. 11)[331−333]. Cancer has developed into a leading cause of human death due to its high malignancy, rapid progression, and difficulty in effective eradication[334]. However, conventional chemotherapy often fails to treat cancer due to severe systemic side effects[335]. Increasing nanomedicines are utilized for targeted cancer therapy *via* the EPR effect[336]. Various nanocarriers, including inorganic, organic, or bionic carriers, have been employed to load chemotherapeutic drugs. The liposomal doxorubicin (Doxil®) is the first approved nanomedicine for cancer treatment. Following their footsteps, various nanomedicines have entered different stages of translation[3] by exploiting various delivery strategies[337] and a better understanding of disease mechanisms and biological barriers[338]. Ren et al.[339] reported a nanoparticle consisting of epigallocatechin-3-gallate (EGCG), phenolic platinum (IV) prodrug (Pt−OH), and polyphenol-modified block copolymer (PEG-*b*-PPOH). This intelligent drug delivery platform demonstrated excellent anticancer efficacy *via* a combination of chemotherapy and chromodynamic therapy, as well as avoidance of systemic toxicity caused by platinum[339].

Furthermore, to adapt to clinical precision treatment and reduce the damage to normal tissues, many nanomedicines are further furnished with complex integrated multifunctionalities[340]. A "Jekyll and Hyde" nanoparticle-hydrogel hybrid delivery system reported by Wu et al.[341] could keep dormant in normal tissues and be activated in the acidic or hyaluronidase-rich tumor microenvironment. The biodegradation of nanoparticle-gel could lead to a unidirectional tumor-targeted release of DOX-loaded nanoparticles for enhanced tumor tissue penetration[341]. In addition, the nanoparticle-hydrogel demonstrated other advantages,

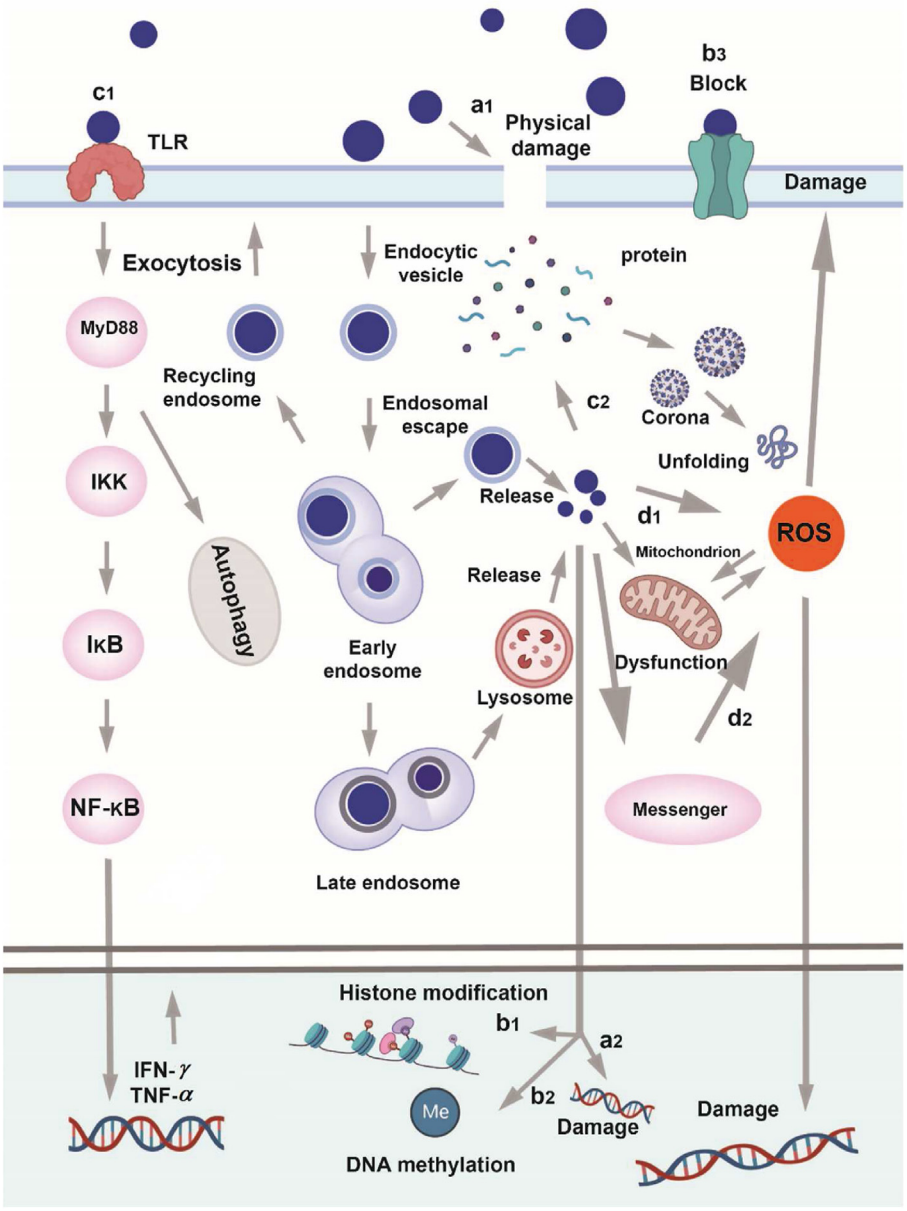

Figure 10 The summary of possible toxigenic pathways for nanomaterials (a_1) Physical injury to biological membranes directly (a_2) Direct deterioration of DNA (b_3) Nanomaterials blocking ion channels (c_1) The activation of autophagy and inflammatory bodily reactions by interactions between nanomaterials and biomolecules (c_2) Interactions with proteins that impact the way they operate (d_1) Directly generated ROS by catalytic reaction (d_2) The activation of ROS-related signaling pathways results in the indirect production of ROS.

such as biodegradability, tissue adhesiveness for continuous on-site activation, and shear-thinning behavior for injection[341]. This preparation demonstrated promising long-acting efficacy and precise anticancer treatment against locoregional treatment[341]. In addition, some stimuli-responsive drug delivery approaches have also been used to enhance the targeting of nanomedicines to cancer cells[342,343], utilizing the active triggers at an amplifying level in the cancer microenvironment.

6.2. *Nucleic acid therapy*

Unlike conventional medications, nucleic acid therapy produces long-lasting therapeutic effects *via* gene addition, replacement, inhibition, and editing, which holds great promise by targeting therapeutic nucleic acids to their genetic blueprints. However, many challenges remain due to degradation by nucleases[344], difficulty in encapsulation[345], poor membrane penetration[346], and off-target effects[347]. Nanocarriers are considered a viable strategy to facilitate the delivery of nucleic acids, *i.e.*, ASO[348], siRNA[349,350], miRNA[351], and mRNA[352]. Especially, the FDA recently approved two nucleic acid-based therapeutics to combat the COVID-19 pandemic[353–355].

An octopus-like multivalent penetratin system, using multi-arm PEG as a core and conjugating with penetratin, was developed to promote compression and delivery of nucleic acids[356]. The multivalent penetratins improved cellular uptake (~100%) and transfection rate (>75%) and efficiently inhibited target protein expression without toxicity[356]. Moreover, combined use

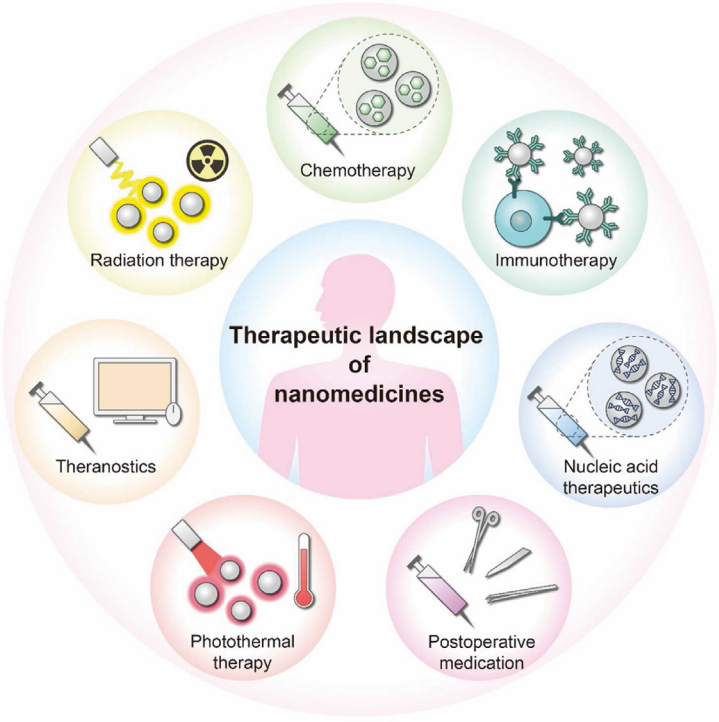

Figure 11 Therapeutic landscape of nanomedicines. Nanomedicines have tremendous potential in several therapeutic fields, such as chemotherapy, immunotherapy, nucleic acid therapy, radiation therapy, photothermal therapy, postoperative medication, etc.

with other carriers or agents could improve the targeting therapy of nucleic acid nanomedicines. For instance, dosing a nanoprimer before administering nucleic acids-loaded LNPs could transiently occupy hepatocytes and, as a result, evade MPS uptake and improve systemic delivery of nucleic acid[357,358].

6.3. *Immunotherapy*

Immunotherapy acts by enhancing or suppressing the innate immune responses to the diseased cells[359]. Nanomedicines against inflammation[360], cancer, and autoimmune disorders[122] have been discovered with great promise for innate immune regulation in conjunction with the adaptive immune system, such as directed immunotherapeutic approaches (*e.g.*, checkpoint blockade), chimeric antigen receptor T cells (*e.g.*, T cell co-stimulation) or by modifying the tumor microenvironment[361]. Especially with the clinical translation of the COVID-19 mRNA vaccines, nanomedicine immunotherapy is attracting tremendous attention[362].

In a recent study, a macrophage-biomimetic nanomedicine was developed by macrophage membrane-coating ROS-sensitive rosiglitazone-loaded β-CD for targeted treatment of ulcerative colitis[363]. The preparation effectively polarized macrophages to M2, regulating the immune response and protecting epithelial cells from oxidative stresses[363]. The macrophage membrane guided the nanomedicine to the inflammatory colon and helped suppress inflammation by sequestering proinflammatory cytokines, exhibiting synergistic therapeutic effects against ulcerative colitis[363]. Wei et al.[364] developed a self-assembled selenopeptide nanoparticle to strengthen tumor chemoimmunotherapy. The constructed nanoparticles delivered DOX to solid tumors and activated the natural killer cells in a programmed manner through enzyme-induced size-reduction and reactive-oxygen-species-driven desalinization[364]. The results indicated that the formulation significantly elevated antitumor efficacy by the chemotherapy and immunotherapy synergy induced by DOX and selenopeptide[364]. Nevertheless, despite many innovative features integrated into laboratory studies[365], nanomedicine immunotherapy must be simple and affordable for success in the clinic[366].

6.4. *Photothermal therapy*

PTT is a promising non-invasive method mediated by photothermal agents to generate hyperthermia under specific laser irradiation to cause local thermal damage at the target site[367]. The photothermal agents could be transformed from the singlet state to the excited singlet state by absorbing the photons' energy upon laser irradiation, leading to collisions between the excited photothermal agents and surrounding molecules[368]. Thus, the increased kinetic energy could generate heating in the confined microenvironment[132]. It is reported that tissues or cells exposed to temperatures up to 45 °C will initiate a heat shock response and causes irreversible damage[369]. Using this warming-killing mechanism, photothermal therapy has been applied in treating bacterial infection[370], rheumatoid arthritis[371], and cancer[372], among others.

PTT shows promise in fighting bacteria with reduced resistance and toxicity. A pH-sensitive nanoparticle grafted by glycol chitosan (GCS) and polyaniline was developed for luminescence imaging-guided precise PTT[373]. The delivery system could respond to the bacterial acidic environment and adhere to bacteria, attaining spatial accuracy of NIR irradiation and specific photothermal effect directed to bacteria[373]. Another study combined PTT with chemotherapy for synergistic treatment of rheumatoid arthritis[374]. The methotrexate-loaded gold nanorods coated with mesoporous silica shells could target activated macrophages *via* surface modification of folate[374]. Under laser irradiation at 808 nm, the delivery system enabled local hyperthermia induced

by gold nanorods' photothermal conversion and rapid release of methotrexate *via* internal heating-mediated hydrogen bond cleavage, leading to efficient macrophage-killing[374]. In recent years, PTT is gaining interest in synergistic cancer therapy by promoting the release of tumor-related antigens and triggering immune responses by inducting immunogenic cell death[375−377].

6.5. Other therapeutic applications of nanomedicines

Nanotechnology demonstrates great potential to integrate multiple functions, such as imaging and diagnostic chemiluminescence, for medical use[378]. Accordingly, nanomedicines are also applied in radiation therapy, theranostics, postoperative medication, etc.[379].

Radiotherapy (RT) is one of the first-line therapies and is always combined with chemotherapy/surgery in oncology[380]. Since the first recorded use to treat lesions *via* X-ray, RT has been increasingly utilized in curative and adjuvant treatment[381]. Furthermore, by employing nanomedicines as radiosensitizers, RT is conferred with improved effectiveness, targeting ability, and reduced toxicity[382]. Always, RT enables the production of intracellular oxygen-centric free radicals and efficient killing effect by directly damaging nuclear or consistently destructing DNA. Recently, Cheng et al.[383] developed a radiosensitizer, a hybrid anisotropic nanostructure constructed by Au and titanium dioxide (TiO_2), for RT against triple-negative breast cancer (TNBC). The designed Au-TiO_2 nanoparticles displayed a significantly enhanced radiation effect, owing to the strong asymmetric electric coupling at their interfaces of the high atomic number metals and dielectric oxides.

Nanotechnology is also used to integrate diagnostics and therapeutics by involving multiple materials[384]. To obtain a chelating magnetic resonance imaging and targeting $\alpha_v\beta_3$-integrin over-expressed on tumor angiogenic endothelium simultaneously, Chen et al.[385] constructed a core−shell structured nanoparticles (HSA-Ce6@HSA-RGD) by inducing the self-assembling of HSA modified with either a photosensitizer chlorine e6 or RGD. This nanotheranostic combined photodynamic and chemotherapy and offered precisely *in vivo* tumor imaging and remarkably improved therapeutic efficacy compared to the monotherapies[385]. Nanotheranostics hold potential in treating complicated diseases[386].

Postoperative patients often encounter wound healing difficulties, infection, or surgical site pain; however, traditional treatment is modest to alleviate the symptoms[387]. The nanomedicines provide a new alternative opportunity for postoperative therapy[388]. For instance, Lu et al.[389] constructed a wound nano-silver/chitosan dressing through nanometer and self-assembly technology. The wound dressing significantly increased the wound healing efficacy and improved the assessed biosafety[389]. Another study reported a nanoemulsion complex constructed using propolis and vitamin C, significantly promoting wound healing in the oral mucosa[390]. In addition, to reduce the pain of postoperative patients, Rose et al.[391] explored liposomes as a parenteral controlled release system to prolong postoperative analgesia. The results indicated that the liposome treatment could significantly alleviate the sustained bout of pain and improve the life quality[391].

7. Challenges and perspectives

Numerous issues, including low stability, nanocarrier toxicity, scaling-up difficulties, and lack of efficient quality control measures, have come to light in company with the development of nanomedicine products. Although these issues are actively addressed, the *in vivo* fate and acting mechanisms of nanomedicine designs remain poorly studied: (a) when and where is the drug released from nanocarriers? (b) Which substances in the body interact with nanomedicines and how? (c) Whether nanomedicines retain structural integrity following a series of *in vivo* disposition processes? (d) How could intact nanomedicines, free drugs, and nanocarrier materials be accurately tracked and distinguished in real time? Translating nanomedicine concepts into clinical therapeutics is constrained by an inadequate understanding of the *in vivo* processes.

A critical barrier to the understanding of the biodistribution, clearance, and long-term fate of nanomedicines is the lack of specialized and reliable analytical methods for quantifying drugs in tissues, organs, and cellular architectures[392]. Fluorescence bioimaging based on FRET[393,394] has been successfully utilized to study nano-bio interactions to direct nanomedicine development[393,395], as well as to visualize molecular signatures of biological systems[396]. Other NIR fluorescent probes based on rationales of ACQ[397−399] and aggregation-induced emission (AIE)[400,401] and a combination of different rationales[402] have been developed to shed light on the integrity and biological fate of nanomedicines in the body. However, there are so far no perfect analytical tools for accurate real-time monitoring of nanocarriers. Dissociation of ACQ fluorophores after aggregation can lead to fluorescence re-illumination[227], and AIE-based methods can also result in fluorescence re-illumination *in vivo* due to re-aggregation and poor linearity between fluorescence and probe concentration[403−405]. Differences in light penetration depth at different wavelengths can affect the accuracy of quantitative analysis by FRET imaging. The development of more reliable and specialized tools in the future may help advance our knowledge of the *in vivo* fate and potential acting mechanisms of nanomedicines and accelerate the translation of nano-delivery concepts from the lab to the clinic.

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Author contributions

Wei Wu, Wei He, and Zhongjian Chen proposed and outlined this review. Qiuyue Liu and Jiahui Zou drafted the manuscript. Wei Wu, Wei He, and Zhongjian Chen revised the manuscript. All of the authors have read and approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

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