REVIEW

Current approaches of nanomedicines in the market and various stage of clinical translation

Xiaoting Shan\textsuperscript{a,c}, Xiang Gong\textsuperscript{a}, Jie Li\textsuperscript{a,b}, Jingyuan Wen\textsuperscript{d}, Yaping Li\textsuperscript{a,c}, Zhiwen Zhang\textsuperscript{a,b,c,*}

\textsuperscript{a}State Key Laboratory of Drug Research & Center of Pharmaceutics, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China
\textsuperscript{b}Yantai Key Laboratory of Nanomedicine & Advanced Preparations, Yantai Institute of Materia Medica, Yantai 264000, China
\textsuperscript{c}School of Pharmacy, University of Chinese Academy of Sciences, Beijing 100049, China
\textsuperscript{d}School of Pharmacy, University of Auckland, Auckland 1142, New Zealand

Received 5 September 2021; received in revised form 16 November 2021; accepted 21 February 2022

KEY WORDS
Nanomedicines; Nanoparticles; Liposomes; Vaccines; Marked products; Clinical translations; Disease-driven design; Quality by design

Abstract

Compared with traditional drug therapy, nanomedicines exhibit intriguing biological features to increase therapeutic efficiency, reduce toxicity and achieve targeting delivery. This review provides a snapshot of nanomedicines that have been currently launched or in the clinical trials, which manifests a diversified trend in carrier types, applied indications and mechanisms of action. From the perspective of indications, this article presents an overview of the applications of nanomedicines involving the prevention, diagnosis and treatment of various diseases, which include cancer, infections, blood disorders, cardiovascular diseases, immuno-associated diseases and nervous system diseases, etc. Moreover, the review provides some considerations and perspectives in the research and development of nanomedicines to facilitate their translations in clinic.

© 2022 Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

*Corresponding author. State Key Laboratory of Drug Research & Center of Pharmaceutics, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China. Tel./fax: +86 21 20231979.
E-mail address: zwzhang0125@simm.ac.cn (Zhiwen Zhang).

Peer review under responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.
1. Introduction

Nanomedicines refer to the nanotechnology-based drug products for the treatment, diagnosis or prevention of various diseases. The U.S. Food and Drug Administration (FDA) clarifies the nanomedicines as the products in the nanoscale range (i.e., with at least one dimension in the size range of approximately one—100 nm) that can exhibit different chemical or physical properties, or biological effects compared to larger-scale counterparts, or products outside the nanoscale range of approximately one—100 nm that can also exhibit similar properties or phenomena attributable to a dimension(s). Nanomedicines are usually formed by the combination of appropriate nanocarriers and active pharmaceutical ingredients (API). In addition, some of them can be prepared by directly turning the API into nano-sized components (e.g., nanocrystals) with the help of stabilizers to prevent aggregations. According to the type and structure of the carriers, nanomedicines are primarily classified into liposome, antibody—drug conjugate, inorganic nanoparticle, polymer nanoparticle, dendrimer, micelle, polymer—drug conjugate, virus-derived vector, nanocrystal, cell-derived carrier and protein-bound nanoparticle.

Nanomedicines impart special biological effects owing to their nano-scale, specific structure and particular surface properties. These features endow them with many advantages, such as improving drug solubility and stability, increasing drug selectivity, modulating controllable drug release in a sustained or responsive manner, synergistic delivery of multiple drugs, elevating bioavailability, enhancing therapeutic effects and reducing the adverse effects.

This review summarized current nanomedicines that have been approved for marketing or entered the clinical stages so far, in order to provide an overview of the current clinical translation of various nanomedicines. Examples are given to illustrate the applications in cancer, bacterial, fungal, viral and parasitic infections, blood diseases, endocrine and metabolic diseases, cardiovascular diseases, immune diseases, nervous system diseases, mental diseases, ocular diseases, skin diseases and other indications. Finally, we proposed some perspectives of nanomedicines in the process of clinical translation and commercialization, the enlightenments of clinical failure and the future directions.

2. Snapshots of nanomedicines in the market or clinical translations

Nanomedicines that have been approved in the market or in clinical trials were retrieved utilizing the Cortellis Drug Discovery Intelligence (CDDI) database. Information search and filtering were carried out in June 2021, and the search results were merged, de-duplicated and sorted in Microsoft Excel. The correlation between the retrieved results and nanomedicines was further confirmed by manually screening the CDDI database fields “chemical name/description”, “product summary”, “product category” of drugs and searching literature on PubMed.gov.

To date, there are 100 nanomedicines on the market, and 563 in clinical process or other stages (663 in total). Most of these nanomedicines (Fig. 2A) are in clinical phase I (33%) and phase II (21%), and mainly focus on cancer (53%) and infection (14%) treatments. Moreover, nanomedicines have been developed for the treatment of nervous system diseases, mental diseases, blood disorders, endocrine and metabolic diseases, immunological diseases, cardiovascular diseases, ocular diseases, skin diseases, endocrine and metabolic diseases, immunological diseases, cardiovascular diseases, ocular diseases, skin diseases and other indications (Fig. 2B). In addition, nanomedicines are used in vaccine development and imaging diagnostic. Among all the nanomedicines accessible in the market or in various stages of clinical translations, liposome or lipid-based nanoparticle is the most prevalent category (33%), followed with antibody-drug conjugate (15%), polymer-drug/protein conjugate (10%) and polymer (10%). Other types of nanomedicines include viral vector (8%), cell-derived vehicle (4%), inorganic nanoparticle (3%), emulsion, protein-based nanoparticle, micelle, nanocrystal, dendrimer, and so on (Fig. 2C).

3. Applications of nanomedicines in various indications

3.1. Cancer treatment

Nanomedicines have been widely used in cancer therapy due to their distinguished features, such as modulating in vivo distribution profiles, promoting specific tumor accumulation via passive or active targeting capability, delivering multiple therapeutic agents at fixed ratios, or reducing the adverse effect of loaded drugs. The passive targeting of nanomedicines mainly depends on the difference of pathophysiological characteristics between tumor and healthy tissues, such as the abnormal structures of the tumor vasculatures. In contrast, the active targeting of nanomedicines can be achieved by their preferential recognition or binding to the over-expressed or specifically expressed receptors in the tumor microenvironments. The nanomedicines for cancer treatment that have been launched on the market or under clinical trials are summarized in the Supporting Information Tables S1–S5. The carrier types of
these anticancer nanomedicines include liposomes or lipid-based nanoparticles, antibody-drug conjugates, polymer-drug conjugates, micelles, dendrimers, inorganic nanoparticles, viral vectors, cell-derived vesicles and protein-bound nanoparticles (Fig. 3). They are used in many types of anticancer modalities, such as chemotherapy, gene therapy, immunotherapy, photothermal therapy, radiotherapy and combination therapy.

3.1.1. Liposomes and lipid-based nanoparticles

Liposomes are spherical vesicles composed of phospholipids, which have amphoteric properties and can deliver hydrophilic as well as hydrophobic drugs, which can be prepared using diverse methods like reverse-phase evaporation, thin-film hydration, microfluidics technique, spray-drying and supercritical fluids techniques, etc. Liposomes have unique advantages as drug delivery carriers because phospholipids are biodegradable, biocompatible, and similar to lipids present in cell membranes. Liposomes that have been approved (Table S1) are mainly based on the passive targeting mechanism, such as Vyxeos (2017), Onivyde (2015), DoceAqualip (2014) and Doxil (1995). It is worth noting that some liposomes based on active targeting have entered the clinical stage, such as C225-ILS-DOX and SGT-94. Among them, the loaded cargoes include versatile...
chemotherapeutic drugs (such as doxorubicin$^{25}$, paclitaxel$^{26}$ and cisplatin$^{27}$) or nucleic drugs (e.g., mRNA$^{28}$, miRNA$^{29}$, DNA oligonucleotide$^{30}$, siRNA$^{31}$ and shRNA$^{32}$).

Doxil is the first liposome formulation approved by the FDA, launched in 1995 by Sequus for the treatment of AIDS-related Kaposi’s sarcoma in patients refractory or intolerant to combination chemotherapy. Doxil is prepared by loading a cytotoxic anthracycline antibiotic, doxorubicin hydrochloride, into long-circulating liposomes, which are formulated with surface-bound polyethylene glycol (PEG) to protect liposomes from clearance by the mononuclear phagocyte system (MPS). The targeting mechanism of Doxil is mainly ascribed to its small size and persistence in circulation$^{25}$. In addition, the quality evaluations of Doxil by FDA have been published and interpreted in detail in the literature$^{25}$.

In addition to the passive targeting, liposomes can be modified with versatile ligands (e.g., antibodies) on the surface to facilitate their target to the overexpressed factors in the tumor. C225-ILS-DOX is an immunoliposome targeting the overexpressed endothelial growth factor receptor (EGFR) in tumors, consisting of Fab fragments from cetuximab (an anti-EGFR monoclonal humanized antibody) covalently coupled to PEGylated liposomes of doxorubicin$^{33}$. A phase I trial has been completed in patients with advanced solid tumors (NCT01702129)$^{34}$.

3.1.2. Polymer–drug/protein conjugates

Polymer–drug/protein conjugates that are used in cancer treatments are mainly PEGylated proteins or drugs (Table S1). Among them, the PEGylated proteins are enzymes (e.g., arginine deimination and enzyme L-asparaginase), and immune-related proteins (e.g., TNF alpha, antibodies and granulocyte colony-stimulating factor). PEGylation can reduce drug renal clearance, protect proteins from degradation, improve drug stability, prolong drug half-life, reduce the risk of immunogenicity, and improve drug distribution$^{35}$.

3.1.2.1. Polymer-drug/protein conjugates in the market.

Calaspargase pegol (Asparlas), first launched in 2019 in the U.S., is a polyethylene glycol-L-asparaginase, as part of a multiagent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia$^{36}$. L-Asparaginase can catalyze the hydrolysis of L-asparagine to L-aspartate and ammonia, thus preventing the proliferation of tumors. PEGylation makes
t-asparaginase lower immunogenicity, higher catalytic activity and longer half-life37.

3.1.2.2. Polymer-drug/protein conjugates under clinical development. Peglated recombinant Adnectin protein derived from the human fibronectin type III domain, targeting vascular endothelial growth factor receptor 2 (VEGFR-2)38. The recombinant Adnectin is linked to a 40-kDa polyethylene glycol (PEG40) moiety through a maleimide derivate39. Peglated recombinant Adnectin has reached the clinical stage by Bristol—Myers Squibb for several cancer indications, including metastatic colorectal cancer, advanced non-squamous non-small cell lung cancer and glioblastoma multiforme40—42. Apart from the PEGylation of enzyme/protein, small molecule drugs can also be PEGylated to improve pharmacokinetic properties. For instance, PEGSN38 is the pegylated form of DNA topoisomerase I inhibitor SN38, the active metabolite of irinotecan hydrochloride. Four SN38 molecules are conjugated to the multi-arm PEG backbone, allowing PEG-SN38 to have high drug loading and water solubility (400- to 1000-fold increase)43. It was developed by Enzon and underwent phase I and II clinical trials for the treatment of solid tumors and lymphoma.

In addition to PEG, other polymers (e.g., polypeptides) are also used to improve the tumor targeting and optimize the biological distribution of anticancer drugs. ANG-1005 is a taxane derivative consisting of three paclitaxel molecules covalently linked to Angiopep-2, designed to cross the blood-brain and blood—cerebrospinal barriers to treat malignant tumors in brain44. ANG-1005 is originated by AngioChem and is currently in phase II clinical development for the treatment of patients with advanced solid tumors with brain metastases. Phase II trials have been completed for the treatment of recurrent malignant glioma.

3.1.3. Polymeric nanoparticles/micelles/dendrimers
Polymer nanoparticles are defined as colloidal particles with a size of one—1000 nm made of natural polymers (e.g., chitosan) or synthetic polymers (such as polyacrylate, poly (D, L-lactide-co-glycolide) (PLGA) and polyethyleneimine)45. Polymer micelles are composed of amphiphilic block copolymers, which can spontaneously form colloidal nanocarriers in aqueous solutions above the critical micellar concentration (CMC)4. The drugs can be incorporated into the micellar core through physical interaction or can be combined with the backbone of the copolymer through environment-sensitive bonds, which can be cleaved under specific conditions46. Dendrimers, synthesized by controlled polymerization, are polymer systems with hyperbranched tree-like structures, which are mainly composed of central core moiety, internal branches and functional surfaces47. Some polymeric nanoparticles and micelles have been approved for marketing, but most products are in the clinical stage, while dendrimers are all currently in the clinical stage (Table S1).

CALAA01 is the first targeted polymer for small interfering RNA (siRNA) therapy of cancer patients and had been in phase I clinical trials by Calando Pharmaceuticals48. CALAA01 is an siRNA targeting human RRM2, which is delivered in nanoparticles consisting of a cycloextrim-based polymer, transferrin protein (Tf) targeting ligands, and PEG49. The cycloextrim-containing polycation binds to the anionic siRNA, making them into nanoparticles smaller than 100 nm in diameter, which can protect the siRNA from nuclease degradation in serum.

3.1.4. Protein-based nanoparticles
The most common protein-based nanoparticles are albumin-bound nanoparticles, such as Abraxane (approved in 2005), Nab-paclitaxel/rituximab (phase I), Nab-docetaxel (phase II) and Fyarro (pre-registered) (Table S2). Albumin, the most abundant protein in human blood, can prolong the circulation half-life of the compounds. Moreover, they tend to accumulate in tumors because tumor cells need tremendous nutrients for rapid growth, making albumin an excellent carrier for selective drug delivery to tumors50. The protein-based nanoparticles can be fabricated by desolvation method, nanoparticle albumin-bound (Nab™ technology and self-assembly technique, which are practical clinically51.

3.1.4.1. Protein-based nanoparticles in the market. Abraxane is the first formulation based on protein-nanotechnology approved by FDA. Abraxane is a nanoparticle formulation of paclitaxel stabilized with human albumin with a particle size of 130 nm, which is prepared by Nab™ technology of Abraxis BioScience1. In Nab™ technology, the hydrophobic paclitaxel is dissolved in organic solvents and emulsified with aqueous albumin, wherein the particle size is controlled by high-pressure homogenizer52. During homogenization, sulfhydryl groups of albumins are oxidized to form disulfide bonds without the use of any crosslinking agent or denaturation of albumin, and the drugs are encapsulated inside the nanoparticles53. Abraxane was approved by FDA in 2005 for the treatment of breast cancer after failure of combination chemotherapy or relapse within six months of adjuvant chemotherapy. Abraxane increases the aqueous solubility of water-insoluble paclitaxel through albumin binding and reduces the serious toxicity and hypersensitivity caused by the Cremophor EL in the traditional paclitaxel formulation (Taxol)54.

3.1.4.2. Protein-based nanoparticles under clinical development. AR-160 is a formulation of paclitaxel albumin-stabilized nanoparticle complexed with a chimeric monoclonal antibody against CD20 (rituximab), developed by Mayo Clinic. It is in an early clinical trial for patients with relapsed or refractory CD20+ B-cell non-Hodgkin lymphoma (NHL), including small lymphocytic lymphoma. In animal experiments, AR-160 exhibited better therapeutic efficacy than ABX or rituximab alone in human B-cell lymphoma models55.

In addition, viral proteins are also established as carriers56. FB-631, a tumor immunotherapy product developed by Folia Biotech, is a rod-shaped virus-like nanoparticle (VLNP) comprising recombinant coat protein of papaya mosaic virus (PapMV) and a single-stranded RNA activating toll-like receptor 7/856. PapMV VLNP has been proved to be an immunomodulator to activate immune cells in tumor microenvironment. The stimulation of human peripheral blood mononuclear cells by VLNP induces the secretion of interferon α and other pro-inflammatory cytokines and chemokines, and thus triggers the anti-cancer immune response.

3.1.5. Cell-derived vehicles
The cell-derived vehicles in clinical or on the market for cancer treatment are mainly exosomes and bacteria-derived vesicles (Table S2). The cell-derived vehicles for tumor therapy discussed in this paper refer to the use of cells or cell derivatives as drug carriers to deliver specific drugs, not including adoptive cell therapy, such as chimeric antigen receptor-modified T cells (CAR T cells). Many CAR T cells products have been approved for the market as of 2021, such as Abecma (2021), Breyanzi (2021), ARI-0001 (2021), Tecartus (2020), Kymriah (2017), Yescarta (2017), and there are more than 700 clinical trials related to T cells57,58. The CAR T cells products can be further reviewed in the articles57,58.
Exosomes are vesicles released by cells, including cancer cells, which contain cell-derived substances such as DNA, RNA, protein, lipid, sugar structure and metabolites. Due to their unique properties, exosomes have many advantages as drug carriers. For example, exosomes contain tumor-derived dsDNA, which can be transported to tumor resident dendritic cells (DCs) to initiate immune response through the STING pathway. Exosomes are usually produced from mammalian cell cultures in bioreactors. The PureTech company extracted exosomes by ultracentrifugation. The International Society for Extracellular Vesicles (ISEV) has initiated the standards for EV isolation and characterization to promote the systematic investigation of efficacy and safety.

To date, no exosome products have been approved for marketing currently because many issues have not been addressed, such as quality control, large-scale repeatable preparation, effectiveness and safety, etc. Exosomes products in the clinical stage include exoSTING, exoIL-12, and iExosomes. exoSTING is an engineered exosome product candidate overexpressing protein X (PrX) and loaded with a cyclic dinucleotide (CDN) small molecule STING agonist (FSA). exoSTING can selectively target antigen-presenting cells (APCs) in tumor microenvironment (TME), enhance the activity of CDN, activate anti-tumor immunity, and reduce systemic inflammatory response. exoSTING is being developed by Codiax Biosciences (founded in 2015) for the intratumoral treatment of advanced solid tumors. A phase I/II clinical trial (NCT04592484) is ongoing in patients with advanced or metastatic solid tumors progressing after standard-of-care therapy, with emphasis on head and neck squamous cell carcinoma, triple-negative breast cancer, anaplastic thyroid cancer and cutaneous squamous cell carcinoma.

Vehicles derived from bacteria are another kind of cell-based vesicle for cancer therapy. Bacteria-derived vesicles in clinical stage include TargomiRs, EGFR-EDV-dox, E-EDV-G682, EEDV-SMit and EGRFminicellsPac, which are developed based on EnGeneIC’s delivery vehicle (EDV) nanocells technology. EGRFminicellsPac is a Salmonella typhimurium-derived EDV nanocells packaged with chemotherapeutic paclitaxel and a bispecific antibody derived from cetuximab targeting both EGFR and o-poly saccharides. They are shown to be safe in patients with advanced solid tumors in phase I clinical trial.

### 3.1.6. Viral vectors

Viral vectors (Table S2) can be used for gene therapy, encoding anti-tumor proteins, such as cytocidal mutant dominant-negative cyclin G1, wild-type P53, human tumor necrosis factor-α (TNF-α), GM-CSF, IL-2 and human interferon α-2b, or encoding enzymes that can activate prodrugs to improve the anti-cancer efficacy, such as cytosine deaminase combined with 5-fluorocytosine and herpes simplex virus thymidine kinase combined with ganciclovir. Adenoviral vectors are the main viral vectors used in cancer treatment. In addition, a small number of retroviral vectors have been approved for marketing or are in clinical trials. Viral vectors approved for cancer therapy include DeltaRex-G (2007) and Gendicine (2004).

DeltaRex-G is a retroviral vector encoding a cytocidal mutant dominant-negative cyclin G1 gene, which is developed by Epeius Biotechnologies and launched in 2007 in the Philippines for the treatment of all solid tumors. To achieve tumor-specific targeting, DeltaRex-G is composed of a murine leukemia virus (MLV)-based amphotropic retrovirus vector that displays a collagen-binding motif on its gp70 surface membrane to targeting abnormal proteins in tumors. The human cyclin-G1 gene is a prospective oncogene that favors the development of many types of cancer, including pancreatic, colon, breast and prostate cancer. DeltaRex-G can block the function of cyclin G1-dependent pathways through mutant cyclin-G1 encoded by the vector, and exert an anti-tumor effect. In 2020, the product received emergency use authorization in the U.S. for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

### 3.1.7. Inorganic nanoparticles

Currently, the main types of inorganic nanoparticle products that have been approved on the market or in clinical trials are superparamagnetic nanoparticles, gold nanoparticles, manganese nanoparticles and silica nanoparticles (Table S2), which are utilized in tumor photothermal therapy, tumor radiotherapy, chemotherapy sensitization and so on.

#### 3.1.7.1. Inorganic nanoparticles in the market

Hensify is a kind of nanoparticle (about 50 nm in diameter) composed of crystalline hafnium oxide (HfO2) core and amorphous thin biocompatible coating. It is a radiosensitizer developed with NanoXray technology of Nanobiotix. Hensify enhances external radiotherapy through the special properties of hafnium. The interaction between ionizing radiation and hafnium can promote higher energy deposition. In 2019, Hensify obtained CE Mark approval in the E.U. for the treatment of locally advanced soft tissue sarcoma in combination with synchronous radiotherapy. The approval of Hensify demonstrates that nanoparticles can provide therapeutic benefits in a complementary and synergistic manner with standard treatment modalities. This strategy is instructive to accelerate the clinical translation of nanomedicines, as researchers conventionally tend to seek nanomedicines that are more effective than existing clinical therapies.

#### 3.1.7.2. Inorganic nanoparticles under clinical development

AuroShell has a silicon core and an ultra-thin gold shell coated with PEG, which is developed by Nanospectra. Auroshell is biocompatible and optically tunable in near-infrared absorption. With a diameter of 150 nm, Auroshell has been used for photothermal ablation of solid tumors, which convert light into heat, thereby destroying solid tumors without causing significant damage to surrounding healthy tissues. It has been validated in clinical trials for the treatment of head and neck cancer.

32P BioSilicon is a porous silicon nanoparticle containing radioactive phosphorus (32P) (purity >99.9%), developed by BioSilicon (TM). 32P is a pure β-particle emitter, which is an ideal nuclide for radiotherapy. The maximum emission range of 32P β-particles in tissues is about 7.6 mm, with a physical half-life of 14.3 days. 32P BioSilicon is administered by percutaneous intratumoral injection to provide local and targeted radiation sources for cancer treatment.

### 3.1.8. Antibody–drug conjugates

In the technical guidelines for quality control of nanomedicines from the Center for Drug Evaluation (CDE), antibody–drug conjugates (ADCs) are considered as a kind of nanomedicines. ADCs utilize the targeting and specificity of antibodies (such as
monoclonal antibodies or bispecific antibodies) as drug carriers to transport toxic drugs to tumor sites. ADCs consist of antibodies, linkers and toxic payloads. The active payloads in ADCs are mainly microtubule inhibitors (such as maytansinoids and auristatins) and DNA-damaging agents (such as pyrrolobenzodiazepine dimer and duocarmycins), which are linked to the antibodies via chemical conjugation or enzymatic conjugations. The properties that need to be characterized include molecular polymorphism, impurities (e.g., residual solvents), potency and so on. Notably, FDA’s approval of ADCs is based on the biological license applications (BLA) process. So far, eleven ADCs have received market approval, and more than 80 ADCs are currently in clinical development (Table S2).

### 3.1.8.1. ADCs in the market

Loncastuximab tesirine is an antibody-drug conjugate consisting of humanized monoclonal IgG1-κ antibody targeting B-cell specific surface antigen CD19, a DNA-alkylating pyrrolobenzodiazepine dimer cytotoxin (SG-3199) and a cathepsin B-sensitive maleimide type linker (valine-alanine dipeptide), with a drug-antibody ratio of 2.3. It was launched in 2021 for adult patients with relapsed or refractory large B-cell lymphoma, including diffuse large B-cell lymphoma (DLBCL).

### 3.1.8.2. ADCs under clinical development

CX-2029 is a proteolytically activated antibody produg (Probody) drug targeting transferrin receptor (CD71; TFRC) conjugated to the microtubule disrupting agent monomethyl auristatin E (vcMMAE). It is in phase I/II clinical trials by CytomX Therapeutics for the treatment of adult patients with DLBCL or with metastatic or locally advanced unresectable solid tumors such as head and neck cancer, non-small cell lung cancer and pancreatic cancer. Clinical phase I results have proved that Probody is capable of targeting CD71 at tolerable doses associated with clinical activity. The most common dose-dependent hematologic toxicities of CX-2029 were anemia and neutropenia.

In addition to complex with anticancer drugs, antibodies can also carry radionuclides (Table S2). Antibody-based radioimmunotherapy utilizes monoclonal antibodies to target cancer-associated cell surface antigens and deliver radionuclides to tumor sites, providing high-dose therapeutic radiation to cancer cells specifically and minimizing the irradiation exposure to normal cells. Antibody-labeled antibodies can be used for tumor imaging.

### 3.1.8.3. Antibody-based radioimmunotherapy products in the market

Capromab pendetide indium, launched in 1997, is an indium-111 radiolabeled immunocugenate derived from anti-prostate monoclonal antibody 7E11-CS, as a radioimmunoscintigraphic imaging agent used in patients with prostate cancer.

### 3.1.8.4. Antibody-based radioimmunotherapy products under clinical development

227Th-Anetumab corixetan is a 227Th-radioimmunoconjugate, comprising an anti-mesothelin monoclonal antibody anetumab (BAY-861903) covalently linked via an amide bond to a 3,2-hydroxypryridone (3,2-HOPO) chelator complexing the alpha-emitter 227Th. Through the alpha decay of 227Th, the radioimmunoconjugate can induce cluster DNA double-strand breaks and thus lead to cell death. 227Th-Anetumab corixetan is in early clinical evaluation in patients suffering from advanced epithelioid mesothelioma, metastatic pancreatic adenocarcinoma and ovarian cancer (NCT03507452).

### 3.2. Cancer imaging and diagnosis

Nanoparticles have the potential to realize multimodal imaging of tumor and the integration of diagnosis and treatment. Many types of nanomedicines have been developed to enhance the sensitivity and specificity of cancer imaging and diagnosis, such as positron emission tomography (PET) imaging agents, fluorescence imaging agents, radioactive and fluorescent hybrid tracers, magnetic resonance imaging (MRI) contrast agents and ultrasound contrast agents.

#### 3.2.1. Nanoparticles for cancer imaging and diagnosis in the market

MRI imaging agent, Resovist, consists of carboxydextran-coated superparamagnetic iron oxide nanoparticles with a hydrodynamic particle size of approximately 60 nm and was approved for liver contrast-enhanced MRI. In addition, Aerosomes, microbubbles of octafluoropropane gas encapsulated liposomes, are launched in 2001 as ultrasound contrast agents.

#### 3.2.2. Nanoparticles for cancer imaging and diagnosis under clinical development

124I-cRGDY-PEG-dots are core-shell silica nanoparticles loading Cy5 dye, and coated with PEG chains linked to 124I-radiolabeled cyclo (Arg-Gly-Asp-Tyr) peptides. The radioactive 124I and fluorescent Cy5 labeling enable the nanoparticles to be used as hybrid PET/optical imaging agents, wherein the cRGDY peptides are used as targeting ligand. 124I-cRGDY-PEG-dots is in phase I clinical trial by the Memorial Sloan-Kettering Cancer Center for the diagnosis of metastatic melanoma and malignant brain tumors.

ONM-100 is a pH-sensitive fluorescence imaging agent that consists of a super-paramagnetic amphiphilic polymer linked to indocyanine green. Upon the accumulation of ONM-100 at the tumor tissue, the unique acidic microenvironment caused by cancer cell metabolism in solid tumors causes the pH-activated fluorescence to switch from “off” (green) to “on” (red). ONM-100, developed by OncoNano, is currently in phase II clinical trial for the detection of tumors and metastatic lymph nodes in patients with solid tumors. ONM-100 has been proved to have good safety, pharmacokinetic properties and imaging feasibility, and can be used for intraoperative and ex vivo detection of cancer tissue.

### 3.3. Cancer vaccine

Cancer vaccine is a hot spot in cancer immunotherapy, and their design largely depends on the antigens, including tumor-associated antigens (TAA) and tumor-specific antigens (TSA). TAA are autoantigens abnormally over-expressed by tumor cells, while TSA are mutated proteins derived from cancer cells, which are tumor-specific and highly immunogenic. Nanoparticles-based cancer vaccines and adjuvants can improve bioavailability, protect antigens from degradation, improve transfection efficiency, control antigen release or enhance immune response. Based on the source of antigens and the type of carriers, cancer vaccine are
3.3.1. Cell-based tumor vaccine

The cell-based tumor vaccines discussed in this paper referred to the nanocarriers that deliver tumor antigens using cells or cell derivatives, or deliver tumor antigens derived from cells (e.g., cell lysates). Since this article deal with marketed or clinical products associated with nanocarriers, dendritic cell vaccines are not discussed here. Dendritic cells (DC) vaccines are a commendable field in developing tumor vaccines, and a number of DC vaccines have been launched, such as Apced-ENP (2017), Apced-EP (2017), Apced-L (2017), Apced-EP (2017), Apcsed-CR (2017), Provenge (2010) and CreaVax-RCC (2007). Further reviews of DC vaccines are available in the articles. Table S4 contains specific examples of cell-based tumor vaccines accessible in the market or in clinical developments.

Bacteria-derived substances, such as the outer membrane vesicles (OMVs) of Neisseria meningitidis, exhibit immune-stimulating properties and can be used as an adjuvant or immune-enhancer. GM3/VSSP is a cancer vaccine comprising small-sized proteoliposomes (VSSPs) formed by linking N-acetyl GM3 (NAcGM3) ganglioside with Neisseria meningitidis-derived OMVs. N-Glycosylated ganglioside is highly expressed in cancer cells but minimally detected in normal tissues, making it an attractive option for tumor immunotherapy. Typically, melanoma and breast cancer are tumors with overexpression of N-glycolyl gangliosides, especially the N-glycolyl GM3 (NGcGM3) gangliosides. VSSPs have been shown to stimulate immune responses by activating DCs, even in immunosuppressed cancer patients. A phase II clinical trial of the GM3/VSSP vaccine administered by intramuscular injection in patients with breast cancer demonstrated that the vaccine was safe and immunogenic, and some patients had better overall survival values than other reports in the literature of patients with non-visceral metastases.

In addition to OMV, autologous tumor cell vaccines are also feasible and emerging methods for personalized immunotherapy. Oncoquest-CLL is an autologous tumor cell vaccine comprising of lysates of autologous tumor chronic lymphocytic leukemia (CLL) incorporated in liposomes along with IL-2, developed by Xeme Biopharma. The product is in early clinical development against CLL.

3.3.2. Virus-based tumor vaccine

Virus-based tumor vaccines (Table S4) express tumor antigens by virus vector or release antigens in situ by virus lysis of tumor cells. Genetically modified oncolytic viruses are designed to specifically replicate in tumors and destroy tumor cells. Oncolytic viruses can induce immunogenic cell death (ICD) to release tumor-associated antigens and promote the activation of new antigen-specific T cells. In addition, oncolytic viruses can express immunomodulatory factors such as cytokines, antibodies and cosimulatory factors. Oncolytic virus products currently approved for marketing (Table S4) include Delytact (2021), Talmigene Laherparepvec (2015), and Oncorine (2006). In addition, there are many new products in the clinical stage, for example, NG-348. Adenovirus and herpes simplex virus (HSV) are the main oncolytic virus on the market or in clinical stage.

3.3.2.1. Virus-based tumor vaccine in the market. Oncorine, the world’s first oncolytic virus medicine, is E1B-55kd deleted oncolytic adenovirus, developed by Shanghai Sunway Biotech and launched in 2006 in China in combination with chemotherapy for patients with nasopharyngeal carcinoma. Adenovirus vectors are safe because they lack the ability of integration and cannot be randomly integrated into the host genome to produce mutagenic effects. The deletion of an E1B-55kd segment in the virus leads to its ability to selectively replicate in and kill tumor cells, while leaving normal cells not affected.

Talmigene Laherparepvec (TVEC) is an oncolytic virus therapy developed by BioVex, which was first launched in the United States in 2015 for the local treatment of unsecretable skin, subcutaneous and nodal lesions in patients with melanoma recurrent after the initial operation. TVEC is ICP34.5- and ICP47-deleted oncolytic HSV-1 carrying the human GM-CSF gene, which is designed to replicate within and lyse tumor cells, release tumor antigen and promote local and systemic anti-tumor immunity. The deletion of the herpes neurovirulence viral genes attenuates TVEC, and the deletion of the ICP47 gene enhances immunogenicity. Besides, the therapeutic vaccine can induce tumor cells to secrete the immune stimulator GM-CSF, which can promote the initiation of the T-cell response. TVEC showed significant improvements in sustained response rate, objective response rate, and progression-free survival for patients with advanced melanoma.

3.3.2.2. Virus-based tumor vaccine under clinical development. Aspartate β-hydroxylase (sASPH) is overexpressed in 70%–90% of human solid tumors, which plays a key role in the malignant progression of solid tumors. PAN-301-1 is a bacteriophage viral vector consisting of UV-irradiated lambda phage with the gpD surface protein fused to the C-terminus portion of human ASPH. It is an anti-ASPH tumor vaccine manufactured by Sensei Biotherapeutics, which is in early clinical development for the treatment of solid tumors and hematological malignancies.

NG-348 is an oncolytic adenovirus virus encoding two immunomodulatory membrane-integrated T-cell-engaging proteins, including a full-length human CD80 and an antibody fragment targeting the human T-cell receptor CD3 complex. NG-348 can specifically infect tumor cells and replicate in them, making tumor cells produce two kinds of membrane-anchored T cell proteins that drive local T-cell immune responses. Compared with CAR-T therapies, NG-348 does not need to extract and modify patients’ T cells in the external environment. As the mirror image of CAR-T therapies, NG-348 can modify tumor cells in situ through gene therapy, and then engage T cells to fight against cancer cells in solid tumors. In 2017, NG-348 was approved for human clinical trials.

3.3.3. Recombinant protein/peptide, DNA and RNA vaccine

The source of antigens in tumor vaccines delivered by nanoparticles can be DNA or RNA encoding tumor antigens, recombinant proteins or antigen peptides. Most of them are currently in clinical trials, mainly RNA vaccines and recombinant protein/peptide vaccines (Table S4).

DNA vaccines encode tumor antigens that are expressed and presented on major histocompatibility molecules (MHC) to activate T cells. The most common delivery methods for DNA vaccines are physical strategies, for instance, electroporation. At present, few tumor DNA vaccines are delivered by nanoparticles in clinical stage. Amoligene bepiplasmid is a DNA vaccine encapsulated in PLGA microparticles, which is expected...
to initiate a humoral immune response as well as induce and expand T cells specific to HPV 16/18 antigens. The vaccine candidate had been in phase II/III clinical trials at MGI Pharma for HPV-associated cervical dysplasia, but was discontinued in 2010 for unknown reasons.

Alternatively, RNA vaccines may have advantages over DNA vaccines, because RNA cannot integrate into the genome and therefore has no carcinogenic potential. Moreover, RNA only needs to enter the cytoplasm, while DNA needs to cross the nuclear membrane barrier to enter the nucleus. However, naked RNA is easy to be degraded by RNase, and the cell transfection efficiency is low. Rationally, delivery vectors or chemical modifications are designed to solve these problems. For instance, mRNA-2416 is a mRNA-based cancer vaccine targeting OX40L, consisting of messenger RNAs (mRNA) encoding OX40 ligands (OX40L) with miR-122 binding sites encapsulated in lipid nanoparticles. The lipid nanoparticles can bind to the cell membrane, then enter the cell through endocytosis, and finally release the mRNA encoding OX40L into the cytoplasm. The translation of mRNA ensures the expression of OX40L on the cytoplasmic membrane, which can interact with the tumor necrosis factor receptor superfamily member 4 (TNFRSF4; OX40) expressed on the activated T cells. The binding of OX40 and OX40L can promote CD4+ and CD8+ T cells expansion, enhance memory response and inhibit regulatory T cell functions.

mRNA-2416 is in phase II clinical trial (NCT01976520) by Moderna for the treatment of ovarian carcinoma in combination with durvalumab. mRNA-2416 is administered by intratumoral injection and durvalumab is given by intravenous injection.

In another strategy, the recombinant protein/peptide vaccines theoretically have several advantages over other types of vaccines such as easy synthesis with low cost, increased stability, and relative safety, promoting their development in numerous preclinical and clinical studies. CHP-NY-ESO-1 is a nanoparticles peptide vaccine originated by the Ludwig Institute for Cancer Research, which consists of cholesterol hydrophobized polysaccharide (CHP, pullulan) complexed with recombinant NY-ESO-1 peptide (cancer-testis antigen). The tumor vaccine candidate, is subcutaneously administered. CHP-NY-ESO-1 is intended to present multiple epitope peptides to MHC class I and II pathways, initiating CD8+ and CD4+ T cell responses. A clinical study (NCT01003808) has confirmed the safety and immunogenicity of the CHP-NY-ESO-1 vaccine. CHP-NY-ESO-1 at a 200 μg dose can induce immune response more effectively and showed better survival benefits. OncoVax-CLb, originated by Jenner Biotherapies, is a recombinant protein vaccine consisting of recombinant epithelial cell adhesion molecule (KSA), formulated with monophosphoryl lipid A (MPLA) in liposomes. KSA is over-expressed in colorectal cancers and can be utilized as tumor antigens. MPLA, a detoxified derivative of the lipopolysaccharide of Salmonella Minnesota R595, can retain the immunostimulatory activity and be used as immune adjuvants. OncoVax-CLb is in clinical trials in the U.S., for therapy of colorectal cancer.

In addition, nanomedicines have also been developed as remedies for tumor treatment-related complications, such as pain and acute radiation syndrome (ARS), which affect the quality of life of patients. For cancer pain treatment, NanaBis, AeroLEF and Substance P-saporin have been developed. AeroLEF, developed by YM Bioscience, is composed of aerosolized liposome encapsulated fentanyl, and is intended to be administered through pulmonary inhalation to achieve rapid absorption. AeroLEF was assessed in early clinical trials for controlling moderate or severe acute pain. ARS is caused by systemic or partial exposure to high-dose radiation for a short period of time. MAXY-G34 is a PEGylated formulation of granulocyte colony-stimulating factor (G-CSF), which can stimulate the bone marrow to produce white blood cells. The product, developed by Maxygen, has been in early clinical trials for the treatment of chemotherapy-induced neutropenia. PEGylation of G-CSF improves pharmacokinetic properties with reduced renal clearance and prolonged circulating half-life. Meanwhile, nanocarriers can be utilized to present antigens and stimulate immune cells to achieve adoptive cell therapy (Table S5). In adoptive cell therapy products, such as CSTD002-NK, K-NK-003, NEXI-002 and NEXI-001, nanoparticles act as artificial antigen-presenting cells (aAPCs) to present antigens to immune cells (NK cells and T cells).

3.4. Infections

Nanomedicines have also been developed for the treatment of diseases caused by infection, such as bacterial/fungal infections, viral infections and parasitic diseases (Supporting Information Table S6).

3.4.1. Bacterial/fungal infections

Traditional antibiotic treatment is easy to produce antibiotic resistance, which is emerging as one of the severe threats to global public health. Nanomaterials are potential to restore the antibacterial activity of traditional antibiotics through optimizing pharmacokinetics, promoting antibiotic internalization, improving biofilm penetration, changing the biofilm microenvironment, and so on. Accordingly, nanomedicines have been developed for local infections or systemic diseases caused by pathogenic bacterial or fungal infections, such as meningococcal meningitis, pulmonary tuberculosis and aspergillosis. To date, liposomes containing polyene antifungal drug amphotericin B or aminoglycoside antibiotic amikacin have been launched, such as SLIT-amikacin (2018, Insmed) and Liposomal amphotericin B (1991, Astellas Pharma).

In addition to intravenously administered liposomes, inhaled oral liposomes have also entered the clinical stage (Table S6). Liposomes are identified as potential carriers for inhalation therapy because of their safety and the ability to penetrate within biofilm as well as provide controlled drug release in the lungs. SLIT-amikacin (Arikace), a liposomal inhaled formulation of amikacin developed by Insmed, can penetrate into airway secretions and biofilm deeply. It was first launched in 2018 in the U.S. for the treatment of Mycobacterium avium complex (MAC) lung disease. In contrast, a novel oral formulation of Amphotericin B, iCo-019, is in early clinical development by iCo Therapeutics for the treatment of vulvovaginal candidiasis. The results from a single-dose study suggested that iCo-019 can prolong the blood circulation time and tissue concentration of amphotericin B, but reduce the possible toxicities in the gastrointestinal tract, liver, and kidney.

3.4.2. Viral infections

Nanomedicines can be designed as antiviral vaccines or as carriers encapsulating antiviral drugs to target the infected cells, which has been used in the treatment and prevention of viral infections, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), respiratory syncytial virus (RSV), hepatitis C (HCV), influenza...
of the S glycoprotein of the B.1.351 variant. Clinical trials (NCT04742738 and NCT04750343). The emergence of SARS-CoV-2 variants has raised concerns about the escape of the virus from vaccine-induced immunity. Some variants have shown reduced susceptibility to vaccine-induced immune neutralization, especially the SARS-CoV-2 B.1.351 (Republic of South Africa) variant. mRNA-1273.351 is a lipid nanoparticle-based variant-specific COVID-19 mRNA vaccine consisting of mRNA encoding a stabilized prefusion form of the S glycoprotein of the B.1.351 variant. Clinical trials (NCT04785144 and NCT04283461) have been initiated by Moderna in adults.

In addition, nanoparticles can also be employed to deliver drugs, such as hydroxychloroquine, transcocetin, artemisinin, curcumin and vitamin C, to treat COVID-19. LEAF-4L6715 is a liposomal formulation containing the kosmotropic agent transcocetin (TC) in early clinical development by LEAF Pharmaceuticals, which is used to improve the impaired transportation of oxygen in patients with severe acute respiratory distress syndrome (ARDS) who are receiving artificial respiratory support due to COVID-19 (NCT04378920). LEAF-4L6715 can promote the sustained release of TC to increase its half-life in blood and finally enhance the reoxygenation of hypoxic tissues.

3.4.3 Parasitic infections
Nanomedicines can also be used to treat parasitic infections, for instance, malaria (Table S6). FMP-013 is a malaria vaccine consisting of a recombinant soluble nearly full-length circumsporozoite protein (CSP) from Plasmodium falciparum, formulated in MPLA-based liposomes.

3.5 Other indications
3.5.1 Nervous system diseases and mental diseases
Nanomedicines also provide an alternative strategy to treat nervous system diseases and mental diseases, such as bipolar disorder, spinal muscular atrophy, hereditary transthyretin-mediated amyloidosis (hATTR), schizophrenia, multiple sclerosis, autism and neurodegenerative diseases (Parkinson’s disease, Huntington’s disease, Alzheimer’s disease and amyotrophic lateral sclerosis). These nanomedicines exert the therapeutic benefits mainly through gene therapy (CRISPR/Cas9, siRNAs and adenso associated viral vectors) or enhanced drug delivery (risperidone, paliperidone and rotigotine). In addition, nanovaccines against pathogenic proteins of neurodegenerative diseases (such as tau, amyloid beta and myelin basic protein) have also entered the clinical stage (Supporting Information Table S7).

3.5.1.1 Nanomedicines for nervous system diseases and mental diseases in the market. Patisiran is the first RNAi drug approved for marketing in the world, which is a milestone in gene therapy. It is composed of an siRNA targeting mutant transthyretin (TTR) delivered by lipid nanoparticles, which can inhibit hepatic synthesis of the disease-causing TTR and thus reduce the formation of amyloid fibrils. The ionizable cationic lipid nanoparticles of Patisiran are composed of (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-(dimethylamino) butanoate (DLin-MC3-DMA), cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and α-(3′,4′,5′,6′)-methoxy polyethylene (PEG2000-C-DMG). Targeted delivery using ionizable cationic liposomes is important for siRNA therapy because the TTR siRNA needs to enter the hepatocytes to play a role. These lipid nanoparticles (Fig. 4) can achieve liver targeting because the adsorption of apolipoprotein E (ApoE) on the surface after intravenous injection could promote their binding to the lipoprotein receptor on the surface of hepatocytes, and trigger the uptake of hepatocytes through endocytosis. After internalization, the ionized liposomes are positively charged and can interact with negatively charged membranes of endosomes/lysosomes to promote the release of siRNA into the cytoplasm. 56% of Patisiran-treated patients showed improvement in modified Neuropathy Impairment Score in phase III clinical trial (NCT01960348). In 2018, the product was launched in the U.S. for the treatment of hATTR polyneuropathy. However, Patisiran still has the problem of immunogenicity, and steroid pretreatment is required to reduce the immune system response to the 80-min intravenous infusion of the product.

3.5.1.2 Nanomedicines for nervous system diseases and mental diseases under clinical development. NTLA-2001 is the first gene editing therapy based on clustered, regularly interspaced, short palindromic repeats (CRISPR)-associated protein-9 nuclease (Cas9) genome editing system (CRISPR/Cas9) under clinical process for the treatment of adult hATTR patients, developed by Intellia Therapeutics. An essential prerequisite for in vivo gene therapy based on CRISPR/Cas9 is to provide a tailored delivery system that can accurately, efficiently and safely deliver therapeutic substances to target cells to minimize off-target cell binding and off-target genome effects. Lipid nanoparticles (LNPs) with liver tropism are designed to deliver a Cas9 messenger RNA and a chemically modified single guide RNA (sgRNA) targeting mouse transthyretin (TTR) in NTLA-2001. After intravenous infusion, the LNPs are opsonized by plasma ApoE in circulation and undergo active endocytosis by hepatocytes through the low-density lipoprotein receptors expressed on the surface of the cells. NTLA-2001 achieved targeted knockout of TTR in patients with
3.5.2. Blood disorders, endocrine and metabolic diseases

Nanomedicines, which have the capacity of prolonging the blood circulation time and reducing the immunogenicity, are also employed to treat blood disorders, endocrine and metabolic diseases, such as diabetes, non-alcoholic steatohepatitis, gout, hypertriglyceridemia, hyperinsulism, hyperphosphatemia, hyperkalemia, and growth hormone secretion disorders. Among them, nanomedicines of liposomes, polymers, inorganic nanoparticles, polymer protein conjugates and cell-derived carriers are involved (Table S7).

3.5.2.1. Nanomedicines for blood disorders, endocrine and metabolic diseases in the market

Feraheme is superparamagnetic iron oxide coated with a low molecular weight semi-synthetic carbohydrate polyglucose sorbitol carboxymethyl ether, with a hydrodynamic diameter of 30 nm. In 2009, FDA approval of Feraheme was assigned for an intravenous iron replacement therapy in patients who are suffering from anemic chronic kidney disease (CKD). In addition, phase II trials are underway at AMAG Pharmaceuticals for magnetic resonance angiography (MRA), and phase II trials for the imaging of primary high-grade brain tumors are conducted by the National Cancer Institute.

3.5.2.2. Nanomedicines for blood disorders, endocrine and metabolic diseases under clinical development

EE-ADA (OT-81) is a drug candidate for enzyme-replacement therapy and had been in clinical trials at St. George’s University of London (SGUL) for the intravenous treatment of adenosine deaminase deficiency. OT-81 consists of native adenosine deaminase (ADA) from bovine calf intestinal mucosal encapsulated in autologous erythrocytes. The erythrocyte membranes, generally prepared by osmotic methods, have low immunogenicity and can protect exogenous enzymes from rapid clearance as well as prolong the half-life of circulation, which can reduce the frequency of administration. Similarly, BAY-79-4980 is recombinant factor VIII (rFVIII) proteins encapsulated in pegylated liposomes to increase the duration of action. The product candidate is in clinical trials at Bayer for the prevention of coagulation factor VIII deficiency (hemophilia A).

3.5.3. Immunological diseases and inflammation

Immunological diseases are generally caused due to the abnormal functioning of the immune system, which includes asthma, rheumatoid arthritis, psoriasis, allergy, multiple sclerosis (MS), systemic lupus erythematosus, inflammatory bowel disease, Guillain-Barre syndrome, type-1 diabetes mellitus, etc. Currently, liposomes, polymer nanoparticles and PEG-drug conjugates for the treatment of immune diseases have been approved (Table S7), such as Joycul (2021), Relieva (2019), Zilretta (2017), and Paigebin (2016). Nanotechnology is efficient to achieve a slow release pattern and prolong the half-life of the encapsulated drugs, which meets the treatment demands of immune-related diseases.

Typically, Zilretta is a sustained-release intra-articular formulation consisting of triamcinolone acetonide polymerized with PLGA, for the management of osteoarthritis pain of the knee. It was first launched in the U.S. in 2017, developed by Flexion Therapeutics. Although the therapeutic effect of corticosteroids is usually short-lived, triamcinolone acetonide in Zilretta is encapsulated in PLGA polymers which can slowly release the corticosteroid in synovium, allowing the drug to persist in the joint for a
long time. In addition, drug encapsulation reduces systemic exposure and thus lessens corticosteroid-related systemic adverse reactions, for instance, elevated blood glucose\textsuperscript{167}.

3.5.4. Cardiovascular diseases

Nanomedicines that have been employed for therapy and diagnosis of cardiovascular diseases (such as atherosclerosis and ischemia\textsuperscript{15}) are summarized in Table S7. Leqvio is a cholesterol-lowering RNAi therapeutic targeting proprotein convertase subtilisin/kexin type 9 (PCSK9), which comprises an optimized double-stranded small interfering RNA (siRNA) conjugated to triantennary N-acetylgalactosamine carbohydrates (GalNAc). In 2020, the PCSK9 expression inhibitor was approved in the E.U. for the treatment of primary hypercholesterolemia or mixed dyslipidemia\textsuperscript{162}.

MRX-815 is lipid nanobubbles thrombolytic comprising of perfluoropropane gas\textsuperscript{163}. It had been in early clinical development by Cerevast Therapeutics for the treatment of acute limb ischemia, deep vein thrombosis (DVT), thrombosed dialysis grafts and obstructive peripheral vascular disease. External ultrasound is applied to cavitate the injectable nanobubbles, so as to dissolve the clots. Compared to the conventional treatment of thrombosis, the nanobubbles thrombolytic may be less invasive than mechanical thrombectomy, as well as be faster to take effect with lower bleeding risk than traditional drug therapy. In addition, Optison is perfluoropropane-filled albumin microspheres for ultrasound contrast enhancement. The 15 nm thick human serum albumin shells protect the bubble core from destruction, as well as make Optison an effective ultrasound scatterer\textsuperscript{164}.

3.5.5. Ocular diseases

For the treatment of ocular diseases, nanomedicines are able to transport across the ocular barriers, prolong the duration of drug release, increase the residence time of drug molecules in the eye tissue and improve the bioavailability, thus enhancing the therapeutic effect and reducing the administration frequency\textsuperscript{165}. Different types of nanomedicine (Table S7), such as adeno-associated viral (AAV) vectors, liposomes, inorganic nanoparticles, cell-derived derivatives and polymer-drug/protein conjugates, have been developed for the treatment of ocular diseases, such as diabetic macular edema, dry eye, glaucoma, inherited retinal disease (IRD) and age-related macular degeneration\textsuperscript{4}.

OC-188 eye drops consist of dexamethasone gamma-cyclodextrin nanoparticles, which can deliver lipophilic drugs across the ocular surface barriers into the eyes\textsuperscript{166}. Phase II clinical trials are ongoing for the treatment of diabetic macular edema and uveitis.

3.5.6. Skin diseases

Due to their ability of penetrating the skin barrier, selectively acting on the target site, or prolonging drug residence in the skin, nanomedicines have been developed for the treatment of skin diseases such as acne vulgaris, dermatitis and burns (Table S7)\textsuperscript{113}. Sebacia microparticles (Sebashells) are photosensitizing gold-coated silica microparticles, attaining regulatory approval as a topical photothermal treatment for acne vulgaris. With a median particle size of about 150 nm, Sebashells exhibits plasmon resonance with strong absorption at 800 nm and can selectively destroy sebaceous glands, delivered to target sites by mechanical vibration\textsuperscript{167}. Acticoat, a silver nanocrystal-coated polyethylene net for burn treatments, can release silver ions to kill microbes via a variety of mechanism including blocking the cell respiration pathway, interfering with components of the microbial electron transport system, and producing DNA damage\textsuperscript{168}.

In addition to the aforementioned indications, nanomedicines are also developed for nutritional supplement, contraception, smoking cessation, hormone replacement therapy, treatment of osteoporosis, fibrosis-related diseases, overactive bladder, mitochondrial DNA depletion syndrome and other diseases. The carrier types involved include polymers, cell-derived carriers, inorganic nanoparticles, liposomes, etc., and most of which are in clinical evaluations (Table S7).

4. Future perspectives

So far, nanomedicines on the market or in the clinical stage have been developed for a variety of indications, involving cancer, infection, cardiovascular disease, nervous system disease and other diseases. Among them, cancer treatment is the most widely used field of nanomedicines, which is owing to the intriguing features of nanomedicines (e.g., improvement of pharmacokinetic properties, versatility for combination therapy and high spatio-temporal precision) that can overcome the defects of drugs currently used in the clinic and meet the unmet clinical needs. Apart from tumors, the applications of nanomedicines in other indications (e.g., viral and bacterial infections) have been expanded. Specifically, the significance of nanomedicines has been highlighted in fighting against the COVID-19 pandemic, for nanoparticles can be developed to deliver vaccines and present multiple antigens to stimulate immunity against the rapidly mutating viruses. In addition, nanoparticles provide a novel solution to the bacterial resistance caused by the overuse of antibiotics because they can penetrate into bacterial biofilms and effectively enhance the bactericidal performance of existing antibiotics. Besides, nanoparticles are potential to overcome drug resistance by generating lethal damages to bacteria through new mechanisms of action (such as physical or biochemical processes)\textsuperscript{169}. What’s more, nanoparticles make the integration of diagnosis and treatment possible. In all, nanotechnology has brought a new paradigm to disease prevention, treatment and diagnosis.

The action mechanisms of nanomedicines elicit a diversified trend, including chemotherapy, gene therapy, immunotherapy, photothermal therapy, hyperthermia, radiotherapy, combination therapy, integration of diagnosis and treatment, etc. Among them, immunotherapy is a breakthrough for treatments of diseases, especially for anti-tumor therapy, which transfers people’s attention from the traditional tumor targeting to the immune microenvironment\textsuperscript{170}. Nanoparticles provide a new strategy for immunotherapy because of their capacity and controllability of targeted delivery. Nanoparticles can edit the immune system in situ, to activate or inhibit the immune responses, which provide feasible strategies for personalized medical treatment. In terms of immune activation, nanomedicines have great potential in inducing ICD, releasing antigens in situ, activating the immunogenicity, and thus boosting the immune responses\textsuperscript{171–173}. For instance, NC-6300 is micellar nanoparticles loaded with ICD inducer of epirubicin, which has successfully entered the phase I/II clinical trial (NCT03168061) in patients with advanced solid tumors. The combination of NC-6300 and anti-programmed death 1 (PD-1) is able to overcome tumor resistance of immune checkpoint inhibitors and potentiate immune response rate (Fig. 5)\textsuperscript{174}. In addition to boosting the immune system for anti-tumor or anti-infection treatments, nanoparticles can also be used to suppress the immune system to tackle organ transplants rejection and autoimmune diseases, such as type one diabetes and...
multiple sclerosis\textsuperscript{175}. Besides, the application of nanomedicines in gene therapy, such as RNAi and CRISPR/Cas9, is also promising in clinical translations.

The development and commercialization of nanomedicines are facing various problems and challenges. The translation rate of nanomedicines from basic scientific research to clinical application is less than 10\%\textsuperscript{54}. Significantly, upon research and development of nanomedicines, many candidates were failed in clinical trials due to insufficient efficacy. A famous example is BIND-014. BIND-014 is PSMA-targeting polymeric nanoparticles containing docetaxel, originated by BIND Therapeutics. BIND-014 failed in phase II clinical trial for the treatment of cervical and head-and-neck cancers, because it was not more effective than docetaxel\textsuperscript{176}. Many factors can affect the clinical translation and commercialization of nanomedicines, such as the selection of patient groups, the pathological characteristics and heterogeneity of diseases, reproducible manufacturing and scale-up, the availability of appropriate characterization and evaluation methods, the physicochemical properties and \textit{in vivo} interaction process of nanoparticles, clinical therapeutic effects, safety, stability, regulatory standards, etc\textsuperscript{177}. In order to facilitate the clinical translation of nanomedicines, it is necessary to rethink the paradigm of nanoparticle design and development, overcome the biological obstacles in drug delivery, and tackle the technological (such as manufacturing, evaluation and quality control) and regulatory issues (Fig. 6).

4.1. Changing the patterns of nanomedicines design

Currently, the development paradigm of nanomedicines needs to be transformed from traditional formulation-driven research to a simplified, disease-driven, patient-centered and rational pattern. Besides, to accelerate clinical translation, the concept of quality by design (QbD) needs to be adopted.

4.1.1. Simplified design of nanomedicines

The design of nanomedicines should be oriented to solve clinical problems, rather than blindly pursuing the versatility of the system. Nanomedicines can achieve multiple functions by introducing a variety of modifications to the core or surface of nanoparticles. Although versatility is the advantage of nanoparticles compared with traditional small molecule therapy, the excessive pursuit of multiple functionality will affect the large-scale preparation and increase the complexity of clinical translation. Moreover, the component ingredients in the nanomedicines need to be tested, especially unapproved materials. As a result, the design of nanomedicines should be simplified on the premise of meeting the clinical needs\textsuperscript{176}. One of the feasible directions is excipient-free nanomedicines that are composed entirely of clinically approved small molecule drugs, which may make the clinical translation easier\textsuperscript{179}.

4.1.2. Disease-driven and patient-centered design of nanomedicines

The traditional paradigm of nanomedicines development often adopts the formulation-driven method, that is, to develop new nanoparticle formulations, and then evaluate the effectiveness and safety. However, the research paradigm based on material properties often ignores physiological factors, \textit{e.g.}, heterogeneity, which may cause the insufficient effect of many nanomedicines and the failure of clinical translation (\textit{e.g.}, BIND-014)\textsuperscript{180}. For instance, the heterogeneity of the tumors, such as cancer types, phase, tumor size, and leakage and density of tumor vessels, would affect the tumor targeting and intratumoral delivery of therapeutic agents, raising an impressive need for the disease-driven and personalized design of nanomedicines\textsuperscript{176}. Patient stratification can identify and select the patients who are most likely to respond to nanomedicines treatment and promote personalized precision medicine, which is vital to solve the problem of patient and disease heterogeneity and improve the response rate\textsuperscript{17}. A successful example of selecting the right patients who are most likely to respond to nanomedicines is paclitaxel poliglumex. Paclitaxel poliglumex (Opaxio), originally developed by the M.D. Anderson Cancer Center, is a poly
(L-glutamic acid) polymer nanoparticles of paclitaxel for the treatment of NSCLC. The results of clinical trials of Opaxio in NSCLC patients showed that women with premenopausal estradiol levels had a significant survival benefit. Related studies reveal that the therapeutic efficacy of Opaxio depends on cathepsin B-mediated activation, and there is a relationship between estrogen level and cathepsin B activity, so the subsequent clinical studies of Opaxio focused on female patients with estrogen levels above a predetermined threshold. In 2006, Opaxio was successfully assigned fast track designation by the FDA for the treatment of women with first-line advanced NSCLC. The enlightenment of this clinical-oriented strategy in nanomedicine development is to find a suitable patient group, understand the pathological characteristics of the disease, the mechanism of action of nanomedicines and the factors affecting the efficacy. Methods that can determine the biological process
and efficacy of nanoparticles in the human will assist nanomedicines translations, such as the development of nanoparticles integrating diagnosis and therapy\(^\text{185}\), utilization of biomarkers and nanoparticle barcoding\(^\text{182,184}\).

4.1.3. **Quality by design of nanomedicines**

The concept of QbD means that the quality of the final product should be considered at the initial stage of research and development. FDA and International Conference on Harmonization (ICH) highly encourage the adoption of the QbD principle in drug development, manufacturing and regulation\(^\text{185}\). QbD requires to identify critical quality attributes (CQAs) and clarify critical process parameters (CPPs) which are usually the principal objective of process review. Design of experiments (DoEs) and response surface methodology (RSM) are useful tools of the QbD paradigm\(^\text{185}\). Besides, risk assessment is also vital to QbD implementation in the pharmaceutics field\(^\text{186}\). A typical example of QbD in accelerating nanoparticles translation is ACCURINS, a clinically advanced polymeric nanoparticle consisting of poly-lactic acid-polyethylene glycol (PLA-PEG), which illustrates that the risk-based QbD paradigm is feasible to bring nanomedicines to the clinic and commercialization\(^\text{187}\).

4.2. **Overcoming obstacles in targeted delivery**

4.2.1. Clarifying and leveraging delivery mechanism of nanomedicines

Elucidating the delivery mechanism of nanomedicines can guide the design of drug carriers. For example, in anti-tumor therapy, many approved nanomedicines (such as Doxil and Abraxane) utilize the passive targeting mechanism based on the EPR effect, although the EPR effect is still controversial in clinic\(^\text{188}\). Recently, active transcytosis of endothelial cells in cancer has been found to be more effective in delivering nanoparticles into solid tumors\(^\text{189}\). The active transcytosis based nanomedicines have been developed (e.g., charge reversible nanoparticles) and derived a more efficient targeted delivery strategy\(^\text{190}\). In addition, convection-enhanced delivery (CED) has also been developed for drug delivery strategies\(^\text{191}\), and has been clinically proved to be able to bypass the blood-brain barrier and deliver drugs to the target brain region\(^\text{192}\). In a phase III clinical study, liposomes containing HSV-tk gene were delivered through CED and more than 50% tumor size reduction was observed in two of eight glioblastoma patients\(^\text{193}\). With more understanding of nanomedicines targeting and transport, it is believed that more nanoparticles with higher targeting efficiency will be developed and translated into clinical practice.

4.2.2. Overcoming biological obstacles in drug delivery process

Most nanoparticles are administered intravenously and need to undergo multiple processes such as circulation, accumulation, penetration and cell internalization when delivered to the target site, which may become obstacles to drug delivery and eventually lead to insufficient efficacy of nanoparticles\(^\text{19}\).

Many approved synthetic nanomedicines, such as liposomes, polymers and inorganic nanoparticles, are modified with PEG on the surface to reduce the unexpected uptake by the reticuloendothelial system and prolong the circulation time. However, PEGylation has some problems, for example, the loss of efficacy due to the accelerated blood clearance phenomenon\(^\text{194}\). In recent years, some new carriers such as cell-derived nanocarriers (e.g., erythrocyte membranes and exosomes) have entered the clinical stages, and have been evidenced with better pharmacokinetic profiles, lower immunogenicity and higher biocompatibility than synthetic nanoparticles\(^\text{195}\), which is emerging as a hotspot of nanomedicines. Cell-derived nanocarriers have been proposed as an alternative strategy of PEGylation to avoid immune clearance or adverse immune reactions. In spite of their satisfactory delivery performance, much attention should be paid to the heterogeneity of cell-derived nanocarriers, the complexity of components and large-scale manufacturing problems (e.g., the variability of EV cells)\(^\text{196}\). In addition, in anti-tumor therapy, the limited penetration of nanomedicine in tumors is an important contributor to the insufficient efficacy\(^\text{197}\). Strategies of regulating tumor microenvironment, cell-penetrating peptide modification, utilizing transcytosis and overcoming binding site barriers, which provide feasible strategies to promote deep tumor penetration and improve targeting efficiency\(^\text{198}\).

4.2.3. Looking for smart and precise nanomedicines

Although nanomedicines can reach the target site through passive and active targeting mechanisms, the off-target effect is still worthy of concern. Taking anti-tumor therapy as an example, many nanomedicines specifically recognize overexpressed receptors at tumor sites through ligands modified on the surface of nanoparticles. However, these receptors in tumor usually exist in healthy cells, so the “on target but off tumor” effect of nanoparticles will occur, resulting in toxicity\(^\text{199}\). Meanwhile, these targeting ligands may be masked by versatile plasma protein corona upon their entry into the blood circulation, thereby abolishing the targeting effects\(^\text{200}\). Therefore, it is necessary to seek more intelligent and precise nanomedicines. Nanorobots with autonomous addressing capability\(^\text{196}\) and nanoparticles with logic-gated (multibiomarker-based) recognition ability\(^\text{200}\) can accurately distinguish normal cells from pathological cells, and have superior targeting as well as controlled release ability, which presents a potential direction of nanomedicines development in the future.

4.3. **Technological challenges in clinical translation**

4.3.1. Manufacturing

The limitations related to traditional preparation methods, such as high polydispersity\(^\text{201}\) and solvent residue\(^\text{202}\), restrict nanomedicines translation from research to clinical application. Therefore, controllable, reproducible and scale-up preparation technologies are essentially required. Microfluidic technology and particle replication in non-wetting template (PRINT) technology, which have sprung up in recent years, are the frontiers of accurate, controllable and repeatable particle fabrication on a large scale\(^\text{202,203}\). Besides, Coaxial turbulent jet mixer technology has been developed for high-throughput synthesis of polymeric nanoparticles for its advantages of homogeneity, reproducibility and adjustability\(^\text{204}\). For the problem of solvent residue, supercritical fluids technology (SCF) has been used in the manufacture of liposomes because of its friendliness, nontoxic to the environment and the possibility of preparing solvent-free nanoparticles\(^\text{203}\).

4.3.2. Evaluation and quality control

The great differences between patients and animal models are also the main reason for the clinical failure of nanotherapeutics. Results from animal models do not ensure the direct extension to humans\(^\text{205}\). It is worth mentioning that there are various models, including orthotopic xenografts, patient-derived xenografts (PDXs) and genetically engineered mouse models (GEMMs), which can more faithfully reflect the complexity, heterogeneity and anatomical histology of human
tumors. Additionally, organ-on-a-chip can imitate organs and physiological microenvironment of diseases, as well as carry out high-throughput screening and evaluation of nanoparticles. At the same time, the large data set generated by the chip can be combined with artificial intelligence (AI) to establish predictive screening models to assist the rational and data-driven design of nanomedicines. This paradigm holds great potential to reduce the blindness and randomness of conventional nanoparticle design based on empirical and trial-and-error strategies.

To promote the production of nanomedicines, some regulatory agencies have introduced quality control standards and defined the CQAs of nanomedicines. FDA encourages the use of Process Analytical Technology (PAT), an in-situ real-time monitoring technology, to obtain continuous and real-time data in the manufacturing process to ensure product quality.

4.4 Overcoming regulatory challenges of nanomedicines

Nanomedicines are generally approved according to the conventional framework, which is unfavorable to the development of nanomedicines. Currently, FDA has not established regulatory definitions of “nanotechnology”, “nanomaterial”, “nanoscale” or other related terms, which may lead to ambiguity. Therefore, it is essential to improve the regulatory regulations (e.g., clarify the CQAs) and establish widely acceptable international standards.

In addition, under the existing regulatory system, seeking additional indications or new applications of approved nanoparticles is expected to improve the clinical translation of nanomedicines. An example of nanoparticles approved for change of application is Ferumoxytol, a superparamagnetic iron oxide nanoparticle. Ferumoxytol was originally approved as an iron supplement for the treatment of anemia. Later, its potential as an MRI contrast agent was explored and approved for MRI imaging in patients with lymphoma and osteosarcoma.

In summary, nanomedicines have displayed promising potential in improving efficacy, targeted drug delivery and reducing side effects associated with conventional drug counterparts. The development of nanomedicines demonstrates a diversified trend in carrier types, applied indications and mechanisms of action. Some new promising carrier types, such as cell-derived nanocarriers, have entered the clinical stage. In terms of treatment strategies, immunotherapy and gene therapy are hot spots in clinical research and development. However, the failure rate in the research and development of nanomedicines is still high. More understanding of the diseases, personalized design, and biological interactions of nanoparticles in vivo should be explored to facilitate clinical translation of nanomedicines. In addition, factors such as reproducible manufacturing, scale-up, and the perfection of guiding principles are also noteworthy.

Acknowledgements

Financial supports by the National Natural Science Foundation of China (32071385, 31771092, 31930066), Shandong Provincial Natural Science Foundation of China (ZR2019ZD25) and Fudan-SIMM Joint Research Fund (FU-SIMM20182005, China) were acknowledged.

Author contributions

Xiaoting Shan wrote the draft of the manuscript. Xiang Gong and Jie Li collected the data of launched or clinically evaluated nanomedicines. Jingyuan Wen and Yaping Li revised the manuscript. Zhiwen Zhang outlined and revised the manuscript.

Conflicts of interest

All the authors declare no conflict of interest.

Appendix A. Supporting information

Supporting data to this article can be found online at https://doi.org/10.1016/j.apsb.2022.02.025.

References

1. Gadekar V, Borade Y, Kannaujia S, Rajpoot K, Anup N, Tambe V, et al. Nanomedicines accessible in the market for clinical interventions. J Contr Release 2021;330:372–97.
2. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress, challenges and opportunities. Nat Rev Cancer 2017;17:20–37.
3. Zhang C, Yan L, Wang X, Zhu S, Chen C, Gu Z, et al. Progress, challenges, and future of nanomedicine. Nano Today 2020;35:101008.
4. FDA. Considering whether an FDA-regulated product involves the application of nanotechnology. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considering-whether-fda-regulated-product-involves-application-nanotechnology.
5. Wolfram J, Ferrari M. Clinical cancer nanomedicine. Nano Today 2019;25:85–98.
6. Wang Y, Tan X, Fan X, Zhao L, Wang S, He H, et al. Current strategies for oral delivery of BCS IV drug nanocrystals: challenges, solutions and future trends. Expert Opin Drug Deliv 2021;18:1211–28.
7. Patel P, Shah J. Safety and toxicological considerations of nanomedicines: the future directions. Curr Clin Pharmacol 2017;12:73–82.
8. Wang H, Li J, Wang Y, Gong X, Xu X, Wang J, et al. Nanoparticles-mediated reoxygenation strategy relieves tumor hypoxia for enhanced cancer therapy. J Contr Release 2020;319:25–45.
9. Klochkov SG, Neganova ME, Nikolenko VN, Chen K, Somasundaram SG, Kirkland CE, et al. Implications of nanotechnology for the treatment of cancer: recent advances. Semin Cancer Biol 2021;69:190–9.
10. Zhang Z, Wang H, Tan T, Li J, Wang Z, Li Y. Rational design of nanoparticles with deep tumor penetration for effective treatment of tumor metastasis. Adv Funct Mater 2018;28:1801840.
11. Tan T, Wang Y, Jiang W, Zhang Z, Wang H, Cao H, et al. Targeting peptide-decorated biomimetic lipoproteins improve deep penetration and cancer cells accessibility in solid tumor. Acta Pharm Sin B 2020;10:529–45.
12. Yin J, Cao H, Wang H, Sun K, Li Y, Zhang Z. Phospholipid membrane-decorated deep-penetrated nanocatalase relieve tumor hypoxia to enhance chemo-photodynamic therapy. Acta Pharm Sin B 2020;10:2246–57.
13. Cui M, Wiraja C, Chew SWT, Xu C. Nanodelivery systems for topical management of skin disorders. Mol Pharm 2021;18:491–505.
14. Liu CH, Huang S, Britton WR, Chen J. MicroRNAs in vascular eye diseases. Int J Mol Sci 2020;21.
15. Archer K, Broskova Z, Bayoumi AS, Teoh JP, Davila A, Tang Y, et al. Long non-coding RNAs as master regulators in cardiovascular diseases. Int J Mol Sci 2015;16:23651–67.
16. Poon W, Kingston BR, Ouyang B, Ngo W, Chan WCW. A framework for designing delivery systems. Nat Nanotechnol 2020;15:819–29.
17. van der Meel R, Sulheim E, Shi Y, Kiessling F, Mulder WJM, Lammers T. Smart cancer nanomedicine. Nat Nanotechnol 2019;14:1007–17.
18. Kutova OM, Guryev EL, Sokolova EA, Alzeibak R, Balalaeva IV. Targeted delivery to tumors: multidirectional strategies to improve treatment efficiency. Cancers 2019;11:68.

19. Zhou Q, Dong C, Fan W, Jiang H, Xiang J, Qiu N, et al. Tumor extravasation and infiltration as barriers of nanomedicine for high efficacy: the current status and transcytosis strategy. Biomaterials 2020;240:119902.

20. Golombek SK, May JN, Theek B, Appold L, Drude N, Kiessling F, et al. Tumor targeting via EPR: strategies to enhance patient responses. Adv Drug Deliv Rev 2018;130:17–38.

21. Dewhirst MW, Secomb TW. Transport of drugs from blood vessels to tumour tissue. Nat Rev Cancer 2017;17:738–50.

22. Gabizon AA, de Rosales RTM, La Beck NM. Translational considerations in nanomedicine: the oncology perspective. Adv Drug Deliv Rev 2020;158:140–57.

23. Maja L, Željko K, Mateja P. Sustainable technologies for liposome preparation. J Supercrit Fluids 2020;165:104984.

24. Shah S, Dhanaw V, Holm R, Nagarsenker MS, Perrie Y. Liposomes: advancements and innovation in the manufacturing process. Adv Drug Deliv Rev 2020;102–22. 154–155.

25. Barenholz Y. Doxil® - the first FDA-approved nano-drug: lessons learned. J Contr Release 2012;160:117–34.

26. Slingerland M, Guchelaar HJ, Rosing H, Scheulen ME, van Warmerdam LJ, Beijnen JH, et al. Bioequivalence of liposome-entrapped paclitaxel easy-to-use (LEP-ETU) formulation and paclitaxel in polyethylene-oxethyloxytocastor oil: a randomized, two-period crossover study in patients with advanced cancer. Clin Therapeut 2013;35:1946–54.

27. Boulikas T. Clinical overview on Lipoplatin (TM): a successful liposomal formulation of cisplatin. Expert Opin Invest Drugs 2009;18:1197–218.

28. Hewitt SL, Bailey D, Zielinski J, Apte A, Musenge F, Karp R, et al. Intratumoral IL12 mRNA therapy promotes TH1 transformation of the tumor microenvironment. Clin Cancer Res 2020;26:6284–98.

29. Yahyanejad S, Gunst Td, Schultz I, Boer Hd, Raimo M, Telford B, et al. Pharmacologic profile of INT-183: a novel synthetic microRNA 193a-3p mimic for therapeutic intervention in oncology. Cancer Res 2018;78:4405.

30. Ebrahim AS, Kandouz M, Liddane A, Sabbagh H, Hou Y, Li C, et al. PNT2258, a novel deoxyribonucleic acid inhibitor, induces cell cycle arrest and apoptosis via a distinct mechanism of action: a new class of drug for non-Hodgkin’s lymphoma. Oncotarget 2016;7:42374–84.

31. Schulteis B, Strumberg D, Kuhlmann J, Wolf M, Link K, Seufferlein T, et al. Safety, efficacy and pharmacokinetics of targeted therapy with the liposomal RNA interference therapeutic Atu027 combined with gemcitabine in patients with pancreatic adenocarcinoma. A randomized phase Ib/Ia study. Cancer 2020;120.

32. Rao DD, Jay C, Wang Z, Luo X, Kamar P, Eysenbach H, et al. Preclinical justification of phi-shRNA EWS/FLI1 Lipoplex (LPX) treatment for ewing’s sarcoma. Mol Ther 2016;24:1412–22.

33. Merino M, Zalba S, Garrido MJ. Immunoliposomes in clinical oncology: state of the art and future perspectives. J Contr Release 2018;275:162–76.

34. University Hospital B. Anti-EGFR immunoliposomes in solid tumors, Switzerland. 2007. Available from: https://ClinicalTrials.gov/show/NCT01702129.

35. Zhang Z, Zhang Y, Song S, Yin L, Sun D, Gu J. Recent advances in the biosynthetic methods of polyethylene glycols and PEGylated pharmaceuticals. J Separ Sci 2020;43:1976–97.

36. Bender C, Maes L, Carter Febres M, Verma A. Clinical utility of pegaspargase in children, adolescents and young adult patients with acute lymphoblastic leukemia: a review. Blood Lymphat Cancer 2021;11:25–40.

37. Radadiya A, Zhu W, Coricello A, Alcaro S, Richards NGJ. Improving the treatment of acute lymphoblastic leukemia. Biochemistry 2020;59:3193–200.

38. Chandler PG, Tan LL, Porebski BT, Green JS, Riley BT, Broendum SS, et al. Mutational and biophysical robustness in a prestabilized monobody. J Biol Chem 2021;296:100447.

39. Herrington Symes AP, Farys M, Khalili H, Broccini S. Antibody fragments: prolonging circulation half-life special issue-antibody research. Adv BioSci Biotechnol 2013;4:689–98.

40. Squibb BM. Ph II trial of a novel anti-angiogenic agent in combination with chemotherapy for the second-line treatment of metastatic colorectal cancer. 2009. Available from: https://ClinicalTrials.gov/show/NCT00851045.

41. Squibb BM. Ph II of a novel anti-angiogenic agent in combination with chemotherapy for the treatment of non-small cell lung cancer. 2009. Available from: https://ClinicalTrials.gov/show/NCT00850577.

42. Adnexus ABMSR, Company D. CT-322 in treating patients with recurrent glioblastoma multiforme and combination therapy with irinotecan. 2007. Available from: https://ClinicalTrials.gov/show/NCT00562419.

43. Zhao H, Rubio B, Sapra P, Wu DC, Reddy P, Sai P, et al. Novel prodrugs of SN38 using multiammon poly(ethylene glycol) linkers. Bioconjugate Chem 2008;19:494–59.

44. Amiri Kordestani L, Men A, Lindenberg ML, Kurzdziel K, Choyke P, Patronas N, et al. 18F-FLT-PET/CT for the prediction of response to ANG-1005 therapy in patients with breast metastases from breast cancer. Cancer Res 2013;73:40109.

45. Mehanna MM, Mohyeldin SM, Eldjindy NA. Respirable nanocarriers as a promising strategy for antitubercular drug delivery. J Contr Release 2014;187:183–97.

46. Cabral H, Miyata K, Osada K, Kataoka K. Block copolymer micelles in nanomedicine applications. Chem Rev 2018;118:6844–92.

47. Mignani S, Rodrigues J, Tomas H, Zablocka M, Shi X, Caminade AM, et al. Dendrimers in combination with natural products and analogues as anti-cancer agents. Chem Soc Rev 2018;47:514–32.

48. Zuckerman JE, Gräti L, Tolcher A, Heidel JD, Lim D, Morgan R, et al. Correlating animal and human phase Ia/Ib clinical data with CALAA-01, a targeted, polymer-based nanoparticle containing siRNA. Proc Natl Acad Sci U S A 2014;111:11449–54.

49. Davis ME. The first targeted delivery of siRNA in humans via a self-assembly, cycloexetrin polymer-based nanoparticle: from concept to clinic. Mol Pharm 2009;6:659–68.

50. Hoogenboezem EN, Duvall CL. Harnessing albumin as a carrier for cancer therapies. Adv Drug Deliv Rev 2018;130:73–89.

51. Lee ES, Youn YS. Albumin-based potential drugs: focus on half-life extension and nanoparticle preparation. J Pharm Investig 2016;46:305–15.

52. Lamichhane S, Lee S. Albumin nanoscience: homing nanotechnology enabling targeted drug delivery and therapy. Arch Pharm Res (Seoul) 2020;43:118–33.

53. Elzogby AO, Samy WM, Eldjindy NA. Albumin-based nanoparticles as potential controlled release drug delivery systems. J Contr Release 2012;157:168–82.

54. Farjadian F, Ghusemi A, Gohari O, Roorian A, Karimi M, Hamblin MR. Nanopharmaceuticals and nanomedicines currently on the market: challenges and opportunities. Nanomedicine 2019;14:93–126.

55. Nevala WK, Butterfield JT, Sutor SL, Knauer DJ, Markovic SN. Antibody-targeted paclitaxel loaded nanoparticles for the treatment of CD20(+) B-cell lymphoma. Sci Rep 2017;7:45682.

56. Cariginan D, Herblot S, Laliberti Gagne ME, Bolduc M, Duval M, Savard P, et al. Activation of innate immunity in primary human cells using a plant virus derived nanoparticle TLR7/8 agonist. Nano medicine 2018;14:2137–27.

57. Wang LL, Jones ME, Kumbhkokar N, Kapate N, Clegg JR, Prakash S, et al. Cell therapies in the clinic. Bioeng Transl Med 2021;6:e01214.

58. Zhao L, Cao YJ. Engineered T cell therapy for cancer in the clinic. Front Immunol 2019;10:2250.

59. Yu W, Hurley J, Roberts D, Chakraborty SK, Enderle D, Noerholm M, et al. Exosome-based liquid biopsies in cancer: opportunities and challenges. Ann Oncol 2021;32:466–77.

60. Kita Y, Kasaiwata T, Sueyoshi T, Kobiyaomi K, Ishii KJ, Zou J, et al. DNA-containing exosomes derived from cancer cells treated with topotecan activate a STING-dependent pathway and reinforce anti-tumor immunity. J Immunol 2017;198:1649–59.
61. Cully M. Exosome-based candidates move into the clinic. Nat Rev Drug Discov 2021;20:6–7.
62. Herrmann IK, Wood MJ, Fuhrmann G. Extracellular vesicles as a next-generation drug delivery platform. Nat Nanotechnol 2021;16: 748–59.
63. Elsharkasy OM, Nordin JZ, Hagey DW, de Jong OG, Schiffelers RM, Andaloussi SEL, et al. Extracellular vesicles as drug delivery systems: why and how? Adv Drug Deliv Rev 2020;159:332–43.
64. Jang SC, Economides KD, Moniz RJ, Sia CL, Lewis N, McCoy C, et al. ExoSTING, an extracellular vesicle loaded with STING agonists, promotes tumor immune surveillance. Commun Biol 2021;4:497.
65. Center MDAC. iExosomes in treating participants with metastatic pancreatic cancer with KrasG12D mutation. 2021. Available from: https://ClinicalTrials.gov/show/NCT03608631.
66. BioSciences C. A first-in-human study of CDK-002 (exoSTING) in subjects with advanced/metastatic, recurrent, injectable solid tumors. 2020. Available from: https://ClinicalTrials.gov/show/NCT04592484.
67. Solomon BJ, Desai J, Rosenthal M, McArthur GA, Pattison ST, Pattison SL, et al. A first-time-in-human phase I clinical trial of bispecific antibody-targeted, paclitaxel-packaged bacterial minicells. PLoS One 2015;10:e0144559.
68. Yu S, Li A, Liu Q, Yuan X, Xu H, Jiao D, et al. Recent advances of bispecific antibodies in solid tumors. J Hematol Oncol 2017;10:155.
69. Morse MA, Chawla SP, Wong TZ, Bruckner HW, Hall FL, Gordon EM. Tumor protein p53 mutation in archived tumor samples from a 12-year survivor of stage 4 pancreatic ductal adenocarcinoma may predict long-term survival with DeltaRex-G: a case report and literature review. Mol Clin Oncol 2021;15:186.
70. Zhang WW, Li L, Li D, Liu J, Li X, Li W, et al. The first approved gene vector-producer cells followed by intravenous ganciclovir administration: a phase I/II multi-institutional trial. Adv Mater 2019;31:3926.
71. Hermann JM, Wild AT, Wang H, Tran PT, Chang KJ, Taylor GE, et al. Randomized phase III multi-institutional study of TNFαeroid biologic with fluorouracil and radiotherapy for locally advanced pancreatic cancer: final results. J Clin Oncol 2013;31:886–94.
72. Pease DF, Kratzke RA. Oncolytic viral therapy for mesothelioma. Front Oncol 2017;7:179.
73. Kulkarni GS. Nadofaragene firadenovec: a new gold standard for BCG-unresponsive bladder cancer? Lancet Oncol 2021;22:8–9.
74. Lee JC, Shin DW, Park H, Kim J, Youn Y, Kim JH, et al. Tolerability and safety of EUS-injected adenovirus-mediated double-suicide gene therapy with chemotherapy in locally advanced pancreatic cancer: a phase 1 trial. Gastrointest Endosc 2020;92:1044–52.
75. Prados MD, McCormott M, McDermott M, Chang SM, Wilson CB, Fick J, Culver KW, et al. Treatment of progressive or recurrent gliblastoma multiforme in adults with herpes simplex virus thymidine kinase gene vector-producer cells followed by intravenous ganciclovir administration: a phase I/II multi-institutional trial. J Neuro Oncol 2003;65:269–78.
76. Al Shihabi A, Chawla SP, Hall FL, Gordon EM. Exploiting onco-genic drivers along the CCNG1 pathway for cancer therapy and gene therapy. Mol Ther Oncolytics 2018;11:122–6.
77. Soheli E, Michel G, Brigham DA, Larkin Gordon E. FDA emergency use authorization of DeltaRex G for severe COVID-19. Mol Ther 2021;29:354–5.
78. Liu C, Luo L, Zeng L, Xing J, Xia Y, Sun S, et al. Porous gold nanoshells on functional NH2-MOFs: facile synthesis and designable platforms for cancer multiple therapy. Small 2018;14:1801851.
79. Zhang K, Loong SL, Connor S, Yu SW, Tan SY, Ng RT, et al. Complete tumor response following intratumoral 32P BioSilicon on human hepatocellular and pancreatic carcinoma xenografts in nude mice. Clin Cancer Res 2005;11:7532.
80. Bonvalot S, Rutkowski PL, Thariat J, Carrere S, Ducassou A, Sunych MP, et al. NBTXR3, a first-in-class radioenhancer hafnium oxide nanoparticle, plus radiotherapy versus radiotherapy alone in patients with locally advanced soft-tissue sarcoma (Act.In.Sarc): a multicentre, phase 2–3, randomised, controlled trial. Lancet Oncol 2019;20:1148–59.
81. Anselmo AC, Mitragoti S. Nanoparticles in the clinic: an update. Biosens Transl Med 2019;4:e10143.
82. CDE. Available from: https://www.cde.org.cn/zydyzdomesticifopage?zdyzIdCODE=3e60526d467585dc77d354545f04bae5c.
83. Chau CH, Steeg PS, Figg WD. Antibody–drug conjugates for cancer. Lancet 2019;394:793–804.
84. Yu B, Liu D. Antibody–drug conjugates in clinical trials for lymphoid malignancies and multiple myeloma. J Hematol Oncol 2019;12:94.
85. Kommuneni N, Pandi P, Chella N, Domb AJ, Khan W. Antibody drug conjugates: development, characterization, and regulatory considerations. Polym Adv Technol 2020;31:1177–93.
86. Hamilton GS. Antibody–drug conjugates for cancer therapy: the technological and regulatory challenges of developing drug-biologic hybrids. Biologicals 2015;43:318–32.
87. Baush S, Laws M, Rahman KM. Antibody-drug conjugates—a tutorial review. Molecules 2021;26:2943.
88. Lee A. Loncastuximab tesirine: first approval. Drugs 2021;81:1229–33.
89. Johnson ML, El-Khoueiry AB, Hafez N, Lakhani NJ, Mamdani H, Ahnert JR, et al. CX-209, a PROBDY drug conjugate targeting CD71 (transferrin receptor): results from a first-in-human study (PROCLAIM-CX-209) in patients (Pts) with advanced cancer. J Clin Oncol 2020;38.
90. Johnson M, El-Khoueiry A, Hafez N, Lakhani NJ, Mamdani H, Rodon J, et al. Phase I, first-in-human study of the probody therapeutics CX-209 in adults with advanced solid tumor malignancies. Ctin Cancer Res 2021;27:4521–30.
91. Larson SM, Carrasquillo JA, Cheung NK, Press OW. Radioimmunotherapy of human tumours. Nat Rev Cancer 2015;15:347–60.
92. Pelekoe MO, Muslimov AR, Zyuzin MV, Timin AS, Dementyeva OV, Chetverikov SV, et al. Novel nano-sized MR contrast agent mediates strong magnetic response on radionuclide delivery systems: from design consideration to translation into clinics. J Nanobiotechnol 2019;17.
93. Berland L, Kim L, Abousaway O, Mines A, Mishra S, Clark L, et al. Nanobodies for medical imaging: about ready for prime time? Bio- molecules 2021;11:637.
94. Lamb HM, Faulds D. Capromab pendetide. Drugs Aging 1998;12:293–304.
95. Hagemann UB, LeJeune P, Karlsson J, Schatz CA, Cuthbertson AS, Hennikes H, et al. MSLN-TTC (BAY 2287411) induces immunogenic cell death and secretion of pro-inflammatory cytokines in vitro and triggers an immune memory effect against a mouse tumor model. Front Immunol 2019;10:117.
96. Wang C, Fan W, Zhang Z, Wen Y, Xiong L, Chen X. Advanced nanotechnology leading the way to multimodal imaging-guided precision surgical therapy. Adv Mater 2019;31:1904329.
97. Smits MLI, Dassen MG, Prince JF, Braat AJAT, Beijst C, Smits MLI, et al. Novel experience in hybrid tracers: clinical evaluation of a first-in-human study of ICG-Tc-99m nanotop for sentinel node?zdyzIdCODE=3e60526d467585dc77d354545f04bae5c.
98. Voskuil FJ, Steinkamp PJ, Zhao T, van der Vegt B, Koller M, Doff JJ, et al. Feasibility and efficacy in using ICG-Tc-99m nanotop for sentinel node imaging of breast cancer patients with locally advanced soft tissue sarcoma. Clin Nucl Med 2019;44:798–806.
99. Sokol M, Vagnozzi R, Cappelletti S, Georgescu OJ, Jochumsen C, et al. Exosomes: a potential cancer biomarker? Nat Rev Cancer 2013;13:680–91.
100. Manca G, Garau LM, Mazzarri S, Mazzuca L, Muccioli S, Ghilli M, et al. Novel experience in hybrid tracers: clinical evaluation of an oncogene-driven breast cancer model. PLoS One 2014;9:e107762.
Hnik P, Wasan EK, Wasan KM. Safety, tolerability, and pharmacokinetics of a novel oral amphotericin B formulation (iCo-019) following single-dose administration to healthy human subjects: an alternative approach to parenteral amphotericin B administration. Antimicrob Agents Chemother 2020; 64.

Elhissi A. Liposomes for pulmonary drug delivery: the role of formulation and inhalation device design. Curr Pharmaceut Des 2017;23:362–72.

Chung JY, Thone MN, Kwon YJ. COVID-19 vaccines: the status and perspectives in delivery points of view. Adv Drug Deliv Rev 2021; 170:1–25.

Sharma A, Kottodimas KS, Bosmann M. Nanomedicine: a diagnostic and therapeutic approach to COVID-19. Front Med 2021;8:648005.

Walls AC, Fiala B, Schafer A, Wrenn S, Pham MN, Murphy M, et al. Elicitation of potent neutralizing antibody responses by designed protein nanoparticle vaccines for SARS-CoV-2. Cell 2020;183:4367–82.

Arunachalam PS, Walls AC, Golden N, Atyeo C, Fischinger S, Li C, et al. Adjuvancing a subunit COVID-19 vaccine to induce protective immunity. Nature 2021;594:253–8.

Wu K, Choi A, Koch M, Elbashir S, Ma L, Lee D, et al. Variant SARS-CoV-2 mRNA vaccines confer broad neutralization as primary or booster series in mice. Vaccine 2021;39:7394–400.

Mertes PM, Collange O, Colliat P, Banerjee M, Diringer MC, et al. Liposomes containing monophosphoryl lipid A and QS-21 serve as an effective adjuvant for soluble circumsporozoite protein malaria vaccine FMP013. Vaccine 2017;35:3865–74.

Adams D, Polydektis M, Gonzalez Duarte A, Wixner J, Kristen AV, Schmidt HH, et al. Liposomal encapsulation of trans-crocin enhances oxygenation in patients with COVID-19-related ARDS receiving mechanical ventilation. J Contr Release 2021;336:252–61.

Genito CJ, Beck Z, Phares TW, Kalle F, Limbach KJ, Stefaniak ME, et al. Elicitation of potent neutralizing antibody responses by designed protein nanoparticle vaccines for SARS-CoV-2. Cell 2020;183:4367–82.

Garber K. Alnylam launches era of RNAi drugs. Nat Biotechnol 2018;36:777–8.

Rudra A, Ji J, Shukar R, Bhagchandani S, Langer R. Trends in therapeutic conjugates: bench to clinic. Bioconjugate Chem 2020;31:462–73.

Akcine A, Maier MA, Manoharan M, Fitzgerald K, Jayaraman G, Barros S, et al. The Onpattro story and the clinical translation of nanomedicines containing nucleic acid-based drugs. Nat Nanotechnol 2019;14:1084–7.

Thi TTH. Suys EJA, Lee JS, Nguyen DH, Park KD, Truong NP. Lipid-based nanoparticles in the clinic and clinical trials: from cancer nanomedicine to COVID-19 vaccines. Vaccines 2021;9:359.

Adams D, Gonzalez Duarte A, O’Riordan WD, Yang CC, Ueda M, Mertes PM, et al. Liposomes containing monophosphoryl lipid A and QS-21 serve as an effective adjuvant for soluble circumsporozoite protein malaria vaccine FMP013. Vaccine 2017;35:3865–74.

Hashmi DL, Haith L. The current state of topically burn treatments: a review. Curr Trauma Rep 2019;5:160–8.

Gao W, Zhang L. Nanomedicines in the market and clinical stage. Trends in nanomedicines containing nucleic acid-based drugs. Nat Nanotechnol 2019;14:1084–7.

Soñatas AM, Combes F, Koschmieder S, Storm G, Lammers T. A paradigm shift in cancer nanomedicine: from traditional tumor targeting to leveraging the immune system. Drug Discov Today 2021;26:1482–9.

Zhang W, Wang F, Yu C, Zhou Y, Gao H, Hu J. The progress and perspective of nanoparticle-enabled tumor metastasis treatment. Acta Pharm Sin B 2020;10:2037–53.

Wang Z, Gong X, Ji L, Wang H, Xu X, Li Y, et al. Oxygen-delivering polyfluorocarbon nanovehicles improve tumor oxygenation and potentiate photodynamic-mediated antitumor immunity. ACS Nano 2021;15:5405–19.

Li J, Wang H, Wang Y, Gong X, Xu X, Sha X, et al. Tumor-activated size-enlargable biocompatible lipoproteins access cancer cells in tumor to elicit anti-tumor immune responses. Adv Mater 2020;32:e2002380.

Kinho H, Quader S, Shibasaki H, Liu X, Maita Y, Yamashita T, et al. Translational nanomedicine boosts anti-PD1 therapy to eradicate orthotopic PTEN-negative glioblastoma. ACS Nano 2020;14:10127–40.

Cifuentes-Rius A, Desai A, Yuan D, Johnston AP, Voelcker NH. Inducing immune tolerance with dendritic cell-targeting nanomedicines. Nat Nanotechnol 2021;16:37–46.

Ledford H. Bankruptcy filing worries developers of nanoparticle cancer drugs. Nature 2016;533:304–5.

Agrahari V, Agrahari V. Facilitating the translation of nanomedicines to a clinical product: challenges and opportunities. Drug Discov Today 2018;23:974–91.

Guidolín K, Zheng G. Nanomedicines lost in translation. ACS Nano 2019;13:11362–6.

Feng B, Niu Z, Hou B, Zhou L, Li Y, Yu H. Enhancing triple negative breast cancer immuno therapy by ICG-templated self-assembly of paclitaxel nanoparticles. Adv Funct Mater 2020;30:1906605.

Hare JJ, Lammers T, Ashford MB, Puri S, Storm G, Barry ST. Challenges and strategies in anti-cancer nanomedicine development: an industry perspective. Adv Drug Deliv Rev 2017;108:25–38.

Langer CJ, O’Byrne KJ, Socinski MA, Mikhailov SM, Lesniewski Knuk K, Smakal M, et al. Phase III trial comparing paclitaxel poliglumex (CT-2103, PXP) in combination with carboplatin versus standard paclitaxel and carboplatin in the treatment of PS 2 patients.
with chemotherapy-naive advanced non-small cell lung cancer. *J Thorac Oncol* 2008;3:623–30.

182. Manzari MT, Shamay Y, Kiguchi H, Rosen N, Scallan M, Heller DA. Targeted drug delivery strategies for precision medicines. *Nat Rev Mater* 2021;6:351–70.

183. de Lazaro I, Mooney DJ. Obstacles and opportunities in a forward vision for cancer nanomedicine. *Nat Mater* 2021;20:1469–79.

184. Adir O, Polev M, Chen G, Froim S, Krinsky N, Shklover J, et al. Integrating artificial intelligence and nanotechnology for precision cancer medicine. *Adv Mater* 2020;32:e1901989.

185. Mishra V, Thakur S, Patil A, Shukla A. Quality by design (QbD) approaches in current pharmaceutical set-up. *Exper Opin Drug Deliv* 2018;15:737–58.

186. Zhang L, Mao S. Application of quality by design in the current drug development. *Asian J Pharm Sci* 2017;12:1–8.

187. Troiano G, Nolan J, Parsons D, Van Geen Hoven C, Zale S. A quality by design approach to developing and manufacturing polymeric nanoparticle drug products. *AAPS J* 2016;18:1354–65.

188. Luan X, Yuan H, Song Y, Hu H, Wen B, He M, et al. Reappraisal of anti-cancer nanomedicine design criteria in three types of preclinical cancer models for better clinical translation. *Biomaterials* 2021;275:120910.

189. Pandit S, Dutta D, Nie S. Active transcytosis and new opportunities for cancer nanomedicine. *Nat Mater* 2020;19:478–80.

190. Zhou Q, Shao S, Wang J, Xu C, Xiang J, Piao Y, et al. Enzyme-activatable polymer–drug conjugate augments tumour penetration and treatment efficacy. *Nat Nanotechnol* 2019;14:799–809.

191. Jahangiri A, Chin AT, Flanigan PM, Chen R, Bankiewicz K, Aghi MK. Convection-enhanced delivery in glioblastoma: a review of preclinical and clinical studies. *J Neurosurg* 2017;126:191–200.

192. Wang Y, Jiang Y, Wei D, Singh P, Yu Y, Lee T, et al. Nanoparticle-mediated convection-enhanced delivery of a DNA intercalator to gliomas circumvents temozolomide resistance. *Nat Biomed Eng* 2021;5:1048–58.

193. Voge J, Reszka R, Gossmann A, Dittmar C, Richter R, Garlip G, et al. Imaging-guided convection-enhanced delivery and gene therapy of glioblastoma. *Ann Neurol* 2003;54:479–87.

194. Kozma GT, Shimizu T, Ishida T, Szebeni J. Anti-PEG antibodies: properties, formation, testing and role in adverse immune reactions to PEGylated nano-biopharmaceuticals. *Adv Drug Deliv Rev* 2020;154:163–75.

195. Witwer KW, Wolfram J. Extracellular vesicles versus synthetic nanoparticles for drug delivery. *Nat Rev Mater* 2021;6:103–6.