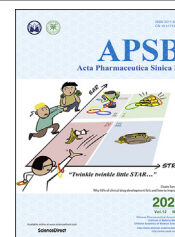




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REVIEW

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



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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.

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1. Introduction

Nanomedicines refer to the nanotechnology-based drug products for the treatment, diagnosis or prevention of various diseases^{1–3}. 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)⁴. Nanomedicines are usually formed by the combination of appropriate nanocarriers and active pharmaceutical ingredients (API)⁵. 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^{1,6}. 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^{7,8}. 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^{3,9–12}.

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 (Fig. 1)^{13–15}. 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](https://pubmed.ncbi.nlm.nih.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, inflammation, cardiovascular diseases, ocular diseases, skin

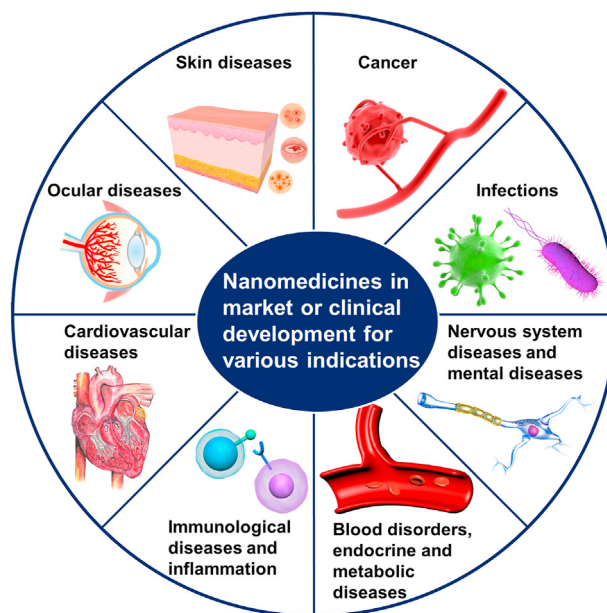


Figure 1 Nanomedicines in the market and various stages of clinical translations for many types of diseases. The skin diagram was reprinted with permission from Ref. 13. Copyright © 2021 American Chemical Society. The eye structure was reprinted under terms of the CC-BY license with the permission from Ref. 14. Copyright © 2020 MDPI, Basel, Switzerland. The cardiovascular graphic was reproduced under terms of the CC-BY license with the permission from Ref. 15. Copyright © 2015 MDPI, Basel, Switzerland.

diseases and other indications (Fig. 2B). In addition, nanomedicines are used in vaccine development and imaging diagnosis. 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^{2,16,17}. 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^{9,18–21}. 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 microenvironments²².

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

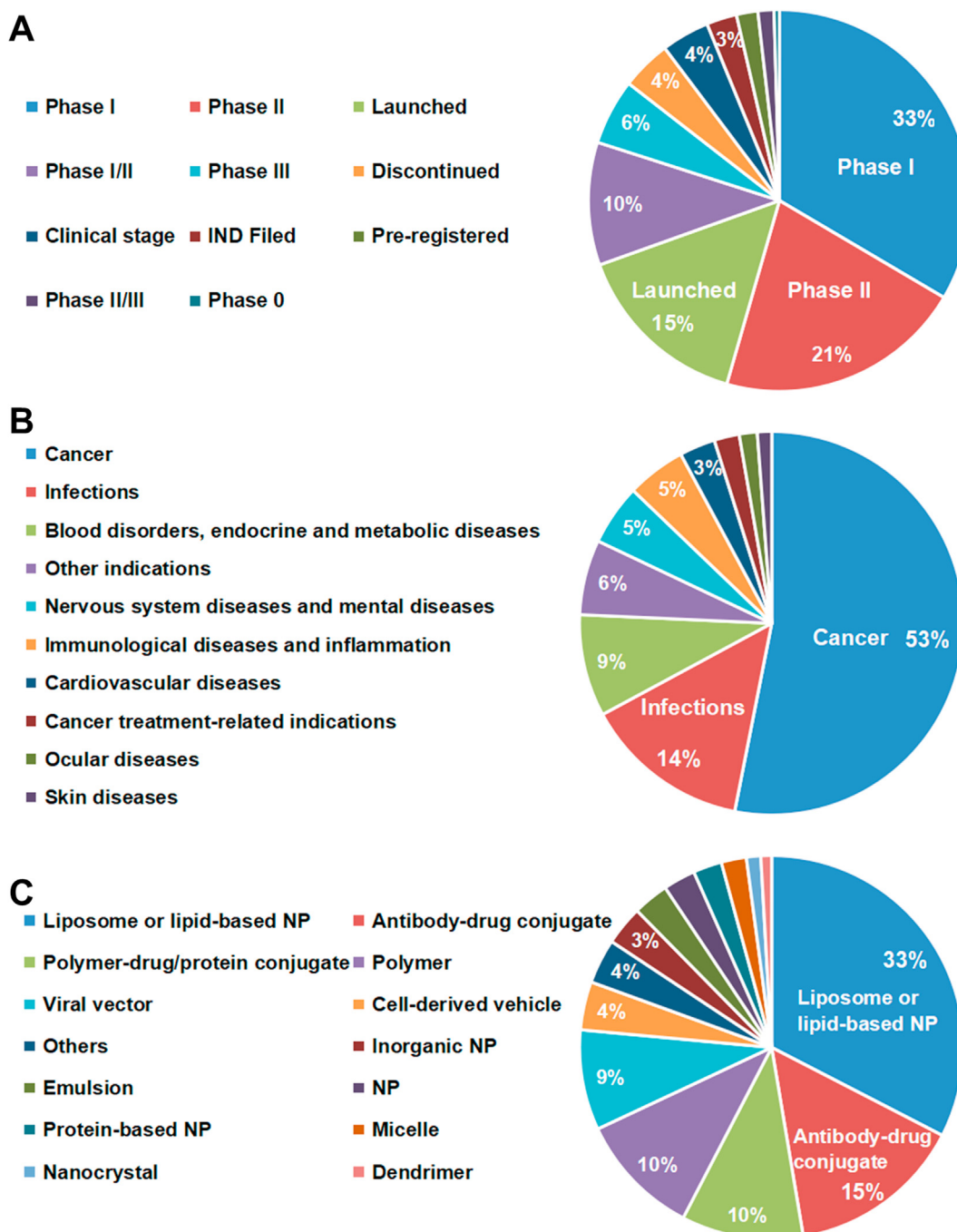


Figure 2 Overview of nanomedicines accessible in the market or in clinical translation. (A) Development status, (B) indications and, (C) formulations. NP, nanoparticle.

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.²³. Liposomes have unique advantages as drug delivery carriers because phospholipids are biodegradable, biocompatible, and similar to lipids present in cell membranes²⁴. 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

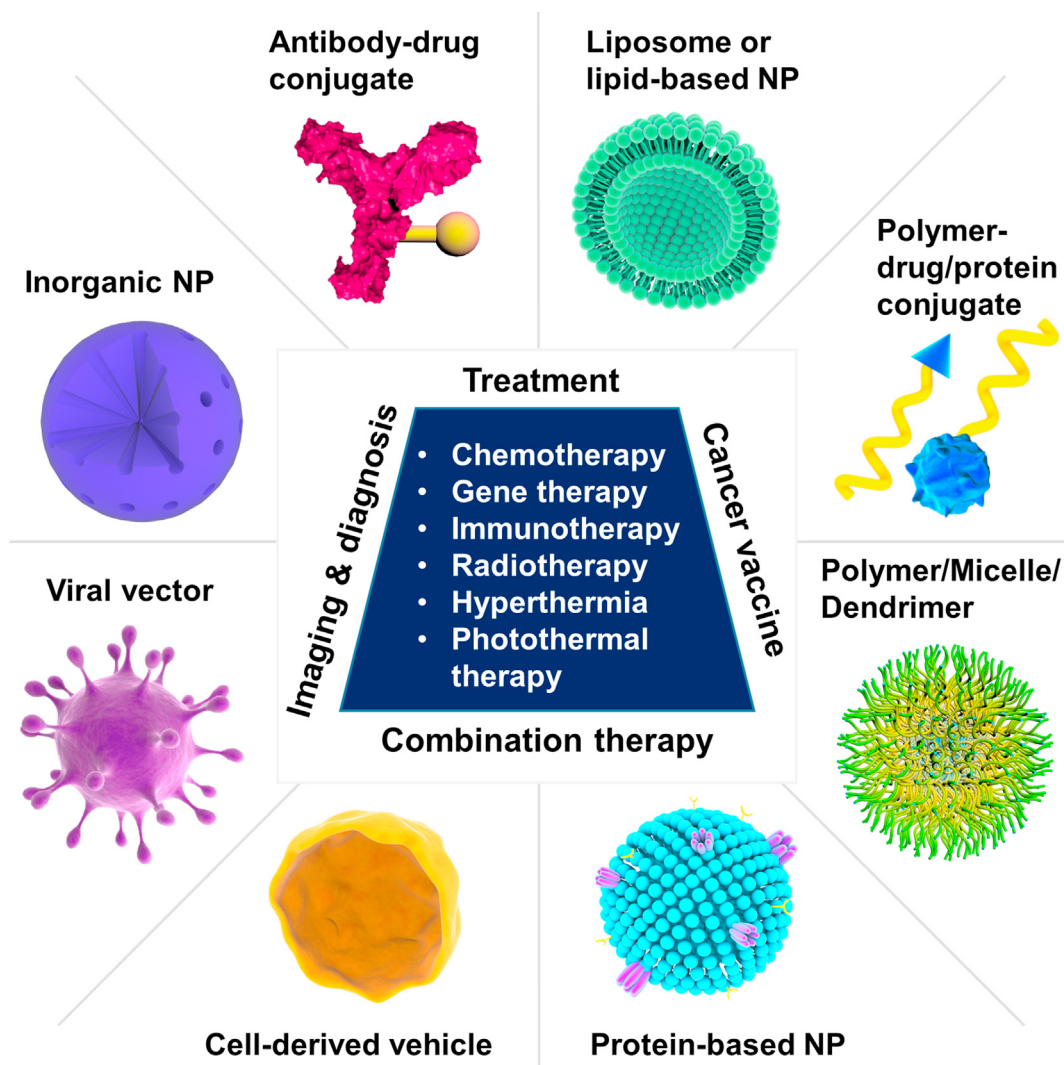


Figure 3 Types and applications of anticancer nanomedicines on the market and under clinical trials.

chemotherapeutic drugs (such as doxorubicin²⁵, paclitaxel²⁶ and cisplatin²⁷) or nucleic drugs (*e.g.*, mRNA²⁸, miRNA²⁹, DNA oligonucleotide³⁰, siRNA³¹ and shRNA³²).

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 circulation²⁵. In addition, the quality evaluations of Doxil by FDA have been published and interpreted in detail in the literature²⁵.

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 doxorubicin³³. 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 deiminase 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 distribution³⁵.

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 multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia³⁶. L-Asparaginase can catalyze the hydrolysis of L-asparagine to L-aspartate and ammonia, thus preventing the proliferation of tumors. PEGylation makes

L-asparaginase lower immunogenicity, higher catalytic activity and longer half-life³⁷.

3.1.2.2. Polymer-drug/protein conjugates under clinical development. Pegdinetanib (CT-322) is a PEGylated 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 derivative³⁹. Pegdinetanib 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 multiforme^{40–42}. Apart from the PEGylation of enzyme/protein, small molecule drugs can also be PEGylated to improve pharmacokinetic properties. For instance, PEG-SN38 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 polylactide, 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)¹. 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 cyclodextrin-based polymer, transferrin protein (Tf) targeting ligands, and PEG⁴⁹. The cyclodextrin-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. The CAR T cells products can be further reviewed in the articles^{57,58}.

Exosomes are vesicles released by cells, including cancer cells, which contain cell-derived substances such as DNA, RNA, protein, lipid, sugar structure and metabolites⁵⁹. 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 pathway⁶⁰. Exosomes are usually produced from mammalian cell cultures in bioreactors. The PureTech company extracted exosomes by ultracentrifugation⁶¹. The International Society for Extracellular Vesicles (ISEV) has initiated the standards for EV isolation and characterization to promote the systematic investigation of efficacy and safety⁶².

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^{62,63}. Exosomes products in the clinical stage include exoSTING⁶⁴, exoIL-12⁶¹ and iExosomes⁶⁵. 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 response⁶⁴. exoSTING is being developed by Codiak Biosciences (founded in 2015) for the intratumoral treatment of advanced solid tumors. A phase I/II clinical trial (NCT04592484⁶⁶) 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, EEDVsMit and EGFRminicellsPac, which are developed based on EnGeneIC's delivery vehicle (EDV) nanocells technology. EGFRminicellsPac is a *Salmonella typhimurium*-derived EDV nanocells packaged with chemotherapeutic paclitaxel and a bispecific antibody derived from cetuximab targeting both EGFR and o-polysaccharides⁶⁷. They are shown to be safe in patients with advanced solid tumors in phase I clinical trial⁶⁸.

3.1.6. Viral vectors

Viral vectors (Table S2) can be used for gene therapy, encoding anti-tumor proteins, such as cytotoxic dominant-negative cyclin G1⁶⁹, wild-type P53⁷⁰, human tumor necrosis factor- α (TNF- α)⁷¹, GM-CSF⁷², IL-2 and human interferon α -2b⁷³, or encoding enzymes that can activate prodrugs to improve the anti-cancer efficacy, such as cytosine deaminase combined with 5-fluorocytosine⁷⁴ and herpes simplex virus thymidine kinase combined with ganciclovir⁷⁵. 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 cytotoxic 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 tumors⁶⁹. 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 effect⁷⁶. 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) infection⁷⁷.

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 therapy⁷⁸, tumor radiotherapy⁷⁹, chemotherapy sensitization⁸⁰ 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 hafnium⁸⁰. The interaction between ionizing radiation and hafnium can promote higher energy deposition⁸¹. 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 modalities⁸¹. 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 tissues⁷⁸. 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 days⁷⁹. 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 nanomedicines⁸². ADCs utilize the targeting and specificity of antibodies (such as

monoclonal antibodies or bispecific antibodies) as drug carriers to transport toxic drugs to tumor sites⁸³. 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)⁸⁴, 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 on⁸⁵. Notably, FDA's approval of ADCs is based on the biological license applications (BLA) process⁸⁶. So far, eleven ADCs have received market approval, and more than 80 ADCs are currently in clinical development (Table S2)⁸⁷.

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 2.3⁸⁸. 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 prodrug (Probody) drug targeting transferrin receptor (CD71; TFRC) conjugated to the microtubule disrupting agent monomethyl auristatin E (vcMMAE)⁸⁹. 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 neutropenia⁹⁰.

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^{91,92}. In addition, radionuclide labeled antibodies can be used for tumor imaging⁹³.

3.1.8.3. Antibody-based radioimmunotherapy products in the market. Capromab pendetide indium, launched in 1997, is an indium-111 radiolabeled immunoconjugate derived from anti-prostate monoclonal antibody 7E11-C5, as a radioimmunoscintigraphic imaging agent used in patients with prostate cancer⁹⁴.

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-hydroxypyridinone (3,2-HOPO) chelator complexing the alpha-emitter ²²⁷Th⁹⁵. 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 treatment⁹⁶. 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 agents⁹⁷, fluorescence imaging agents⁹⁸, radioactive and fluorescent hybrid tracer^{99,100}, magnetic resonance imaging (MRI) contrast agents^{101,102} and ultrasound contrast agents¹⁰³ (Table S3).

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 MRI¹⁰². In addition, Aerosomes, microbubbles of octafluoropropane gas encapsulated liposomes, are launched in 2001 as ultrasound contrast agents¹⁰³.

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 ligand⁹⁹. 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 an ultra-pH-sensitive 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)⁹⁸. 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 immunogenic¹⁰⁴. Nanoparticles-based cancer vaccines and adjuvants can improve bioavailability, protect antigens from degradation, improve transfection efficiency, control antigen release or enhance immune response¹⁰⁵. Based on the source of antigens and the type of carriers, cancer vaccine are

categorized as cell-based, viral vector-based or molecular-based (peptide, DNA or RNA) vaccines¹⁰⁵.

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 Apceden-P (2017), Apceden-O (2017), Apceden-L (2017), Apceden-CR (2017), Provenge (2010) and CreaVax-RCC (2007). Further reviews of DC vaccines are available in the articles^{105,106}. 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-enhancer¹⁰⁷. GM3/VSSP is a cancer vaccine comprising small-sized proteoliposomes (VSSPs) formed by linking *N*-acetyl GM3 (NAcGM3) ganglioside with *Neisseria meningitidis*-derived OMVs¹⁰⁸. *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) gangliosides¹⁰⁹. VSSPs have been shown to stimulate immune responses by activating DCs, even in immunosuppressed cancer patients¹¹⁰. 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 metastases¹¹¹.

In addition to OMV, autologous tumor cell vaccines are also feasible and emerging methods for personalized immunotherapy¹¹². 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 Biopharma¹¹³. The product is in early clinical development against CLL¹¹⁴.

3.3.2. Virus-based tumor vaccine

Virus-based tumor vaccines (Table S4) express tumor antigens by virus vector¹¹⁵ or release antigens *in situ* by virus lysis of tumor cells^{116,117}. Genetically modified oncolytic viruses are designed to specifically replicate in tumors and destroy tumor cells¹⁰⁵. 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 costimulatory factors¹⁰⁶. Oncolytic virus products currently approved for marketing (Table S4) include Delytact (2021), Talimogene 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 carcinoma¹¹⁶. 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.

Talimogene 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 unresectable 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 immunity¹¹⁸. 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^{117,119}. TVEC showed significant improvements in sustained response rate, objective response rate, and progression-free survival for patients with advanced melanoma¹¹⁷.

3.3.2.2. *Virus-based tumor vaccine under clinical development.* Aspartate β -hydroxylase (sASPH) is overexpressed in 70%–90% of human solid tumors¹²⁰, 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 ASPH¹¹⁵. 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 adenoviral 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 complex¹²¹. 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 cells¹²². The most common delivery methods for DNA vaccines are physical strategies, for instance, electroporation¹²³. At present, few tumor DNA vaccines are delivered by nanoparticles in clinical stage. Amolimogene 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 antigens¹²⁴. 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 reasons¹²⁵.

Alternatively, RNA vaccines may have advantages over DNA vaccines, because RNA cannot integrate into the genome and therefore has no carcinogenic potential¹⁰⁴. 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 low¹²⁶. Rationally, delivery vectors or chemical modifications are designed to solve these problems. For instance, mRNA-2416 is an mRNA-based cancer vaccine targeting OX40L, consisting of messenger RNAs (mRNA) encoding OX40 ligands (OX40L) with miR-122 binding sites encapsulated in lipid nanoparticles¹²⁷. 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 functions¹²⁸. 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 injection¹¹⁴.

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 pre-clinical and clinical studies¹²⁹. CHP-NY-ESO-1 is a nanoparticles peptide vaccine originated by the Ludwig Institute for Cancer Research, which consists of cholesteryl hydrophobized polysaccharide (CHP, pullulan) complexed with recombinant NY-ESO-1 peptide (cancer-testis antigen)¹³⁰. 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 benefits¹³¹. 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 liposomes¹³². 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 patients¹³³. 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 absorption¹³⁴. AeroLEF was

assessed in early clinical trials for controlling moderate or severe acute pain¹³⁵. ARS is caused by systemic or partial exposure to high-dose radiation for a short period of time¹³⁶. MAXY-G34 is a PEGylated formulation of granulocyte colony-stimulating factor (G-CSF), which can stimulate the bone marrow to produce white blood cells¹³⁷. 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 on¹³⁸. 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)¹³⁹ and Liposomal amphotericin B (1991, Astellas Pharma)¹⁴⁰.

In addition to intravenously administered liposomes, inhaled or 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 lungs¹⁴¹. SLIT-amikacin (Arikace), a liposomal inhaled formulation of amikacin developed by Insmed, can penetrate into airway secretions and biofilm deeply¹³⁹. 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 kidney¹⁴⁰.

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

virus, Ebola virus, HIV, rabies virus and Zika virus infection (Table S6).

Of note, the rapid spread of SARS-CoV-2 around the world in recent years has caused devastating morbidity and mortality, which prompted several clinical trials related to nanoparticles, especially lipid nanoparticles, for the treatment and prevention of the virus infection (COVID-19)^{142,143}. The spike (S) glycoprotein of SARS-CoV-2 is the main target for vaccination, which enables the virus to attach and enter the host cells. The S protein contains three key elements: S1, receptor-binding domain (RBD) and S2 subunits¹⁴². Nanoparticle-based COVID-19 vaccines in the clinical stage mainly deliver virus surface protein antigens or mRNA encoding the antigens, such as coronavirus' surface antigen S glycoprotein, RBD, mRNA encoding RBD and mRNA encoding S protein.

IVX-411 is a recombinant SARS-CoV-2 vaccine made of virus-like particle (VLP)-based self-assembling protein nanoparticles that display 60 copies of the SARS-CoV-2 surface antigen spike (S) glycoprotein RBD. Antibodies induced by the RBD nanoparticles are able to target multiple distinct epitopes, which may not be susceptible to escape mutations¹⁴⁴. Preclinical results of IVX-411 and precursor candidates in rhesus macaques demonstrate that the vaccine candidates can induce robust and durable neutralizing antibody titers, and protect against viral attack¹⁴⁵. The vaccine is currently in phase I/II 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 variant¹⁴⁶. 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, transocetin, artemisinin, curcumin and vitamin C, to treat COVID-19. LEAF-4L6715 is a liposomal formulation containing the kosmotropic agent trans-crocetin (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 tissues¹⁴⁷.

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 liposomes¹⁴⁸.

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 adeno associated virtual 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 fibrils¹⁴⁹. The ionizable cationic lipid nanoparticles of Patisiran are composed of (6Z,9Z,28Z,31Z)-heptatriacontan-6,9,28,31-tetraen-19-yl-4-(dimethylamino) butanoate (DLin-MC3-DMA), cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and α -(3'-[[1,2-di (myristyloxy)propoxy]carbonylamino]propyl)- ω -methoxy polyoxyethylene (PEG2000-C-DMG)^{150,151}. 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 endocytosis¹⁵². 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 cytoplasm¹⁵³. 56% of Patisiran-treated patients showed improvement in modified Neuropathy Impairment Score in phase III clinical trial (NCT01960348)¹⁵⁴. 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 product¹⁵⁰.

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 effects¹⁵⁵. 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-2001¹⁵⁶. 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

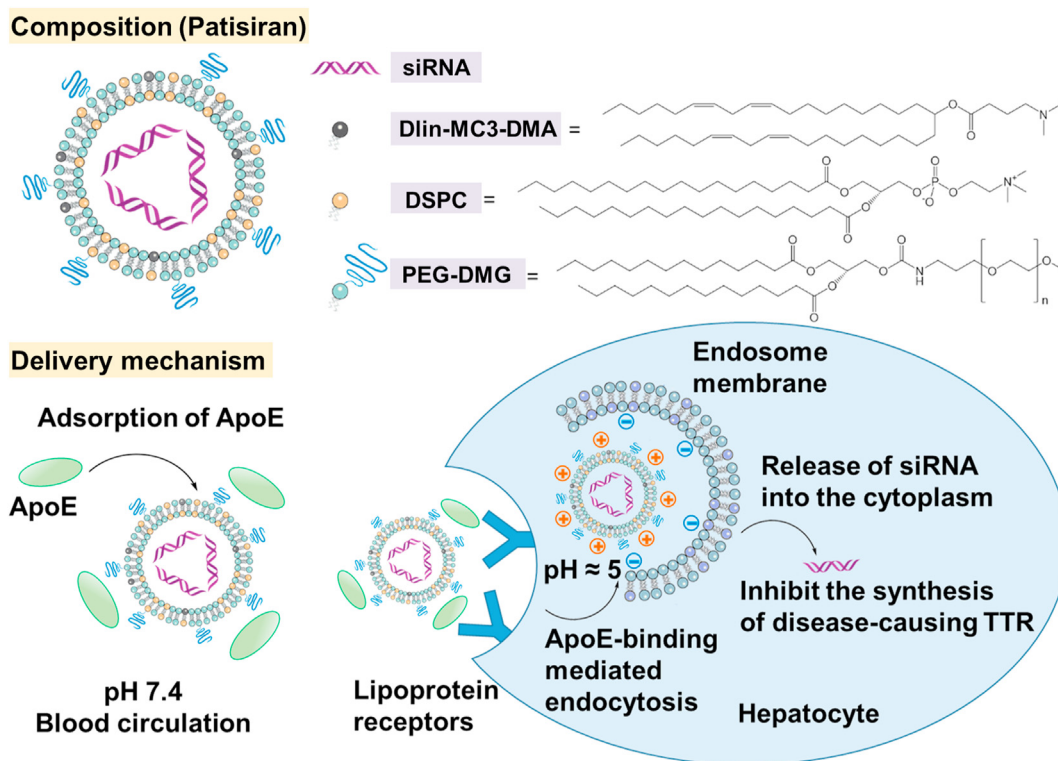


Figure 4 The composition and the mechanism of targeting delivery to hepatocytes of Patisiran, the first RNAi drug approved for marketing in the world for the treatment of hATTR polyneuropathy. Adapted from Ref. 151. Copyright © 2020 American Chemical Society.

hATTR and effectively reduced the plasma concentration of TTR protein (NCT04601051)¹⁵⁶.

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, hyperinsulinism, 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 nm¹⁵⁷. 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 administration¹⁵⁸. 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)¹⁵⁹.

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 Joyclu (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 diseases¹⁶⁰.

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 glucose¹⁶¹.

3.5.4. Cardiovascular diseases

Nanomedicines that have been employed for therapy and diagnosis of cardiovascular diseases (such as atherosclerosis and ischemia¹⁵) 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 dyslipidemia¹⁶².

MRX-815 is lipid nanobubbles thrombolytic comprising of perfluoropropane gas¹⁶³. 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 scatterer¹⁶⁴.

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 frequency¹⁶⁵. 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 degeneration¹⁴.

OC-188 eye drops consist of dexamethasone gamma-cyclodextrin nanoparticles, which can deliver lipophilic drugs across the ocular surface barriers into the eyes¹⁶⁶. 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)¹³. 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 vibration¹⁶⁷. 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 damage¹⁶⁸.

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)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 micro-environment¹⁷⁰. 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^{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)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 sclerosis¹⁷⁵. 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%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 docetaxel¹⁷⁶. 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 *in vivo* interaction process of nanoparticles, clinical therapeutic effects, safety, stability, regulatory standards, etc¹⁷⁷. 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 needs¹⁷⁸. One of the feasible direction is excipient-free nanomedicines that are composed entirely of clinically approved small molecule drugs, which may make the clinical translation easier¹⁷⁹.

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, *e.g.*, heterogeneity, which may cause the insufficient effect of many nanomedicines and the failure of clinical translation (*e.g.*, BIND-014)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 nanomedicines¹⁷⁶. 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 rate¹⁷. 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

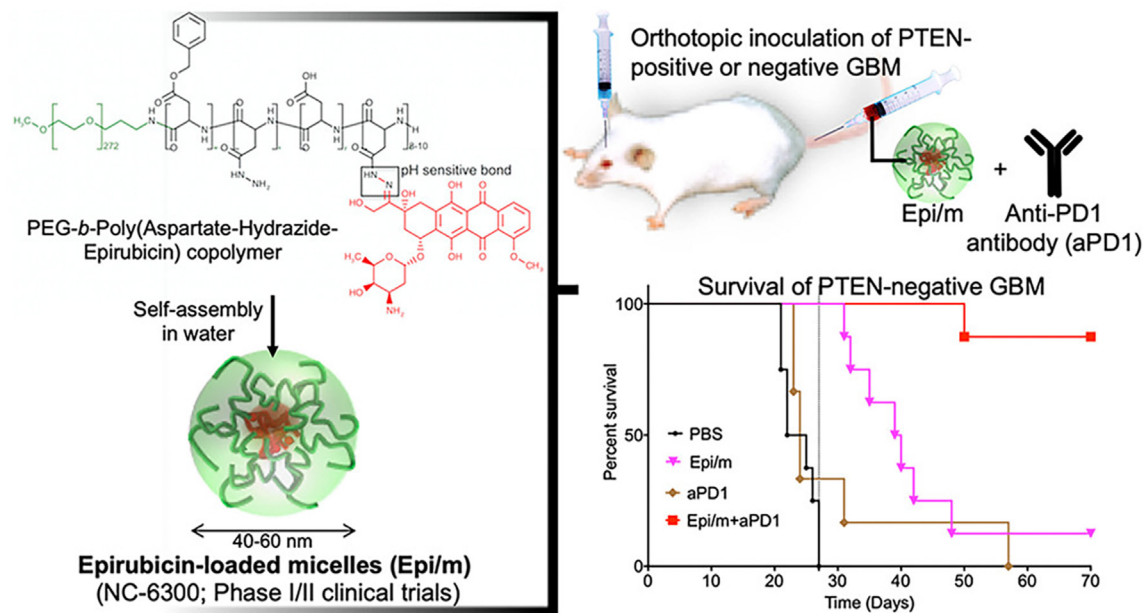


Figure 5 The combination therapy of NC-6300 (micellar nanoparticles loaded with ICD inducer anthracycline epirubicin) and anti-PD1 antibody is able to overcome tumor resistance to immune checkpoint inhibitors and improve response rate by changing tumor immunosuppressive microenvironment through ICD. Reprinted with the permission from Ref. 174. Copyright © 2020 American Chemical Society.

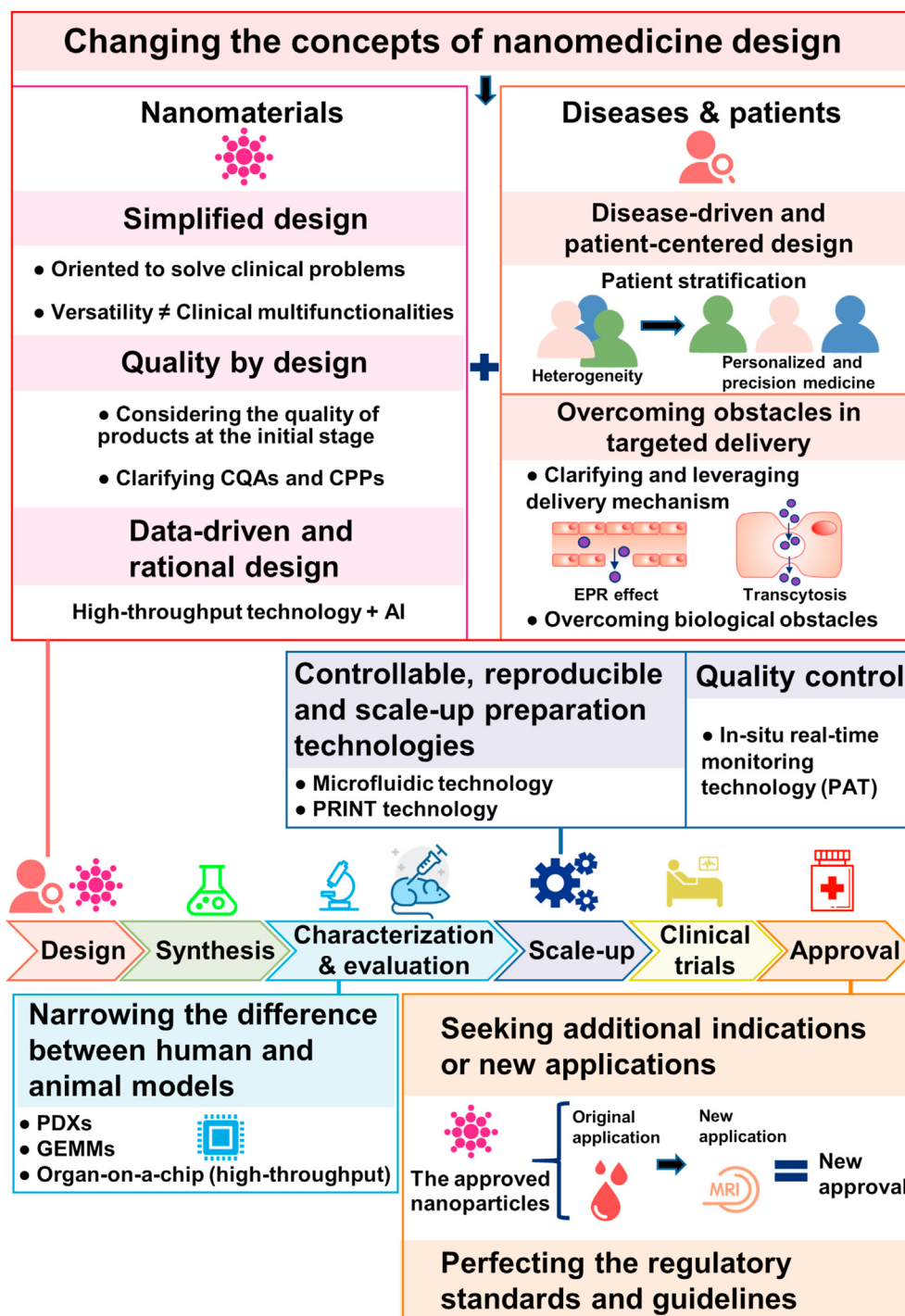


Figure 6 Perspectives of accelerating the clinical translation of nanomedicines. CQAs, critical quality attributes; CPPs, critical process parameters; AI, artificial intelligence; EPR, enhanced permeability and retention effect; PDXs, patient-derived xenografts; GEMMs, genetically engineered mouse models; PRINT, particle replication in non-wetting template technology, PAT, process analytical technology.

(L-glutamic acid) polymer nanoparticles of paclitaxel for the treatment of NSCLC¹⁸¹. The results of clinical trials of Opaxio in NSCLC patients showed that women with premenopausal estradiol levels had a significant survival benefit¹⁸¹. 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 threshold¹⁸⁰. 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 therapy¹⁸², utilization of biomarkers and nanoparticle barcoding^{183,184}.

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 regulation¹⁸⁵. 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 paradigm¹⁸⁵. Besides, risk assessment is also vital to QbD implementation in the pharmaceuticals field¹⁸⁶. A typical example of QbD in accelerating nanoparticles translation is ACCURINS, a clinically advanced polymeric nanoparticle consisting of polylactic acid-polyethylene glycol (PLA-PEG), which illustrates that the risk-based QbD paradigm is feasible to bring nanomedicines to the clinic and commercialization¹⁸⁷.

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 clinic¹⁸⁸. Recently, active transcytosis of endothelial cells in cancer has been found to be more effective in delivering nanoparticles into solid tumors¹⁸⁹. The active transcytosis based nanomedicines have been developed (e.g., charge reversible nanoparticles) and derived a more efficient targeted delivery strategy¹⁹⁰. In addition, convection-enhanced delivery (CED) has also been developed for drug delivery strategies¹⁹¹, and has been clinically proved to be able to bypass the blood-brain barrier and deliver drugs to the target brain region¹⁹². In a phase I/II 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 patients¹⁹³. 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 nanoparticles¹⁹.

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 phenomenon¹⁹⁴. 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 nanoparticles¹⁹⁵, 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)¹⁹⁵. In addition, in anti-tumor therapy, the limited penetration of nanomedicine in tumors is an important contributor to the insufficient efficacy¹⁰. 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 efficiency¹⁹⁶.

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 toxicity¹⁹⁷. Meanwhile, these targeting ligands may be masked by versatile plasma protein corona upon their entry into the blood circulation, thereby abolishing the targeting effects¹⁹⁸. Therefore, it is necessary to seek more intelligent and precise nanomedicines. Nanorobots with autonomous addressing capability¹⁹⁹ and nanoparticles with logic-gated (multibiomarker-based) recognition ability²⁰⁰ 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 polydispersity² and solvent residue²⁰¹, 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^{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 adjustability²⁰⁴. For the problem of solvent residue, supercritical fluids technology (SCF) has been used in the manufacture of liposomes because of its friendliness, non-toxic to the environment and the possibility of preparing solvent-free nanoparticles²⁰¹.

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 humans²⁰⁵. 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

tumors². 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^{183,206}. This paradigm holds great potential to reduce the blindness and randomness of conventional nanoparticle design based on empirical and trial-and-error strategies¹⁶.

To promote the production of nanomedicines, some regulatory agencies have introduced quality control standards and defined the CQAs of nanomedicines⁸². 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 quality¹⁷⁷.

4.4. Overcoming regulatory challenges of nanomedicines

Nanomedicines are generally approved according to the conventional framework, which is unfavorable to the development of nanomedicines¹. Currently, FDA has not established regulatory definitions of "nanotechnology", "nanomaterial", "nanoscale" or other related terms⁴, which may lead to ambiguity. Therefore, it is essential to improve the regulatory regulations (e.g., clarify the CQAs) and establish widely acceptable international standards²⁰⁷.

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 nanoparticle¹⁷⁸. 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.

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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>.

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