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Biologics, theranostics, and personalized medicine in drug delivery systems

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ABSTRACT

The progress in human disease treatment can be greatly advanced through the implementation of nanomedicine. This approach involves targeted and cell-specific therapy, controlled drug release, personalized dosage forms, wearable drug delivery, and companion diagnostics. By integrating cutting-edge technologies with drug delivery systems, greater precision can be achieved at the tissue and cellular levels through the use of stimuli-responsive nanoparticles, and the development of electrochemical sensor systems. This precision targeting – by virtue of nanotechnology – allows for therapy to be directed specifically to affected tissues while greatly reducing side effects on healthy tissues. As such, nanomedicine has the potential to transform the treatment of conditions such as cancer, genetic diseases, and chronic illnesses by facilitating precise and cell-specific drug delivery. Additionally, personalized dosage forms and wearable devices offer the ability to tailor treatment to the unique needs of each patient, thereby increasing therapeutic effectiveness and compliance. Companion diagnostics further enable efficient monitoring of treatment response, enabling customized adjustments to the treatment plan. The question of whether all the potential therapeutic approaches outlined here are viable alternatives to current treatments is also discussed. In general, the application of nanotechnology in the field of biomedicine may provide a strong alternative to existing treatments for several reasons. In this review, we aim to present evidence that, although in early stages, fully merging advanced technology with innovative drug delivery shows promise for successful implementation across various disease areas, including cancer and genetic or chronic diseases.

1. Introduction

Drug delivery systems play a pivotal role in personalized medicine. By tailoring drug administration to individual patient characteristics, these systems allow for improved treatment outcomes, reduced side effects, and enhanced patient compliance. Personalized medicine aims to customize medical interventions based on a person's unique genetic makeup, lifestyle, and medical history. Here, we summarize how drug delivery systems contribute to this approach and provide several examples to illustrate their impact. Merging advanced technologies with drug delivery has paved the way for next-generation drug delivery systems, particularly in the treatment of cancer and chronic diseases. These systems aim to enhance target efficiency at both tissue and cellular levels through the controlled release of engineered nanoparticles. These nanoparticles are designed to respond to specific stimuli such as pH, enzymes, or reactive oxygen species (ROS). This enables precise and personalized therapies, tailored to the unique needs of individual patients. By incorporating these innovative approaches, biologic drug delivery systems offer exciting possibilities for improved treatment outcomes in the realm of neoplasia and chronic diseases, meeting the need for personalized therapies in drug delivery, tailoring diagnostic and therapeutic manoeuvres (theranostics) to individual patients, and precision medicine in biologics use. Areas covered in this review include terms as itemized below, and search was performed to identify relevant articles in the electronic databases PubMed, Web of Science, Scopus, Cochrane, EMBASE, and Google Scholar. Databases were searched up to December 2023.

Although there are excellent recent reviews on the subject [1–3], the Authors want to emphasize how some current technologies (such as mRNA/lipid nanoparticle systems) could be optimized in the future by drug delivery approaches that improve on tissue-specific, intracellular delivery as well as quantitative and controlled drug delivery. Along this direction, it is the Authors' opinion that an up-to-date review of nanotechnology for biomedical applications offers several advantages,

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including the potential to provide a thorough understanding of the current state of the field, identify research gaps, and propose novel approaches for addressing biomedical challenges. By justifying and expanding upon this information, we can highlight the significance of such reviews in advancing the field of nanomedicine. Thus the advantages of a review of the latest applications nanotechnology, even those still in their infancy, include:

i. Synthesizing Existing Knowledge: A comprehensive review allows for the synthesis of existing knowledge, enabling researchers to gain a comprehensive understanding of the various nanotechnologies and their applications in biomedicine. This can help in identifying trends, challenges, and opportunities in the field.
ii. Identification of Research Gaps: Reviewing the literature on nanotechnology for biomedical applications can help in identifying gaps in current knowledge and research. This can guide future research efforts, allowing for the development of new and innovative approaches to address these gaps.
iii. Proposal of Novel Approaches: By analyzing the current state of the field, a comprehensive review can propose novel approaches and strategies for the development of nanotechnology-based biomedical tools, diagnostics, and therapeutics. This can lead to the advancement of personalized medicine and targeted therapies [4].
iv. Main Experimental Conditions Used in the Literature: The main experimental conditions used in studies on nanotechnology for biomedical applications can vary depending on the specific application, such as drug delivery, imaging, or diagnostics. Some common experimental conditions include:

- Nanoparticle Synthesis: Methods for synthesizing nanoparticles, including chemical methods, physical methods, and biological methods. These methods include ecofriendly synthesis of therapeutic nanoparticles [5], synthesis of nanoparticles from bacteria [6],
- Characterization Techniques: Use of techniques such as transmission electron microscopy (TEM), scanning electron microscopy (SEM), dynamic light scattering (DLS), and X-ray diffraction (XRD) to characterize the physicochemical properties of nanoparticles.
- *In vitro* and in vivo Studies: Evaluation of nanoparticle behavior and efficacy in cell culture systems and animal models to assess biocompatibility, targeting, and therapeutic effects.

As to the importance of describing data homogeneously and reinforcing the relevance of novel alternatives, it should be noted that describing data from the literature in a homogeneous manner is important because it allows for a clear and standardized presentation of information, making it easier for researchers to compare and analyze studies. Homogeneous descriptions facilitate the identification of common trends, challenges, and potential areas for innovation in nanomedicine. Reinforcing the relevance of novel alternatives underscores the importance of pushing the boundaries of current research and developing innovative solutions to biomedical challenges.

2. Targeted therapy

Targeted therapy refers to a type of medical treatment that focuses on specific characteristics of a disease to effectively target specific cells without affecting healthy cells [7–12]. Drug delivery systems can be designed to specifically target diseased cells or tissues, sparing healthy ones [7,13–15]. For instance, in cancer treatment, nanocarriers can be loaded with chemotherapy drugs that are released selectively at the tumor site, minimizing damage to healthy tissues [16]. Such targeted therapy maximizes drug efficacy while minimizing potential side effects [17,18]. Here are a few remarkable examples of targeted therapies: *i*) Imatinib (Gleevec): This targeted therapy drug revolutionized the treatment of chronic myeloid leukemia (CML). Imatinib specifically targets and inhibits the activity of a protein called BCR-ABL, which is responsible for the abnormal growth of cancer cells in CML patients [19,20]; *ii*) Trastuzumab (Herceptin): Trastuzumab is an example of a targeted therapy for breast cancer. It specifically targets and blocks the activity of HER2 receptors, which are overexpressed in around 25% of breast cancer cases [21,22]. By inhibiting HER2 signaling, trastuzumab helps slow down or stop the growth of HER2-positive breast cancer cells [23]; *iii*) Pembrolizumab (Keytruda): This immunotherapy drug is used in targeted therapy for various types of cancer, including melanoma, lung cancer, and certain types of bladder and stomach cancers [24]. Pembrolizumab combined with chemotherapy has been established as the preferred first-line therapy for treating metastatic triple-negative breast cancer (mTNBC) with programmed cell death ligand-1 (PD-L1)-positive disease since its approval for that indication [25]; *iv*) Vemurafenib (Zelboraf): Vemurafenib is a targeted therapy drug used to treat a specific type of skin cancer known as BRAF V600E mutation-positive melanoma [26]. By selectively inhibiting the activity of mutated BRAF protein in cancer cells, vemurafenib helps slow down the growth of melanoma tumors [27]. These examples highlight the power of targeted therapies in treating various types of cancer by specifically targeting the underlying genetic or molecular abnormalities associated with the disease [28]. However, it's important to note that these examples are just a few among several targeted therapies available today. Fig. 1 provides an outline of targeted therapy in breast cancer.

Undoubtedly, the field of targeted therapy continues to evolve, offering hope for more precise and effective treatments in the future in a broader context [8,18,30–32]. As an example, inhaling is a common way of delivering small-molecule and non-peptide medications to the respiratory system [33–36]. This method allows for precise and efficient delivery. Our recent studies focused on the u se of anakinra, a synthetic protein that inhibits the proinflammatory cytokine interleukin 1, in experimental cystic fibrosis (CF). CF is a respiratory condition characterized by inflammation, primarily affecting the airways. We have recently succeeded in directly delivering anakinra to the lungs. To achieve this, we successfully developed an inhalable dry powder formulation of anakinra, specifically designed for lung drug delivery [37]. We conducted in vitro studies to assess its aerodynamic performance, activity, pharmacokinetics, treatment schedule, antimicrobial and anti-inflammatory effects, and systemic toxicity. The protein remained structurally intact and pharmacologically active both immediately after preparation and over time when stored at room temperature. When anakinra was delivered to the lungs, it demonstrated improved and prolonged therapeutic efficacy in CF animal models compared to systemic delivery. Furthermore, it exhibited greater potency while reducing peripheral side effects, likely due to lower serum levels compared to systemic treatment.

On the other hand, in the age of precision medicine, the concept of utilizing multivalent and multispecific therapeutics offers a promising strategy for targeted intervention in diseases. These therapeutics are specifically designed to engage with multiple targets simultaneously, which holds the potential for improved effectiveness, minimized side effects, and increased resilience against drug resistance [38]. To fully leverage the therapeutic benefits, it is crucial to understand the underlying principles that govern the design of multivalent biologics and address the associated challenges. Various factors, such as domain affinities, valency, and spatial presentation, play an important role in the engineering of multivalent and multispecific biologics. It is essential to consider these elements in relation to the molecular targets and strike the right balance between target avidity and specificity. Recent advancements in biomolecular and cellular engineering, coupled with computational approaches, have paved the way for the application of these principles in the development of protein and cell therapies [39,40].

By shedding light on these principles and their practical implementation, we can uncover exciting opportunities for the future of this field. This progress holds great potential in revolutionizing disease

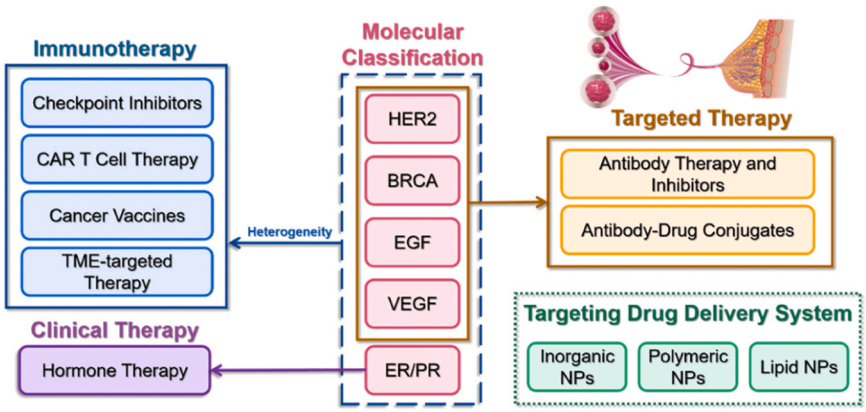

Fig. 1. Targeted therapy in breast cancer. Molecular categorizations play a significant role in clinical identification and function as markers of diversity within tumors, enabling the risk-based allocation of patients for individualized treatment. Traditional biomarkers such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) are regularly utilized in global pathology studies with established staining methods. Meanwhile, newer biomarkers such as BRCA, EGF, and VEGF have been recognized and hold promise for precise diagnosis and therapy selection. NPs, nanoparticles. Taken in whole from Sun, X., et al., Cancers, 2022. 14 (21): p. 5456; Ref. [29]. Licensee MDPI, Basel, Switzerland, under Creative Commons License (CC BY 4.0 DEED).

treatment, and ongoing research in biomolecular and cellular engineering will continue to drive innovation in multivalent and multispecific therapeutic design [40–42]. However, omics sciences and precision medicine call for an integration of real-world data to accelerate and guide drug development and delivery to an individual patient [43]. The following is a synopsis of factors that may impact on Integration from various sources as well as the increased need for multidimensional-omics data that can better guide the development of personalized and predictive medicine [44–46].

3. Controlled drug release

Drug delivery systems can regulate the release of medication over time, optimizing therapeutic outcomes [47–49]. For example, implantable drug-eluting devices can be used for localized and sustained release of drugs, such as pain relievers or anti-inflammatory agents. By providing a steady concentration of medication, these systems improve patient comfort and reduce the need for frequent dosing [50–52].

Controlled drug release is a crucial aspect in the field of therapeutics, aiming to optimize the delivery of medications to achieve maximum efficacy and minimize side effects. The ability to control the release of drugs at a desired rate, duration, and location plays a pivotal role in enhancing treatment outcomes and patient compliance. It involves the design and development of drug delivery systems that can regulate the release of therapeutics over a predetermined period, precisely targeting the affected tissues or cells [53]. The conventional immediate-release formulations often result in rapid drug absorption, followed by a quick decline in plasma concentrations, which may necessitate frequent dosing and potentially lead to fluctuations in drug levels. This can limit the therapeutic benefits and pose challenges in maintaining proper drug concentrations within the therapeutic window.

There are several techniques employed to achieve controlled drug release, including the use of specialized formulations such as microspheres [54,55], nanoparticles [9,16,18,56,57], hydrogels [58,59], or liposomes, the latter including means of delivering nucleic acids/genes based on controlled intracellular trafficking as well as controlled biodistribution for nanomedicines [60]. These delivery systems can be engineered to respond to various stimuli, such as pH [47], temperature [61], enzymes [62], or external triggers [63], allowing for personalized and targeted drug delivery. Additionally, advancements in nanotechnology, biocompatible materials, and bioengineering have opened up new avenues for developing sophisticated and intelligent drug release systems. Attempts are underway for engineering carrier nanoparticles with biomimetic moieties for improved intracellular targeted delivery of mRNA therapeutics and vaccines [31,64,65]. Box 1 and Fig. 2 epitomize the principles of nanoparticle fabrication and "decoration" (or "engineering"), which is meant to improve target cell selectivity. The topic has recently been reviewed elsewhere in detail [66].

In summary, controlled drug release plays a critical role in optimizing therapeutic outcomes. By manipulating drug release kinetics and site-specific targeting, these systems provide a means to tailor treatment regimens, maximize drug effectiveness, and enhance patient well-being. The ongoing advancements in this field continue to pave the way for innovative and effective drug delivery strategies, opening up new possibilities in the realm of personalized medicine [10,72]. Fig. 3 provides an overall scheme of the potential use of stimuli-responsive nanoparticles for controlled drug delivery in synergistic cancer immunotherapy.

4. Pharmacokinetics considerations

Drug delivery systems allow for individualized pharmacokinetics, tailoring drug absorption, distribution, metabolism, and excretion to a patient's specific needs. Traditionally, this is particularly crucial for patients with variations in drug metabolism enzymes or those with impaired renal or hepatic function. By adjusting drug release rates or modifying delivery routes, personalized drug kinetics can be achieved [74,75].

The advent of biologicals – most of which are represented by monoclonal antibodies (mAbs) – poses, however, new problems [76,77]. As an example, in order to enhance the efficacy of mAbs in treating lung diseases, it is preferable to administer them through inhalation rather than parenteral routes [78–80]. However, the pulmonary delivery of mAbs using aerosol technology and inhalation formulations presents challenges [81–83]. Overcoming these challenges and successfully delivering mAbs via inhalation to individuals with lung disorders require careful consideration of various factors such as the specific illness, the patient group, the chosen therapeutic molecule, its interaction with lung barriers, formulation components, and administration systems [84,85]. A thorough investigation is necessary to ensure the stability and efficacy of inhaled mAbs, including addressing problems related to instability and protein aggregation [86]. Furthermore, the development of additional excipients and novel carriers for lung topical delivery is essential, as they can significantly enhance the stability and pharmacokinetic profile of proteins [87].

A prototypic example is represented by treatment of severe asthma, which has greatly benefited from multiple available mAbs [88–91]; there is likewise growing evidence that mAbs, primarily

Box 1
Intracellular delivery by nanoparticles.

Various techniques can achieve intracellular delivery, utilizing carriers or methods that disrupt the cell membrane. Conventional approaches involve physical and mechanical means to permeabilize the cell membrane. Modalities like microinjection, sonoporation, electroporation, and others have been developed to induce temporary disruptions in the plasma membrane through mechanical, electrical, thermal, optical, or chemical forces. Unfortunately, these methods have limitations for large-scale treatments and pharmaceutical applications due to their low-throughput nature and reliance on sophisticated and expensive instrumentation [67]. Bio-degradable nanoparticles (NPs) offer multiple applications as effective drug delivery vehicles. They possess desirable characteristics such as acceptable bio-availability, lower toxicity, and the ability to encapsulate drugs for controlled release. However, their interaction with macrophages in the reticuloendothelial system (RES) can reduce their effectiveness for medical purposes. To mitigate this, the surface of the NPs is commonly treated with neutralizing molecules, such as poly(ethylene glycol) (PEG), which is a widely used stealth polymer. This modification aims to limit NP clearance through the RES system by resisting clearance and protein adsorption. Unfortunately, modifying PEG has its drawbacks, including synthesis difficulties and potential immune reactions [68].

To obviate the obstacles of artificially synthesized, biomimetic NPs are becoming a research focus. In 2011, Zhang's team first synthesized red blood cell (RBC) membrane-camouflaged NPs [64]. The method described in this study was based on a top-down approach that involved transferring red blood cell membranes onto biodegradable polymeric cores. This technique allowed for the retention of lipids, proteins, and carbohydrates from the RBC membrane, preserving the inherent biological properties of the source cells. When foreign invaders enter the body, the immune system recognizes them based on the absence of "markers of self" typically present on host cells or the presence of certain determinants. One such marker of self is the surface protein CD47 (integrin-associated protein) found on RBC membranes. CD47 acts as a "marker of self," reducing the immune reaction and significantly prolonging the half-life of the nanoparticles to approximately 40 h [69]. In contrast to the 15.8-hour half-life of PEGylated NPs, the use of red blood cell membrane camouflage offers a distinct advantage by significantly extending the blood retention of the NPs. Building on this success, researchers have also explored the use of other biological membranes sourced from cancer cells, white blood cells, platelets, and exosomes to create biomimetic NPs. These biomimetic NPs, as compared to artificially synthesized ones, exhibit significantly enhanced drug delivery efficiency. As a result, they hold great promise for improving the effectiveness of treatments for cancer, inflammation, and immune diseases [31].

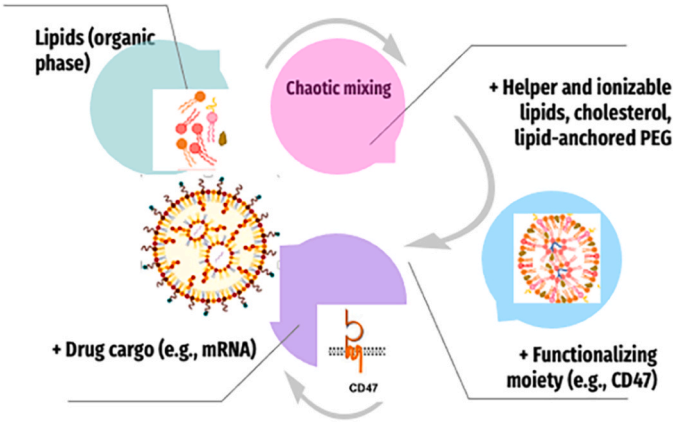

Fig. 2. Lipid nanoparticle (LNP) formulation and engineering. Components are mixed via chaotic mixing through a microfluidic device. The mixture typically includes ionizable lipid which aids in the encapsulation of nucleic acids via electrostatic interactions, "helper" lipids meant to improve LNP stability and fusogenicity, cholesterol – which decreases permeability while augmenting stability – and polyethylene glycol (PEG)-lipid, which prevents non-specific protein absorption, particle aggregation and exhibits mucus-penetrating properties, and controls LNP size. Cationic and ionizable cationic lipids are also included in LNP formulations. The inclusion of a "biomimetic" targeting moiety – a target cell-specific ligand (e.g., CD47, externally obtained from different cellular sources) – is meant to bind a cognate acceptor and/or a surface interactor on a specific cell type. The process is often referred to as nanoparticle surface "engineering" or "functionalization", making the LNP a "decorated" nanoparticle. The cognate receptor for CD47 is SIRPα, which, upon ligation by CD47 on cells of the reticuloendothelial system, delivers a "*don't-eat-me*" signal to those cells [70], thus avoiding phagocyte-mediated clearance of the LNP. The process can considerably improve target selectivity in delivering the drug cargo and increase LNP's half-life [66]. In addition, Ref. [31] provides exhaustive information on engineering methods. The issue of biomimetic cell-derived nano-carriers in cancer research is extensively dealt with in Ref. [71].

immunoglobulin G (IgG) molecules with a molecular weight of around 150 kDa, hold promise for personalized treatment of chronic obstructive pulmonary disease (COPD) [79] and allergic bronchopulmonary aspergillosis in patients with asthma and cystic fibrosis [92]. Additionally, mAbs are considered effective in managing respiratory infections [93–95], and new classes of mAbs are emerging as potential treatments for lung cancer [96–98]. However, mAbs are large molecules that are predominantly delivered systemically, resulting in only a small fraction reaching the lungs [99]. Typically, the concentration of mAbs in the lungs is significantly lower (500–2000 times) than their systemic circulation concentration. Consequently, high systemic doses are often required to achieve therapeutically effective concentrations in the lungs, which increases the risk of exposing the rest of the body to potential toxicity and adverse effects. Injectable mAbs, in particular, have been associated with negative effects such as allergies, immune reactions, and other undesirable responses [100,101].

Undoubtedly, development of inhaled formulations to deliver large, delicate molecules such as mAbs has proven challenging, but success has been achieved using spray drying to generate respirable powders of small molecules for drug delivery to the deep lung [102]. Direct administration of mAbs to the airways through inhalation ensures a higher proportion of the administered dose reaches the intended site in the lungs. This allows for the use of much lower doses compared to systemic administration, while still achieving equivalent therapeutic effectiveness [103]. Studies in mice and macaque models have demonstrated that delivering mAbs via the pulmonary route increases concentration at the target site while limiting systemic exposure, resulting in effective therapeutic responses [104,105]. Furthermore, administering mAbs via inhalation leads to persistent and consistent accumulation in the lungs, preserving their physical and immunological characteristics, at least in non-human primate experimental contexts. For instance, a dual interleukin (IL)– 4/IL-13 antagonist, pitrakinra, showed improved therapeutic response when administered via inhalation compared to systemic subcutaneous delivery in an asthma model [106].

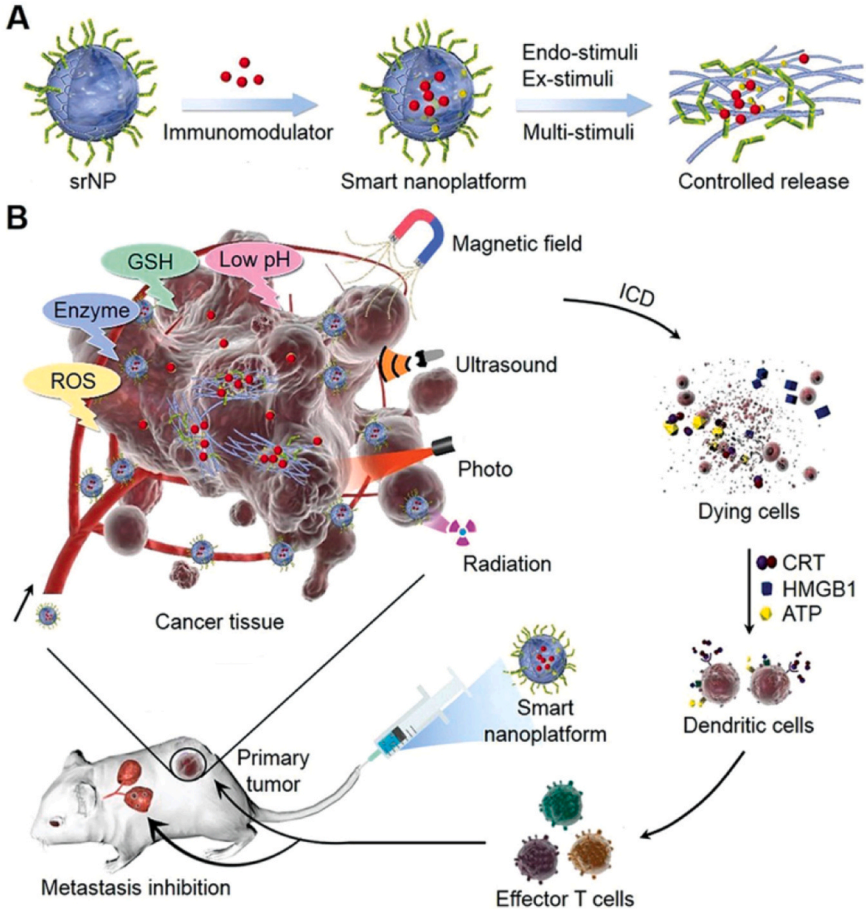

Fig. 3. Stimuli-responsive nanoparticles (srNPs) for controlled drug delivery. (A) The development of smart nanoparticles allows for their activation by a variety of internal and external stimuli. These stimuli include weak acidity, enzymes, high concentrations of ROS/GSH, photons, ultrasound, magnetic fields, and radiation. This activation enables the controlled release of drugs, providing a targeted and efficient approach to treatment. Furthermore, srNPs can also be designed to release immunomodulators specifically for primary tumor treatment under controlled release. (B) Additionally, dying cells expressing CRT, HMGB1, and ATP provide "*eat-me*" signals, which are captured by maturing dendritic cells (DCs), helping the maturation process of the DCs themselves, so as to make them capable of efficiently priming $CD8^+$ and $CD4^+$ T cells. The activation of these T cells leads to their accumulation and subsequent attack on both the primary and metastatic cancer sites. CRT, calprotectin; HMGB1, damage-associated molecular pattern molecule released by ferroptotic cells in an autophagy-dependent manner. Taken in whole from Wiley Online Library – Zhang, J., et al., Stimuli-Responsive Nanoparticles for Controlled Drug Delivery in Synergistic Cancer Immunotherapy. Advanced Science, Volume: 9, Issue: 5; Ref. [73] – under Creative Commons License (CC BY 4.0 DEED).

The concentration of a biomolecule at its site of action is believed to influence its pulmonary efficacy. Inhalation delivery may enable faster onset of action (within minutes to hours) on respiratory organs compared to other routes of administration (which may take days) [104]. Moreover, mAbs exhibit slow and minimal systemic absorption following aerosol delivery. Considering this pharmacokinetic/pharmacodynamic behavior, inhalation administration of mAbs reduces the risk of adverse events associated with high systemic bioavailability while increasing the therapeutic efficacy due to localized concentration of the biologics in the lungs [107].

There is currently no approved dry-powder inhaler product for inhaled biologics therapy. As mentioned above, challenges persist in the pulmonary administration of mAbs, particularly in terms of aerosol technology and formulation for inhalation, primarily due to their macromolecular nature [108]. Several anatomical, physiological, and immunological factors influence the effectiveness of inhaled biologics. These factors include the highly complex airway structure, mucociliary clearance, macrophage uptake, pulmonary surfactant, alveolar epithelial permeation, enzymatic metabolism, the post-inhalation cough reflex, low delivery efficiency to specific lung regions, and the ability of inhaled therapies to penetrate cellular phospholipid membranes and maintain therapeutic concentrations intracellularly. These biological barriers pose limitations to the use of inhaled mAbs and the consistent and safe delivery of inhaled particles remains a critical concern. For a comprehensive review of these topics, please refer to the source herein mentioned [80]. Box 2 epitomizes the variety of inhalable biologics that have proposed for treatment or prevention of COVID-19. Aside from certain antibodies like itolizumab, levilimab, and leronlimab, which have been repurposed to alleviate inflammation, the focus of SARS-CoV-2 neutralizing antibodies is primarily on the spike glycoprotein. By targeting this glycoprotein, these antibodies effectively hinder the interaction between the virus and the angiotensin-converting enzyme 2 (ACE2) receptor in the host, thereby preventing the virus from entering host cells [109].

5. Personalized dosage forms

Drug delivery systems can be designed to accommodate individual patient preferences or limitations. For example, transdermal patches offer an alternative to conventional oral medications, providing a non-invasive delivery route for patients who have difficulty swallowing oral formulations. Additionally, customized oral dosage forms, such as modified-release tablets, can allow for personalized dosing schedules based on a patient's daily routines and medication requirements [112], including metronomics [113,114]. It follows that personalized dosage forms aim to optimize drug therapy by considering individual patient

Box 2
Proposed biologics for pulmonary administration in COVID-19.

In response to the urgent need for COVID-19 treatments, several inhalable biologics have been identified and are currently being evaluated in clinical trials. One notable example is HH-120 aerosol, an inhaled decoy receptor comprised of the soluble extracellular domain of ACE2 (sACE2). *In vitro* studies have shown that HH-120 aerosol effectively neutralizes SARS-CoV-2, with Phase I clinical trials being now completed (NCT05116865). Promising results have also been reported for anti-SARS-CoV-2 single-chain variable fragment (scFv) antibodies. Intranasal administration of scFv76, a molecule weighing approximately 28 kDa, completely prevented SARS-CoV-2 infection at a dosage of 74 μg/mouse (~3 mg/kg dose). Notably, nebulized scFv76 efficiently reached the alveolar space, as confirmed by immunohistochemistry assay. Among the biologics, nanobodies have emerged as potential candidates for nebulization due to their small molecular weight (approximately 15 kDa) and favorable biophysical properties. ALX-0171, a nanobody developed as an inhalable anti-RSV drug, has been evaluated in seven clinical trials. Additionally, the anti-SARS-CoV-2 nanobody PiN21 demonstrated efficacy in animal models when administered via aerosol at a minimal dose of 0.2 mg/kg [110]. Inhalation of low doses of medications can also minimize side effects. However, the use of nanobodies derived from camelids is restricted for therapeutic applications in humans. To overcome this limitation, a technology platform for the development of fully human single-domain antibodies (UdAbs) has been recently developed. UdAbs, such as the bispecific UdAb bn03 weighing approximately 28 kDa, have demonstrated a suitable cutoff diameter of 3–5 μm for deposition in the respiratory tract. Intranasal inhalation of bn03 provided robust protection against SARS-CoV-2 infection in both mild and severe mouse models [109]. A new approach to combating viruses involves delivering a recombinant viral trap through inhalation. This trap consists of ten copies of angiotensin-converting enzyme 2 (ACE2) fused to the IgM Fc. Its purpose is to block the entry of SARS-CoV-2 regardless of the specific variations in the viral RBD sequence. It has been found to effectively neutralize all known variants of SARS-CoV-2, including Omicron (BQ.1, BQ.1.1, XBB.1, and XBB.1.5). Moreover, it also shows potency against SARS-CoV-1, human NL63, as well as bat and pangolin coronaviruses. This multivalent trap is capable of providing protection in both preventive and therapeutic scenarios. When administered intranasally, a single dose can shield human ACE2 transgenic mice from viral challenges. Furthermore, this molecule remains stable at room temperature for over twelve weeks and can withstand the physical stress of aerosolization. These findings highlight the potential of a ten-unit ACE2 viral trap as an inhalation solution for ACE2-dependent coronaviruses, both in the current pandemic and any potential future outbreaks.

[111].

factors, treatment goals, and the specific characteristics of the drug. These customized formulations help ensure patients receive the most effective and safe treatment outcomes while addressing their unique needs and requirements. Prototypic examples are: *i*) Modified release formulations: These dosage forms are designed to release the drug in a controlled manner over an extended period. They can be tailored to match the patient's specific dosing schedule, ensuring a consistent drug concentration within the therapeutic range and potentially reducing the frequency of dosing [115–118]; *ii*) Patient-specific doses: Some patients may require specific doses that deviate from standard formulations due to factors such as age, weight, renal or hepatic function, or drug interactions. Personalized dosage forms can be prepared to deliver precise doses that are appropriate for individual patients [119–122]; *iii*) Combination therapy: Personalized dosage forms may involve the combination of multiple drugs in a single formulation, facilitating simplified dosing regimens for patients who require multiple medications for their treatment. This approach improves convenience, reduces the risk of medication errors, and enhances patient adherence [123,124]; *iv*) Pediatric dosage forms: Children often have unique dosage requirements due to differences in physiology and metabolism. Personalized pediatric dosage forms can be formulated to deliver accurate doses that are age-appropriate and easy to administer [125]. These may include liquids, oral dispersible tablets, or flavored formulations to enhance acceptability; *v*) Topical preparations: Some patients may have specific dermatological or localized conditions that require customized topical formulations. Personalized topical dosage forms can be prepared to provide precise drug concentrations, tailored vehicle systems, and appropriate penetration characteristics for optimal therapeutic effects; *vi*) Palliative care dosage forms: For patients requiring palliative care, personalized dosage forms can be developed to meet specific needs, such as liquids, sublingual tablets, or transdermal patches, which provide alternative routes of administration to ensure comfort and ease of use [126–128].

6. Injectable Biologics

Drug delivery systems, on the one hand, have revolutionized the administration of biologic therapies, such as proteins, peptides, and antibodies. These molecules are often highly sensitive and require specialized delivery methods to maintain their stability and therapeutic efficacy [129,130]. Controlled-release platforms, including microneedles or nanocarriers, can ensure proper delivery and protection of these complex therapeutics.

Injectable biologics are a class of therapeutic agents that are administered via injection, typically intravenous, subcutaneous, or intramuscular routes. On the other hand, while injectable biologics have revolutionized the treatment of various diseases, there are several general issues that need to be considered when utilizing these medications: *i*) Administration: Injectable biologics require specialized administration techniques that may involve healthcare professionals or trained individuals. Proper injection technique is crucial to ensure accurate dosing, minimize the risk of infection or injury, and optimize drug delivery [131–133]; *ii*) Stability: Many injectable biologics are sensitive to various environmental factors, such as temperature, light, and agitation. It is essential to handle and store these medications correctly to maintain their stability and efficacy. Deviations from recommended storage conditions can result in decreased potency or even degradation of the biologic, compromising its therapeutic effect [131,134]; *iii*) Immunogenicity and potential for autoimmunity: Injectable biologics, being foreign to the body, have the potential to elicit an immune response. The immune system may recognize the biologic as a foreign substance, leading to the production of anti-drug antibodies, which may further cross-react with the host's own tissue antigens, owing to molecular mimicry [135]. The presence of anti-drug antibodies can impact the biologic's efficacy, leading to potential loss of response or adverse effects [136,137]; *iv*) Safety and adverse events: While generally safe, injectable biologics can be associated with specific adverse events [138,139]. These may include local reactions at the injection site (such as

pain, redness, or swelling), infusion-related reactions (such as fever, chills, or allergic reactions), or systemic side effects specific to the biologic's mechanism of action. Close monitoring and patient education are essential to identify and manage any potential adverse events; *v*) Patient compliance and self-injection: Some injectable biologics are suitable for self-administration by patients or their caregivers, particularly for chronic diseases. Ensuring proper training, education, and ongoing support are vital to empower patients and caregivers to self-inject safely and effectively. Issues such as needle anxiety, fear of injections, or difficulties with self-injection techniques may impact patient compliance and treatment adherence; *vi*) Dosing and treatment monitoring: Injectable biologics often require individualized dosing regimens based on factors such as patient body weight, disease severity, and response to therapy. Regular monitoring of treatment response and appropriate dose adjustments are necessary to optimize therapeutic outcomes. This may involve laboratory tests, clinical assessments, or imaging studies depending on the specific indication [140,141].

The difficult issue of selecting optimal doses of biologics administration is clearly exemplified by the licensed doses of approved COVID-19 vaccines, as discussed at large in Ref. [142]. Despite the widespread administration of more than 13 billion doses of COVID-19 vaccines globally, there has been limited emphasis on determining the best dosage. To address this issue, an extensive review has examined the results of initial phase trials conducted on the nine COVID-19 vaccines approved by the World Health Organization. The objective was to gather information on the study design, reactogenicity (adverse reactions), and early findings on humoral immune responses. The administered doses varied significantly across the vaccines, ranging from 1 to 7, with varying numbers of participants per dose (ranging from 15 to 190). As expected, adverse reactions tended to increase in frequency and severity with higher doses. However, most reactions were manageable from a clinical perspective. Higher doses generally elicited stronger immune responses, although the differences between the highest and second-highest doses assessed were typically modest, amounting to less than a 1.6-fold increase in binding antibody concentration and neutralizing antibody titer. Some limitations in the trial designs were also identified, including a limited number of evaluated doses, long intervals between consecutive doses, or inadequate sample sizes. It should be noted that these limitations do not imply any criticism toward the study investigators, who faced immense time pressures during the early stages of the pandemic. Consequently, a valid concern emerged regarding whether the single dose used in clinical efficacy trials, subsequently authorized by regulatory agencies, is truly optimal [142].

7. Gene therapy

Advances in drug delivery systems have greatly contributed to the development of personalized gene therapy [143–145]. The efficient and targeted delivery of therapeutic genes to specific cells or tissues is critical for successful gene-based interventions. Viral vectors, lipid nanoparticles, or polymer-based systems are being explored to enhance the delivery efficiency and safety of gene therapies, allowing for individually tailored treatment strategies. Gene therapy has immense potential in tackling diseases at their genetic roots by introducing, countering, or replacing genes. Various technologies, including RNA interference [146], genome editing [147], DNA transformation [148], and mRNA vaccines [149], have been extensively explored to modulate gene expression for treating diverse diseases. However, the success of gene therapeutics is hindered by several intracellular and extracellular barriers. These include rapid clearance in the bloodstream, insufficient accumulation at the target site, suboptimal cellular uptake, and low transfection efficiency [150].

Nevertheless, the field of gene delivery has witnessed significant advancements, with a focus on developing delivery systems that enhance the bioavailability and biocompatibility of gene therapeutics [151–153]. One notable approach is the utilization of bioinspired and biomimetic strategies, drawing inspiration from natural processes and imitating the desirable features and functions of viruses, bacteria, exosomes, and eukaryotic cells. By integrating bioinspired and biomimetic designs, these delivery systems can overcome biological barriers, improve the pharmacokinetic profile, and efficiently transport gene therapeutics to target cells. This helps amplify therapeutic efficacy while minimizing side effects, thus facilitating the clinical translation of gene therapy. We [11,66] and others [154] have recently presented the latest advancements in designing bioinspired or biomimetic delivery systems, highlighting their advantages and addressing the challenges that can be overcome through rational designs.

8. Wearable drug delivery

The advent of wearable technologies has enabled personalized drug delivery systems that can continuously monitor and provide medication as needed. For instance, smart insulin pumps can measure glucose levels and automatically administer appropriate doses of insulin to individuals with diabetes. Such devices optimize drug delivery based on real-time data, enhancing patient convenience and management of chronic conditions. Prototype examples of wearable drug delivery systems include: *i*) Transdermal patches [155–157]: Transdermal patches are adhesive patches that adhere to the skin and deliver medication through the skin barrier. They can continuously release drugs over an extended period, allowing for controlled and sustained drug delivery. Transdermal patches are commonly used for delivering medications such as nicotine, hormones, pain relievers, and cardiovascular drugs; *ii*) Insulin pumps [158,159]: Insulin pumps are wearable devices used by individuals with diabetes to deliver a continuous supply of insulin. These small devices are usually worn on a belt or carried in a pocket and feature a thin, flexible tube (catheter) inserted under the skin to deliver insulin into the body. Insulin pumps allow for personalized insulin delivery, mimicking the natural insulin release of the pancreas; *iii*) Inhalation devices [160]: Wearable inhalation devices are designed to deliver medication directly to the respiratory system. Examples include inhalers or nebulizers that can be worn as belt-mounted or portable devices. These devices convert liquid medication into a fine mist or aerosol, allowing it to be easily inhaled into the lungs for targeted drug delivery; *iv*) Smart wearable injectors [161]: Smart wearable injectors are portable devices worn on the body that deliver medication through subcutaneous injections. These devices are often reusable and can be pre-programmed to deliver precise doses of medication at specific times. They are commonly used for treatments such as insulin delivery, growth hormone therapy, and fertility treatments; *vi*) Smart contact lenses [162]: Smart contact lenses are being developed as a potential platform for drug delivery to the eye. These lenses can contain microreservoirs or nanotechnology-based systems that release medication gradually onto the surface of the eye. They have the potential to provide controlled and continuous drug release for conditions such as glaucoma or ocular inflammation.

These are just a few examples of wearable drug delivery systems that showcase the possibilities of incorporating drug delivery functionality into wearable devices. Ongoing advancements in technology continue to drive the development of innovative wearable drug delivery systems to enhance patient comfort, convenience, and treatment outcomes.

9. Smart nanoparticles in cancer therapy

Various approaches have been employed to create nanocarriers tailored for conveying chemotherapeutic drugs in cancer. The overall issue deals with the applications of nanomaterials with the typical techniques used to refine targeted drug carriers vs. the specific successful carriers designed for conveying chemotherapeutic drugs that work as smart nanoparticles, which can respond to biological cues or be guided by them, and are emerging as a promising drug delivery platform for precise cancer treatment [163]. Smart nanoparticles include polymeric nanoparticles [164], dendrimers [165], micelles [166], liposomes

[167], protein nanoparticles [168], cell membrane nanoparticles [169], mesoporous silica nanoparticles [170], gold nanoparticles [171], iron oxide nanoparticles [172], quantum dots [173], carbon nanotubes [174], black phosphorus, MOF nanoparticles, and others [169,175]. In particular, a polymeric blueprint typically refers to a design or framework for the creation of drug delivery systems using polymers, which are large molecules composed of repeating subunits. In the context of drug delivery, polymeric blueprints are essentially the structural basis for creating carrier systems that can effectively transport therapeutic drugs to specific targets in the body. These blueprints allow for the development of nanocarriers and other drug delivery vehicles that utilize polymers as a key component in their design and function. For instance, when utilizing nanotechnology to transport drugs via polymeric blueprints, typically, three sorts of targeting strategies are utilized: passive, active, and stimuli-responsive targeting [174]. Passive targeting, also known as the enhanced permeability and retention (EPR) effect, capitalizes on the leaky vasculature within solid tumor formations, enabling particles of a particular size to penetrate and gather within tumor tissues [176–178]. After the drug is released, these biocompatible polymers are eventually cleared through the excretory system. Despite the EPR effect's ability to enhance drug accumulation, there are several hurdles, including high interstitial fluid pressure in tumor tissues, the requisite tissue penetration depth for therapeutic drugs, and the accumulation of these particles in the liver and spleen. Consequently, additional targeting strategies are needed to augment the distribution of the therapeutic macromolecules [179]. Active targeting methods utilize tumor-specific receptor ligands to achieve a level of specificity, serving as a promising supplementary strategy to the EPR effect [180]. In a recent analysis, the focus is on advancements in nanomodulators targeting the tumor microenvironment, covering drug delivery and drug-free approaches. The review examines nanomodulators designed to work alongside various immunomodulatory agents, such as gene tools (mRNA, siRNA, miRNA, plasmid DNA, and CRISPR system), cytokines, immune agonists, and inhibitors. It also discusses newly developed drug-free nanomodulators aimed at altering the physical and biological properties within the microenvironment of solid tumors. Additionally, the analysis provides integrated insights into the future development and challenges of nanomodulators in supporting cancer immunotherapy [181].

10. Companion diagnostics

Drug delivery systems can be combined with companion diagnostics to guide personalized treatment decisions. Biomarker-based assays can identify patients who are likely to respond to specific medications, allowing for targeted drug administration. For instance, therapeutic drug monitoring systems can assess drug levels in a patient's blood to ensure optimal dosing and minimize adverse effects [182]. Noteworthy examples of companion diagnostics are: *i*) HER2/neu Companion Diagnostic: In breast cancer treatment, HER2/neu testing is crucial. A companion diagnostic is used to identify patients with HER2-positive tumors who are likely to benefit from targeted therapy like Herceptin [183]; *ii*) KRAS Companion Diagnostic: KRAS mutations affect the response to certain cancer treatments such as EGFR inhibitors. A companion diagnostic helps identify patients with wild-type KRAS genes who may benefit from these targeted therapies; *iii*) EGFR Companion Diagnostic [184]: In lung cancer, EGFR mutations are important for determining the response to EGFR inhibitors like erlotinib [185] or gefitinib [185]. Companion diagnostics can identify patients with EGFR mutations who are most likely to respond well to these treatments; *iv*) BRAF Companion Diagnostic: In metastatic melanoma, mutations in the BRAF gene are indicative of responsiveness to targeted therapies such as Vemurafenib or Dabrafenib. A companion diagnostic helps identify patients with BRAF V600E or V600K mutations who may benefit from these treatments [186].

The concept of companion diagnostics, indeed – as epitomized by the term "theranostics" – refers to the integration of diagnostics and therapeutics into a single approach for personalized medicine [187–190]. Theranostics combines therapeutic interventions and diagnostic tools to select the most effective treatment based on individual patient characteristics (Box 3). It allows for the targeted delivery of specific treatments to patients who are most likely to benefit from them. In the context of companion diagnostics, a companion diagnostic test is developed hand in hand with a specific therapeutic product. It helps identify which patients are most likely to respond positively to the therapy and those who are at a higher risk of adverse reactions. Companion diagnostics enable healthcare providers to make well-informed treatment decisions by selecting patients who are likely to derive the most benefit from the therapy while reducing unnecessary exposure and potential harm to non-responsive patients. Theranostics, therefore, embodies the

Box 3
Theranostics and Nanomedicine.

Nanomedicine, the application of nanotechnology in medicine, relies on various medical and scientific methods. One such method involves using nanoparticles in theranostics. The primary goal of combining nanomedicine and theranostics is to significantly enhance disease and patient-specific outcomes. Nanoparticles have the ability to target specific organs or tissues and can be manipulated for multifunctionality, making them highly advantageous for use in theranostic medicine. In accordance with the previous statement, nanoparticles can target diseased areas in the body, thus avoiding harm to healthy tissues. Once the target area is identified, nanoparticles can provide information about the extent of the disease and even indicate the response to treatment, if applicable. Following the acquisition of this information, nanoparticles can proceed with delivering the necessary therapy. By responding to internal or external stimuli, these nanoparticles can administer precise concentrations of therapeutic agents. Moreover, they can also play a role in monitoring drug delivery, release, and effectiveness in that nanoparticles have the ability to evade premature destruction. Of interest, a new electrochemical test for detecting 17-β-estradiol (E2) was recently suggested. The process involves altering a glassy carbon electrode (GCE) with a nanocomposite comprising α-Fe_2O_3 nanoparticles supported on carbon nanotubes (CNTs) - referred to as α-Fe_2O_3-CNT/GCE. The α-Fe_2O_3-CNT nanocomposite was created through a cost-effective hydrothermal process. Morphological and chemical characterization were conducted using scanning electron microscopy (SEM), Raman spectroscopy, and energy-dispersive X-ray spectroscopy (EDX). The presence of the α-Fe_2O_3-CNT film on the GCE surface improved the electrochemical response to E2, preventing electrode surface fouling and reducing the decrease in peak current intensity during E2 oxidation. These findings support the rationale for modifying the GCE. After optimizing experimental conditions, E2 was measured using the square wave voltammetry technique with a 0.1 mol L^{-1} KCl solution (pH = 7.0) and 20% ethanol as a supporting electrolyte. A linear concentration range of 5.0–100.0 nmol L^{-1} and a low limit of detection of 4.4 nmol L^{-1} were achieved. The electroanalytical method utilizing α-Fe_2O_3-CNT/GCE was used to analyze E2 in pharmaceutical, lake water, and synthetic urine samples. The results were confirmed via recovery tests and high-performance liquid chromatography as a comparative technique at a 95% confidence level. Consequently, the developed electrochemical sensor is straightforward and quick to obtain, delivers high accuracy, and is applicable for routine E2 analysis [192].

integration of both diagnostic and therapeutic components to guide the selection, monitoring, and optimization of personalized treatment plans. For example, in cancer theranostics, specific molecular markers or genetic alterations are identified through companion diagnostics that indicate the presence or absence of specific therapeutic targets. This helps physicians determine the most suitable targeted therapy or approach to treat the patient's cancer. By employing companion diagnostics and theranostics, healthcare providers can maximize treatment efficacy, minimize adverse effects, and ultimately improve patient outcomes. These approaches align with the personalized medicine paradigm, aiming to tailor treatments to individual patients based on specific clinical, genetic, or molecular characteristics [191].

It should be noted that theranostics is still in its infancy, aiming at combining diagnostic and therapeutic capabilities to create personalized treatment strategies for various diseases, including cancer. In the context of cancer treatment, theranostics involves the use of diagnostic techniques to identify specific molecular targets or biomarkers associated with the patient's cancer, followed by the administration of targeted therapeutic agents that are tailored to the individual's unique disease characteristics. The process typically involves the following steps:

i. Diagnosis and Molecular Imaging: Theranostics starts with the use of advanced imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT), to visualize specific molecular targets or receptors within the patient's tumor cells. This allows physicians to identify the presence of specific biomarkers that can be targeted for treatment.
ii. Selection of Targeted Therapy: Once the molecular characteristics of the cancer have been identified through diagnostic imaging, healthcare providers can select a targeted therapeutic agent that is designed to specifically interact with the identified molecular targets. These targeted therapies may include radiopharmaceuticals, which are drugs that contain a radioactive isotope and are designed to deliver radiation directly to cancer cells.
iii. Treatment and Monitoring: The selected targeted therapy is administered to the patient, with the goal of selectively destroying cancer cells while minimizing damage to healthy tissues. The response to treatment can be monitored using imaging techniques to assess the effectiveness of the therapy and make adjustments as needed.

By integrating diagnostic imaging with targeted therapy, theranostics offers the potential for more precise and effective treatment of cancer. This personalized approach can lead to better outcomes and reduced side effects compared to traditional, non-targeted treatments. Additionally, theranostics holds promise for identifying suitable treatment options for patients whose cancers may not respond well to standard therapies.

11. Personalized medicine

In personalized medicine, theranostics can be applied in various ways using drug delivery systems: *i*) Diagnostic nanoparticles: Nanoparticles can be designed to carry both diagnostic and therapeutic components. These nanoparticles can be engineered to specifically target diseased cells or tissues and deliver both diagnostic agents, such as contrast agents or molecular probes, and therapeutic agents to the desired site simultaneously. This enables real-time monitoring of disease progression and treatment response while delivering targeted therapy to the affected area; *ii*) Image-guided drug delivery: Advanced imaging techniques, such as ultrasound, MRI, or nuclear imaging, can be employed to guide the delivery of therapeutic agents. Using image guidance, drug delivery systems can be precisely directed to the target site, ensuring accurate and efficient drug distribution. This approach allows for real-time monitoring of drug delivery and localization, optimizing treatment efficacy; *iii*) Therapeutic drug monitoring: Drug delivery systems can also incorporate sensors or biosensors to monitor drug levels or biomarkers in the body. This feedback can be used to adjust drug dosing or delivery rates for personalized medication regimens. For example, implantable devices can continuously monitor drug levels in the bloodstream and trigger drug release accordingly, ensuring therapeutic drug levels are maintained; *iv*) Personalized nanomedicine: Theranostic approaches can integrate patient-specific data, such as genetic profiles, molecular markers, or imaging findings, to customize the design of drug delivery systems. Tailored nanoparticles or nanocarriers can be engineered to deliver therapeutics to specific disease subtypes or biomarker-driven targets. This personalized nanomedicine approach maximizes treatment efficacy while minimizing off-target effects.

By combining diagnostics and therapeutics, theranostics can guide personalized treatment decisions and optimize drug delivery systems for improved patient outcomes. It enables the selection of the most appropriate drug delivery strategy based on individual patient characteristics and disease status, leading to better-targeted therapies and more effective treatment responses. Box 4 provides examples of theranostics applications. These examples demonstrate how theranostics combines diagnostics and therapeutics to provide personalized treatment strategies and improved patient outcomes. By integrating diagnostic imaging with targeted drug delivery, theranostics enables precise disease detection, ongoing monitoring, and tailored therapy administration, thereby offering significant potential for advancing personalized medicine.

12. Theranostics in inflammatory diseases and the olistic approach

Theranostics in the context of inflammatory diseases involves utilizing diagnostic tools to identify specific molecular or cellular targets associated with the disease and combining them with therapeutic interventions to guide personalized treatment strategies. This approach aims to optimize therapeutic outcomes by tailoring treatments to individual patients based on their unique disease characteristics and response to therapy. In the field of inflammatory diseases, theranostics plays a crucial role in identifying and targeting key pathways and mechanisms involved in inflammation. By combining diagnostics and therapeutics, clinicians can better understand the underlying immune processes driving the disease and choose the most appropriate therapeutic interventions. Immunometabolism, on the other hand, focuses on the relationship between metabolism and immune system function. It explores how metabolic pathways and cellular energy production impact immune cell activation, differentiation, and inflammatory responses. Aberrations in immunometabolism have been implicated in the pathogenesis of various inflammatory diseases. Theranostics in inflammatory diseases can leverage the knowledge of immunometabolism to develop personalized treatment approaches. By understanding the metabolic profiles of patients and affected tissues, clinicians can identify specific metabolic pathways dysregulated in inflammatory diseases. This information can then be used to select or develop targeted therapies that modulate immune cell metabolism, restoring balance and reducing inflammation [198].

For example, in conditions like rheumatoid arthritis or inflammatory bowel disease, theranostic approaches can involve identifying specific biomarkers [199] or genetic signatures [200] associated with the disease to guide therapy selection. This may include using diagnostic tests to detect specific cytokines, cell surface markers, or genetic mutations, and matching them with targeted therapies designed to modulate these pathways.

The incorporation of immunometabolism understanding into theranostics presents exciting prospects for tailored treatment in inflammatory diseases. This integration not only facilitates the selection of appropriate therapies but also paves the way for innovative approaches

Box 4
Examples of theranostics applications.

1. *Prostate Cancer Theranostics*: Prostate-specific membrane antigen (PSMA) is a protein that is overexpressed in prostate cancer cells. Theranostic approaches utilize PSMA-targeted imaging and therapy to diagnose and treat prostate cancer. For diagnosis, PSMA-based imaging agents tagged with radioactive isotopes, such as Gallium-68 or Fluorine-18, can be used to detect PSMA-positive tumors through PET imaging. Following diagnosis, PSMA-targeted nanoparticles or radiolabeled agents can be used to deliver therapeutic agents, such as chemotherapy drugs or radionuclides, directly to the prostate cancer cells for treatment [193]. 2. *Precision Oncology Theranostics*: In precision oncology, theranostics can aid in personalized treatment selection for cancer patients. Molecular profiling and genetic testing can identify specific mutations or biomarkers in tumors. This information can guide the selection of theranostic agents that target those specific markers. For example, human epidermal growth factor receptor 2 (HER2)-targeted theranostic agents can be utilized in breast cancer patients with HER2-positive tumors to not only diagnose and monitor the disease but also deliver HER2-targeted therapies like trastuzumab or antibody-drug conjugates [194,195]. 3. *Theranostics in Cardiology*: In cardiology, theranostic approaches can provide real-time monitoring of cardiac conditions while delivering targeted therapies. For example, nanoscale systems loaded with cardiac biomarkers or imaging contrast agents can be used to visualize and track the progression of cardiovascular diseases using imaging techniques like MRI or ultrasound. Simultaneously, these systems can deliver therapeutic agents like anti-inflammatory drugs or growth factors to promote cardiac tissue regeneration and repair. An example of theranostics in cardiology is the use of positron emission tomography imaging with a radioactive glucose analog (FDG) to detect inflammation in atherosclerotic plaques. This information can then be used to guide the delivery of therapies that specifically target the inflamed plaques to mitigate the risk of cardiovascular events [196]. 4. *Neurodegenerative Disease Theranostics*: In neurodegenerative diseases like Alzheimer's or Parkinson's, theranostics can be used for early diagnosis, monitoring disease progression, and targeted drug delivery to affected brain regions. Radiolabeled ligands targeting disease-specific protein aggregates or imaging agents can help identify neurodegenerative biomarkers through PET or Magnetic Resonance Imaging (MRI) scans. Moreover, theranostic systems can deliver neuroprotective agents, gene therapies, or potential disease-modifying drugs to specific areas of the brain, aiming to slow disease progression or enhance neuronal regeneration. One example of theranostics in neurodegenerative diseases is the use of positron PET imaging with radiolabeled amyloid tracers to detect and quantify amyloid-beta plaques in the brains of individuals with Alzheimer's disease. This imaging technique can provide valuable information about the presence and extent of amyloid pathology, aiding in early diagnosis and disease staging. Furthermore, this diagnostic information can also be used to identify suitable candidates for targeted therapies, such as anti-amyloid antibody treatments that specifically target and clear amyloid plaques from the brain. In this way, theranostics can enable more accurate diagnosis, treatment selection, and monitoring of neurodegenerative diseases. 5. *Infectious Disease Theranostics*: Theranostics can also be applied to infectious diseases. For instance, in bacterial infections, nanoparticles can be designed to target bacterial cell markers or enzymes specific to the infectious agent. These nanoparticles can deliver antibiotics directly to the site of infection while simultaneously providing imaging capabilities to monitor the treatment response and disease resolution [197].

specifically targeting metabolic pathways involved in immune dysregulation. By personalizing treatment based on these insights, we have the potential to enhance treatment outcomes, minimize side effects, and elevate overall patient care in the realm of inflammatory diseases.

Finally, as to targeted therapy, theranostic approaches can be used to develop targeted therapies that specifically address the presence of bacterial metabolites. For example, in the context of infections, theranostics can facilitate the development of antibacterial agents that are selectively activated in the presence of specific bacterial metabolites, allowing for precise and localized treatment while minimizing off-target effects. By analyzing the profile of bacterial metabolites in an individual's microbiome, theranostics can contribute to personalized treatment strategies. This approach can help identify the most effective therapies for conditions influenced by the composition of the microbiota, such as certain gastrointestinal disorders and metabolic diseases [201].

13. Green nanomaterials

Green nanomaterials refer to nanoscale substances that are derived from sustainable and environmentally friendly sources, or are manufactured using processes that minimize harm to the environment. These materials offer the potential for a wide range of applications across various fields, including healthcare, clean energy, environmental remediation, and more. Due to their eco-friendly nature, green nanomaterials are becoming increasingly important in the development of innovative and sustainable technologies. Their use can lead to reduced environmental impact, improved resource efficiency, and minimized ecological footprint. In the context of healthcare, green nanomaterials can contribute to the development of biological sensors, drug delivery systems, and diagnostic tools with reduced environmental impact and enhanced biocompatibility. Embracing green nanomaterials in research and product development represents a step forward in creating more sustainable and environmentally conscious technologies [202].

14. Limitations and challenges of nanoparticles

NPs still face several delivery barriers, including nonspecific serum protein interactions, rapid clearance, off-target localization, and degradation in the endosome. Furthermore, mRNA delivery induces transient protein production, requiring repeated administration for sustained expression. Finally, the development of anti-PEG antibodies raises concerns about potential allergic responses to LNPs; Pfizer–BioNTech BNT162b2 and Moderna mRNA-1273 mRNA vaccines against COVID-19, viral mRNA, or oligonucleotides thereof may exert dual effects – including potent proinflammatory activity or, vice versa, immune suppression – depending on dosage and predominant target cell type due to direct interactions with Toll-like receptors (TLRs), a class of proteins that play a key role in the innate immune system [203]. Lipid-based nanocarriers are mostly internalized by accessory cells of the immune system that are present in peripheral lymphoid tissues, via either phagocytosis or receptor-mediated endocytosis. The size of nanoparticles is key to the mechanism whereby uptake occurs, which, in turn, accounts for the size-dependent immunogenicity of particles [204]. Nanocarriers less than 150 nm are taken up by clathrin-mediated endocytosis, whereas particles in the size range of micrometers undergo phagocytosis [205]. The phospholipids present in the nanocarriers have a key role in the initiation of innate immune responses.

With a view to initiating the desired immune response, the composition of the nanocarriers can be adjusted through actions on the physicochemical properties of the vesicles, including size, charge, and type of phospholipid, and surface modifications such as attachment of a targeting moiety. Cationic lipids are found to be more effective vaccine adjuvants in comparison to anionic and zwitter ionic lipids due to a

stronger electrostatic interaction between the cationic lipid-based nanocarrier and the negatively charged moieties on the membrane of the accessory cells [205], thus fostering fusion of nanocarriers, its cellular uptake and concomitant release of the antigen payload. The immunoenhancing effects of a wide range of cationic lipid carriers have been described, with the most widely studied being cationic lipids such as dimethyl dioctyldecylammonium and 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP) [206]. Once recognition, fusion, and cellular uptake have all occurred, the antigens are processed within the antigen-presenting cells and presented to MHC class I or class II molecules. MHC class II presentation results in activation of the T-helper cells, thus stimulating antibody production and cellular immunity as well. In general, exogenous pathogen peptide antigens or toxins are usually presented to Major Histocompatibility Complex (MHC) Class II molecules, whereas Class I MHC plays a critical role in the adaptive immune response by binding to peptides processed by Proteasome and Transporter associated with antigen processing complex and presenting them on the cell surface to cytotoxic T-cells. However, the induction of immune response through vaccination necessitates the presentation of exogenous antigens to MHC Class I molecules. This is usually referred to as cross-presentation, which eventually leads to the generation of cytotoxic T-lymphocytes [207]. Relevant in this regard is therefore the finding that lipid-based nanocarriers are also found to exhibit the 'depot effect' that allows retention of the antigen at the site of injection, thereby enhancing the time of vaccine exposure to cells of the immune system [208]. Optimizing LNP is as yet un unsolved problem for delivery in primates: LNP parameters – and mostly size – that have historically been optimized in rodents and found that seemingly innocuous changes result in large potency differences between species [15].

15. Future directions in targeted drug-delivery systems of biologics

The future of drug delivery systems holds immense potential for revolutionizing the field of medicine, particularly regarding intracellular delivery of protein drugs and achieving selectivity for target recipient cells or tissues. Here are some major future directions in this domain:

i. Nanotechnology-based Delivery Systems: Nanoparticles and nanocarriers offer promising strategies for intracellular protein drug delivery. With their precise control over size, surface properties, and drug loading capacity, nanoparticles can effectively penetrate cell membranes and deliver proteins directly into the cytoplasm or specific organelles. Advances in nanotechnology may enable improved targeting, enhanced stability, and controlled release of protein drugs within cells [209].
ii. Cell-Penetrating Peptides (CPPs): CPPs are short amino acid sequences that can facilitate the cellular uptake of various cargo molecules, including proteins. These peptides can be engineered to possess selectivity for specific cell types or tissues. Future research may focus on designing CPPs that offer high selectivity, minimal toxicity, and efficient delivery of protein drugs to desired intracellular targets [210,211].
iii. Ligand-Receptor Interactions: Exploiting specific ligand-receptor interactions can aid in achieving selective targeting of protein drugs to particular cell types or tissues. By attaching ligands to protein drugs or delivery systems, it becomes possible to bind to specific receptors on target cells, enhancing the selectivity of delivery [11,66].
iv. Gene-Based Therapies: Gene therapies hold promise for intracellular delivery of proteins by utilizing genetic constructs that produce therapeutic proteins inside target cells. Techniques such as viral vectors, non-viral delivery systems, and gene editing technologies (e.g., CRISPR-Cas9) present exciting avenues for precise and selective intracellular protein delivery [45,212].
v. Bioresponsive Delivery Systems: Developing delivery systems that respond to specific triggers or biomarkers within target cells can enhance selectivity in protein drug delivery. These systems can be engineered to release proteins in response to particular intracellular signals or conditions encountered within target tissues. In particular, Responsive Drug Delivery Systems (DDSs) have the potential to revolutionize healthcare by facilitating precision medicine. By harnessing pH, temperature, enzyme, and redox responsiveness, these innovative systems can achieve enhanced therapeutic outcomes, as evidenced by the case studies presented. Nevertheless, several challenges remain, including the intricate design and optimization of bio-based materials, which play a critical role in the successful translation of these systems from the laboratory to clinical practice. Recent advancements in magnetically and temperature-responsive DDSs demonstrate promising developments for healthcare applications. However, to fully realize their potential, it is essential to address concerns related to stability, durability, penetration depth, sensitivity, and the implementation of active targeting strategies. The future of responsive DDSs envisions the integration of therapeutic and diagnostic functionalities into theranostic systems that cater to personalized healthcare needs. Bio-based materials emerge as a pivotal element in this vision, offering a nuanced approach to tackling complex diseases such as cancer and diabetes. The emergence of these materials holds the potential to reshape the healthcare landscape by enabling tailored and effective treatments [213].
vi. Combination Therapies: Combining protein drugs with other therapeutic modalities, such as small molecules or nucleic acids, can improve targeting selectivity and the overall efficacy of treatment. Synergistic approaches that simultaneously target multiple pathways within recipient cells or tissues may offer enhanced therapeutic outcomes [214].
vii. Advanced Imaging Techniques: Advancements in imaging technologies can aid in characterizing and optimizing drug delivery systems. Techniques such as live-cell imaging, fluorescence microscopy, and advanced imaging modalities enable real-time visualization of intracellular drug release and distribution, facilitating the development of more effective delivery strategies [215].

Overall, the future of drug delivery systems lies in achieving efficient and selective intracellular delivery of protein drugs. Advances in nanotechnology, ligand-receptor interactions, gene therapies, bioresponsive systems, combination therapies, imaging technologies, and further understanding of cellular biology are expected to drive innovation in this field, ultimately enhancing therapeutic outcomes and enabling personalized medicine approaches.

16. Conclusions

The biodrug market is experiencing rapid growth, leading to increased innovation in device design and discussions about traditional injectables versus oral, inhalatory and alternative forms medication. As regulators approve more biologics that can replace daily conventional-drug regimens, especially long-acting medications that enhance patient compliance, it prompts the question of whether biodrugs will become the standard in the future. Conventional injectables such as prefilled syringes, auto-injectors, and pen-injectors are expected to gain popularity due to their convenience and potential for at-home delivery. This push for more efficient devices is driven by the need to treat chronic and age-related conditions like diabetes and arthritis. Additionally, the COVID-19 pandemic has emphasized the importance of improved remote self-administered care, signaling the arrival of novel biologic formulations.

Evidence of this trend is evident in the FDA's approval of leqvio

(Inclisiran) from Novartis in 2021. This long-acting injectable medication, the first of its kind, utilizes siRNA to reduce LDL cholesterol levels. With just two maintenance doses per year, leqvio effectively controls "bad" cholesterol levels. Compared to a placebo, leqvio can sustain LDL reduction by up to 52% for certain patients with atherosclerotic cardiovascular disease who are already on maximally tolerated statin therapy. This disease occurs due to the buildup of lipids on the inner lining of arteries, and its complications, like heart attacks and strokes, account for the majority of cardiovascular disease deaths [216].

Diabetes is another area where long-acting injectables are being developed. In 2021, a study led by Harpreet S. Bajaj of LMC Diabetes and Endocrinology Brampton in Ontario, Canada, found that a new once-a-week injectable insulin therapy was as safe and effective as daily injections for people with Type 2 diabetes. Traditional diabetes treatment has relied on daily insulin injections, which can be painful, inconvenient, and stigmatizing for some patients. A once-a-week insulin treatment that is both effective and safe would be a significant breakthrough [217].

One legitimate question may be if all of the potential therapeutic modalities summarized here represent solid alternatives to existing therapeutics. Overall, the use of nanotechnology in biomedicine represents a solid alternative to existing therapeutics due to several reasons:

- Targeted Delivery: Nanoparticles can be designed to specifically target diseased cells or tissues, minimizing off-target effects and enhancing the therapeutic efficacy of drugs.
- Enhanced Pharmacokinetics: Nanoparticles can improve the pharmacokinetic profile of drugs, including prolonged circulation times, improved bioavailability, and controlled release kinetics.
- Multifunctionality: Nanoparticles can be engineered to carry out multiple functions simultaneously, such as imaging, drug delivery, and diagnostics, offering a versatile platform for therapeutics.

In conclusion, an up-to-date review of nanotechnology for biomedical applications is crucial for advancing the field, identifying research gaps, and proposing novel approaches. By describing the most important data in a homogeneous manner, researchers can reinforce the relevance of novel alternatives, ultimately contributing to the development of solid alternatives to existing therapeutics.These innovative solutions represent the driving force behind the global connected drug delivery market, which is projected to experience double-digit growth rates over the next decade. However, changing a drug's primary packaging is not always a straightforward process. It can be costly, time-consuming, and require validation or revalidation of various parameters like container closure integrity, biocompatibility, stability, reformulation, extractables, and leachables. As a result, pharmaceutical companies often resort to existing delivery systems that may not be the most suitable fit for a new application. Nevertheless, with the increasing range of potential drug administration uses and the effectiveness of connected technology in facilitating remote monitoring of self-medication programs, investing in the innovation of drug delivery systems will soon become imperative.

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CRediT authorship contribution statement

Giovagnoli Stefano: Investigation, Conceptualization. **Ricci Maurizio:** Data curation. **Puccetti Matteo:** Conceptualization. **Pariano Marilena:** Data curation. **Schoubben Aurélie:** Data curation.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author's contribution

All authors equally contributed to conceptualization, writing and editing. All authors have read and agreed to the published version of the manuscript.

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