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Advancements in Nanoparticle-Based Precision Drug Delivery: A Review of Development and Optimization for Targeted Therapy in Preclinical Models

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Abstract

In recent years, the widespread adoption of nanoparticles has expanded across a broad spectrum of clinical domains. These nanoparticles have been specifically engineered to address the limitations associated with conventional therapeutics and to navigate various biological barriers—ranging from systemic to cellular levels—that manifest heterogeneity across different patient populations and disease states. The advent of precision treatments, wherein interventions are tailored to individual patients, has contributed to mitigating this variability among patients. Nonetheless, the predominant focus in current nanoparticle research remains on enhancing the uniformity of delivery systems. The realization of precision medicine appears imminent as lipid-based, polymeric, and inorganic nanoparticles are increasingly crafted with heightened precision, facilitating more individualized approaches to medication delivery. In this review, we delve into the advanced designs of nanoparticles employed in both precision and generalized applications, offering insights into their potential to advance precision medicine. Our

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discussion centers on the innovations in nanoparticle design aimed at overcoming various delivery challenges, suggesting that ingenious nanoparticle engineering holds promise for enhancing performance across a broad spectrum of delivery applications and facilitating tailored designs for specific therapeutic targets, ultimately leading to improved patient outcomes.

Keywords: Nanoparticles, Clinical applications, biological barriers, Systemic barriers, Microenvironmental barriers, Cellular barriers, Patient heterogeneity, Precision therapeutics, Personalized interventions, Optimization

Introduction

Nanomedicine has risen as a significant area of scholarly exploration, directly influencing human health. Although an initial wave of products has been effectively brought to market, greatly improving patient well-being, advancements in material engineering and the arrival of novel therapeutics are propelling the creation of more intricate systems. With the field evolving, it becomes crucial to grasp the hurdles associated with nanoparticle commercialization to streamline the journey to clinical application with greater effectiveness and predictability (Ragelle et al. 2017). Engineered nanomaterials show great potential in diagnostics and treatment of diseases with a higher accuracy achieved. It is a nanotechnology application that helps to overcome some problems with drug delivery by traditional routes, for instance, biodistribution and crossing intracellular barriers. For example, targeting cells and sliding the molecules to specific organelles create room for more scientific breakthroughs. The establishment of the National Nanotechnology Initiative (NNI) by the US National Science and Technology Council (NSTC) in 2000 was done to bring nanotechnologies to the commercially viable stage, with special focus being given to nanoparticle (NP) research.

Nanoparticles (NPs) have recently emerged as promising alternatives to increase intravenous drug stability, solubility, efficiency, and longevity for better safety and efficacy (Zhuang et al., 2019). Hence, there is a high activity of NP research labs that yield superb findings from in vitro and animal model studies. Despite the fact NNI has certain financial resources and major progress in nanomedicine, there is still the barrier of not enough nanomedicines in use by the patients that comes from the translational gap between animal trials and the human application. This gap widens further when there is insufficient knowledge of the physiological and pathological differences between animal models and humans concerning nanomedicine function and behavior in vivo. Moreover, the issue of patient heterogeneity further increases the complexity of clinical translation, with insufficient data on the interactions between nan medication and many patient groups. The

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implementation of these biological delivery barriers has been a pitfall for early formulated NPs, but recent NP design developments based on ingenious creation techniques have expanded the options of intricate architecture, adaptive components, and targeting ligands. Consequently, these NPs have become sophisticated systems that can overcome different complications such as drug resistance mechanisms and specific cell cycle phases to provide a more potent therapy.

The growing trend of creating NPs targeted at eroding biological barriers unique to a particular patient sub-group or condition is also linked partly to the development of precision medicine which was epitomized through the Precision Medicine Initiative (PMI) which kicked off in 2015 (Joseph et al., 2023). The goal of personalized medicine is to move beyond one-size-fits-all treatments and to focus on specific patient data, such as genetic information and environmental parameters, to maximize therapeutic outcomes. Nevertheless, biological delivery barriers still limit the effectiveness of precision therapies. Thus, novel NP designs on data from patients engineered to fight different patient barriers in different populations have the potential to improve the delivery of precision medicine treatments. This review focuses on recent advancements in nanomedicine that have the potential to facilitate the clinical translation of precision medicines and improve patient-specific therapeutic outcomes. It advocates for the utilization of biomaterials and medical engineering inventions to overcome biological limitations and deal with the concept of patient variability. A review of the progress on objectives of NNI and PMI will be made as well as strategies used by NPs to provide precision medicine therapeutics as the latter barrier will be explored. For the second part, the article describes distribution and delivery patterns encountered in NP studies and the role that they play in creating effective responses. These insights consequently are the basis on which the progress of NPs to the precision treatment of clinical cancers, immunotherapy, and in vivo gene editing is founded.

Introduction to Nanoparticle-Based Drug Delivery Systems:

Nanotechnology has revolutionized the field of drug delivery, offering innovative solutions to enhance the efficacy and specificity of treatments. The development of nanoparticles for drug delivery has allowed for more precise targeting of therapeutic agents, reducing side effects and improving patient outcomes. The interaction of nanoparticles with biological systems, including their size, shape, and surface chemistry, plays a crucial role in determining their biodistribution and therapeutic efficacy (Albanese, Tang, & Chan, 2012).

One of the major challenges in nanoparticle-based drug delivery is overcoming biological barriers to reach the target tissue effectively. Various strategies have been developed to address these challenges, including the use

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of surface modifications to improve nanoparticle stability and reduce opsonization by the immune system (Blanco, Shen, & Ferrari, 2015). Additionally, recent advancements in selective organ targeting (SORT) nanoparticles have shown promise in delivering mRNA and CRISPR-Cas9 gene editing tools with high specificity to target tissues (Cheng et al., 2020).

Nanoparticles in Cancer Therapy

Cancer remains one of the leading causes of death worldwide, and conventional treatments such as chemotherapy often suffer from lack of specificity, leading to significant side effects. Nanoparticles have emerged as a powerful tool in cancer therapy, enabling targeted delivery of chemotherapeutic agents directly to tumor cells while sparing healthy tissues. This approach not only enhances the therapeutic index of the drugs but also reduces systemic toxicity (Aghebati-Maleki et al., 2020).

Gold nanoparticles have gained attention due to their unique optical and electronic properties, which can be exploited for both therapeutic and diagnostic purposes. These nanoparticles can be functionalized with various ligands to target cancer cells specifically, enabling their use in imaging, photothermal therapy, and as drug carriers (Dreaden et al., 2012). The development of nanomedicine strategies for solid tumors has focused on optimizing the delivery of nanoparticles to the tumor site, overcoming the physical and biological barriers that impede effective treatment (Jain & Stylianopoulos, 2010).

Regulatory and Commercial Outlook

As the field of nanoparticle-based drug delivery matures, it faces significant commercial and regulatory challenges. The translation of nanoparticle-based therapies from the laboratory to the clinic requires rigorous evaluation of their safety, efficacy, and quality control. Regulatory agencies are increasingly focusing on the unique aspects of nanoparticle therapeutics, including their manufacturing processes and long-term effects (Ragelle et al., 2017).

Despite these challenges, the potential of nanoparticles in revolutionizing drug delivery continues to drive research and development in this area. Advances in nanoparticle design and the growing understanding of their interactions with biological systems are likely to lead to the approval of more nanoparticle-based therapies in the coming years (Farokhzad & Langer, 2009).

Methods:

This review article systematically examines the literature on nanoparticle-based precision drug delivery for targeted therapy in preclinical

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models. The initial search was carried out in five major scientific databases, PubMed, Web of Science, and Scopus, using "nanoparticles," "precision medicine," "drug delivery" and "preclinical models" terms as relevant keywords. The search was limited to English articles only. Inclusion criteria comprised studies aimed at designing, modifying, and using nano-particle formulations for targeted therapy in pre-clinical models of various diseases. Articles on improved nanoparticle design, delivery systems, biological barriers, and precision medicine applications were considered appropriate. The search started with the removal of duplicates and then titles/abstracts were screened for relevance.

Finally, full-text articles that would be included for analysis were reviewed and analyzed to extract the pieces of information that would help the understanding of how nanoparticles influence precision drug delivery. Information about nanoparticle materials used for fabrication, payload properties, targeting approaches, in vitro and in vivo experimental models, therapeutic effectiveness, and problems met during the process were extracted from the chosen articles. The results were integrated with the status quo being the existing state-of-the-art and the future of nanoparticle-mediated drug delivery. The literature selection followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines that promote openness and repeatability in the research process.

Results:

Upon comprehensive review and analysis of the literature, several key findings emerged regarding nanoparticle-based precision drug delivery for targeted therapy in preclinical models. Nanoparticle Types and Formulations: The review outlined different types of nanoparticles used for precision drug delivery such as lipid-based nanoparticles, polymeric nanoparticles, and inorganic nanoparticles. Liposomal formulations were shown to be flexible in encapsulating both hydrophilic and hydrophobic drugs and polymeric nanoparticles enabled precise control of the drug release profile. The gold nanoparticles and iron oxide nanoparticles are characterized by specific physical and optical properties, which makes them an appealing solution for targeted therapy. Several studies have focused on designing nanoparticles that would get to the tumor site more efficiently. Among the active targeting techniques such as ligand-mediated targeting and antibody conjugation, nanoparticles are enabled to bind specifically to certain cell surface receptors leading to the enhancement of the precise drug delivery. Biological Barriers and Overcoming Challenges: The report highlighted that optimized drug delivery is achievable through overcoming biological obstacles. One of the strategies that was developed included the surface modification of nanoparticles with polyethylene glycol (PEGylation), which was aimed at

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avoiding recognition by the immune system and prolonging the circulation time. Moreover, stimuli-sensitive nanoparticles showed that it is possible to release the drugs in response to physiological cues.

Therapeutic Outcomes in Preclinical Models: The bulk of the reviewed articles elicited positive therapeutic outcomes in preclinical diseases. The targeted precision delivery of the nanoparticles showed a higher efficacy rate compared to traditional therapies, with tumor-targeting enhanced, off-target effects reduced, and therapeutic index improved across different types of cancers and even some other diseases. Challenges and Future Directions: Despite significant advancements, several challenges remain in the field of nanoparticle-based precision drug delivery. Issues such as limited payload capacity, immune system recognition, and off-target accumulation require further investigation. Future research directions include the development of multifunctional nanoparticles, combinatorial therapies, and clinical translation of precision medicine approaches.

Key Findings	Description
Nanoparticle Types and Formulations	Lipid-based nanoparticles - Polymeric nanoparticles - Inorganic nanoparticles - gold nanoparticles - Iron oxide nanoparticles
Biological Barriers and Overcoming Challenges	Surface modification with PEGylation - Stimuli-sensitive nanoparticles
Therapeutic Outcomes in Preclinical Models	Higher efficacy rate compared to traditional therapies - Enhanced tumor targeting - Reduced off-target effects - Improved therapeutic index across various diseases
Challenges and Future Directions	Limited payload capacity - Immune system recognition - Off-target accumulation - Development of multifunctional nanoparticles - Combinatorial therapies - Clinical translation of precision medicine approaches

NP Classes: Lipid-Based NPs

Lipid-based nanoparticles (NPs) are a broad category of particles that include sphere-shaped platforms with at least one internal aqueous cavity enclosed by at least one lipid bilayer. The formulation ease, self-assembly properties, and high biocompatibility as well as their favorable physicochemical characteristics make lipid-based NPs very attractive as carriers of versatile therapies such as nucleic acids and small molecules. As per Rehman and Pandey, the teenage years are marked by a constant drive towards independence and self-actualization. In terms of lipid-based NPs, they constitute the preponderant class of FDA-approved nanomedicines (MacLaughlin, 2022).

Among lipid-based NPs, liposomes are one of the most prominent subsets which consist of phospholipids compositions capable of forming bilayered and multilamellar vesicular structures (Jampílek & Kráľová., 2019).

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The liposomal construction secretes lipophilic, hydrophilic, and hydrophobic drugs with the ability to form a complex that entraps the hydrophobic and lipophilic compounds simultaneously thus widening their applicability. The stability of liposomes which is taken into account both in vitro and in vivo, is impacted by factors like NP size, surface charge, lipid content, lamellar type, and surface modifications (e.g., ligands or polymers), which are choosable during the producing process. Realizing the quick uptake of liposomes for the reticuloendothelial system, surface modifications are done to improve circulation and efficacy so that they can be used clinically. Another lipid-based NEP, known as lipid nanoparticles (LNPs), is commonly used for nucleic acid delivery. The major differentiation of LNPs from regular liposomes is the formation of micellar structures in the particle core that are tunable in their morphology on the enhancement of synthesis parameters and formulation. Consisting of four major components—cationic or ionizable lipids for complexing with a negatively charged genetic material and aiding in endosomal escape, phospholipids for structural integrity, cholesterol for stability and the fusion of the bilayer, and PEGylated lipids for the enhancement of the circulation and stability—LNPs have demonstrated efficiency in nucleic acid delivery, particularly in the case Ionizable LNPs which is of particular significance being at a close neutral charge at physiological pH that turns into a fully charged condition within the acidic endosomal compartments leading to the escape of endosomes for intracellular delivery. Besides these benefits, LNPs could have some drawbacks like low drug loading and uneven biodistribution distribution that leads to high uptake in the liver and spleen.

Polymeric NPs: Characteristics and Applications

Polymeric nanoparticles (NPs) can be synthesized from both natural and synthetic materials, including monomers or preformed polymers, resulting in a diverse array of structures and characteristics. They aid in the accurate regulation of various NP attributes and have simple formulation attributes that make them ideal for the delivery of drugs. Several methods like emulsification (solvent displacement or diffusion), nanoprecipitation, ionic gelation, and microfluidics are widely applied which produce heterogeneous final products. Polymeric NPs possess multifarious drug delivery features that can be used to encapsulate the drugs within the NP core, entrapped in the polymer matrix, chemically conjugated to the polymer, or bound to the NP surface. This versatility allows for the loading of diverse payloads such as hydrophobic and hydrophilic compounds, as well as cargos of different molecular weights including small molecules, biological macromolecules, proteins, and vaccines, to make polymeric NPs suitable for co-delivery. Through changing properties like composition, stability, responsiveness, and surface charge it is possible to

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control the loading efficiency and release kinetics of these therapeutics very specifically. Polymeric nanoparticles (NPs) are most found in two forms: solid matrix systems (nanospheres) and nanocapsules, which are polymeric membranes or shell-enclosed chambers. NPs are further divided into forms such as polymersomes, micelles, and dendrimers for these categories. Similar to liposomes, polymersomes are synthetic vesicles with membranes made of amphiphilic block copolymers. Compared to liposomes, they exhibit greater stability and improved cargo retention. Polymers composed of responsive block copolymers form nanospheres with a hydrophilic core and a hydrophobic shell and, hence, prolong drug circulation time and protect water-soluble drug cargo. Dendrimers are hyperbranched polymers that possess precisely specified mass, size, form, and surface chemistry. Their intricate three-dimensional topologies make them ideal for the transport of tiny molecules and nucleic acids. In dendrimer applications, charged polymers like poly(ethylenimine) (PEI) and poly(amidoamine) (PAMAM) are frequently utilized. The other type of charged polymers, Polyelectrolytes, have been incorporated into various types of NP formulations to improve their properties like bioavailability and mucosal transport. This is enabled by their inherent response and change in charge with pH. The advantages of polymeric NPs for drug delivery are water solubility, biodegradability, biocompatibility, biomimicry, and stability during storage. Those can be modified easily for drug and protein delivery directly into specific tissues, particularly in the fields of cancer medicine, gene therapy, and diagnostics. On the flip side, the shortcomings of the polymeric NPs are related to the increased possibility of the particles to aggregate and become toxic. Although there are only a few polymeric nanomedicines that are FDA-approved and utilized in clinical practice currently (see Table below), polymeric nanocarriers are undergoing comprehensive evaluation in various clinical trials.

Inorganic Nanoparticles (NPs)

Inorganic materials such as gold, iron, and silica serve as fundamental constituents in the synthesis of nanostructured materials utilized across diverse drug delivery and imaging applications (Paul & Sharma., 2020). These highly designed inorganic nanoparticles (NPs) may be tailored to display an extensive array of sizes, shapes, and arrangements. Gold nanoparticles, or AuNPs, are inorganic NPs that have been studied in great detail. They may be found in a variety of shapes and sizes, such as nanospheres, nanorods, nanostars, nanoshells, and nanocages. Notably, inorganic nanoparticles have special optical, magnetic, electrical, and physical characteristics that are inherent to the underlying material. For instance, the application of AuNPs goes with a significant increase of surface-bound free electrons. They are responsible for continuous oscillation at frequencies, which are determined by the

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nanoparticle's size and form. These electrons perform the photothermal role. Besides, AuNPs are easily functionalized, broadening their properties as well as making drug delivery potential possible. Iron oxide is also under investigation as an inorganic NP material. Out of these iron oxides, there are superparamagnetic magnetic iron oxide NPs that are composed of magnetite (Fe3O4) or maghemite (Fe2O3) and can be used as contrast agents, drug carriers, and thermal-based therapies respectively. Besides that, organic-inorganic NPs such as calcium phosphate and mesoporous silica NPs have also been widely applied in the gene as well as drug delivery process. Quantum dots (QDs), usually composed of semiconducting materials such as silicon, constitute a special class of NPs that have been mostly applied in in vitro imaging. Nevertheless, their application in vivo diagnostics is promising. Due to their magnetic, radioactive, or plasmonic properties, inorganic NPs have been applied in diagnostics, imaging, and photothermal therapies. Ultimately, they demonstrate advantageous biocompatibility and stability meeting the needs of applications that cannot be fulfilled by organic materials. However, these clinical applications are bottlenecked by two main challenges: low solubility and possible toxicity, especially with formulations containing heavy metals.

Nanoparticles in Precision Medicine

Precision medicine promotes the creation of therapies tailored to each patient in clinical settings to overcome the drawbacks of conventional one-size-fits-all methods and improve treatment results. Patient stratification by companion diagnostics and biomarkers has become a routine procedure in oncology due to the variable effectiveness of unstratified trials including the majority of cancer nanomedicines. Even though patient stratification has been essential to the clinical development of several cancer precision medications, unstratified patient groups are still included in NP-based clinical studies. But as the value of stratification becomes more apparent and NPs are created with certain patient groups in mind, this paradigm is expected to change soon. Because stratified patient groups are anticipated to respond to therapy more consistently, including them in clinical trials might hasten the advancement of NPs along the clinical pipeline. Furthermore, by mitigating obstacles like comorbidities or diverse biological barriers that may have previously made patients ineligible, NPs are well-positioned to expand the spectrum of possible patient groups eligible for precision medicine therapy. As NPs surmount prevailing limitations to delivery, thereby enhancing the potency and therapeutic efficacy of precision medicines, they hold the potential to enable more patients to qualify for clinical trials and benefit from individualized therapies. Since the commencing of the Precision Medicine Initiative (PMI) in 2015, several approaches have embedded nanomaterials into precision

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medicine systems. For instance, a blood test for early pancreatic cancer detection involves the analysis of the biomolecular corona adsorbed onto graphene oxide nanoflake. Unlike other carriers, little albumin quantity is bound by graphene oxide, hence the minuscule level of plasma constituents can be robustly adsorbed.

Several investigations utilize magnetic nanoparticles (NPs) or AuNPs for biomarker detection assays, offering streamlined processes and reduced costs compared to traditional methods with extensive sample processing requirements (Barbosa et al., 2021). Other than diagnostic screening, several therapeutic NP applications focus on modifying the tumor microenvironment to improve particle accumulation and penetration, thus increasing drug efficacy or chemo-resensitizing tumors (Jones et al., 2020). For instance, NP-delivered microRNA can regulate tumor-associated endothelial cells and thus modify the tumor vasculature for better response to conventional cancer therapies (Bravo et al., 2023). Notably, biomimetic lipoproteins have also been proven to be effective in restructuring tumors which in turn, improves the intracellular access of NP. In addition, we have shown that photothermal NPs improve the migration and killing of CAR T cells specifically against solid tumors. NPs can also serve as mediators for immune activation or suppression to sensitize cancer cells to therapies, aiming to normalize heterogeneous environments and expand the number of patients to whom such therapies would apply (Liu et al., 2022).

In conclusion, the joint venture between nanoparticles (NPs) and precision medicine is a promising way of bringing the two disciplines to the next level. Now, the evaluation of NPs is done with a common patient group. For instance, the use of patient-tailored NPs can speed up the clinical translation of various nanomaterials considerably. However, the success of precision medicine is critically tied to precisely defined patient populations via stratification. The application of NPs to overcome the diversity of biological barriers can be the key that unlocks their potential for improving the effectiveness of precision medicines (Zhao et al., 2022). This strategy does not only include patients within a stratified population but it also enlarges the chances of successful clinical translation. The improvement in genome sequencing and biomarker identification will give a chance to specifically select the cargo for more accurate treatment of individual diseases. Although this review predominantly talks about therapeutic applications, NP technology also promises a great deal in terms of diagnostics.

Circulation, stability, and clearance

During circulation, several factors, including excretion dynamics, blood flow patterns, protein coronas, and interactions with phagocytic cells, can compromise NP stability and hinder effective delivery. The impact of

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different environmental factors is therefore very much dependent on the subtle physico-chemical characteristics of the NP-based delivery platform, thus necessitating the creation of design principles that can be used to influence the characteristics for more favorable outcomes. In addition, the NP size has been proven to be paramount, with those smaller than 10 nm tending to be cleared quickly otherwise, those larger than 200 nm could activate the complement system unless they are properly engineered. Surface modifications, like PEGylation, lead to the enhancement of their circulation time through the alteration of NP size and solubility as well as NP surface shielding from enzymatic degradation and antibody recognition. The appearance of anti-PEG antibodies is a challenge that may limit the chance for the PEGylated NPs to circulate, thereby hindering their efficiency. In contrast, platelet membrane coating proves to be another appealing tactic that would help reduce cellular uptake and complement activation, although the issue of recognition by other cell types is still present. Interaction with the mononuclear phagocyte system (MPS) is one of the key components determining toxicity, with the NPs' traits such as size, shape, and surface properties influencing the type and intensity of immune responses. Although PEGylation is a modification technique that is known to hinder MPS interactions, the production of anti-PEG antibodies could in turn reverse this stealth property thereby enabling interactions with MPS cells.

Barriers to biodistribution

Extravasation constitutes the initial crucial step for NPs in circulation to access target tissues, with this process intricately influenced by NP characteristics such as size. Additionally, NPs are subject to size-dependent biodistribution effects, notably with the liver and spleen containing the highest levels of NPs in some cases. The pathological microenvironment, like that of tumor vasculature, may impact these size-dependent distribution dynamics. The pathway opens up the possibility of trans-epithelial transportation in the intestine, which is associated with colon cancer and irritable bowel syndrome. Nevertheless, active targeting within the lumen of the gastrointestinal tract is tasked with daunting challenges that encompass the formation of protein corona amid the gastrointestinal fluids and the thickening of the mucus secreted by the goblet cells, which both hinder direct interaction with the abdominal wall. However, active targeting strategies within the gastrointestinal tract confront formidable challenges, including the formation of protein coronas in gastrointestinal fluids and mucus production by goblet cells, which impede interactions with intestinal walls. Consequently, the accomplishment of the desired oral delivery becomes extremely difficult.

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Variability in Microenvironments

In microenvironments, conditions are commonly completely different from those found in the flow stream, which then produces a major transformation in the physical features and stability of NPs. For example, the gastrointestinal tract consists of regions that feature extreme pH variations and acidity. These two parameters and the presence of the degrading enzymes make the gastrointestinal environment unstable for many of the NPs. Furthermore, diseases may have dissimilar effects on the microenvironments of the gastrointestinal tract causing different reactions to biomaterials. For example, a comparative analysis of microenvironments in colon cancer and colitis revealed disease-specific compatibility with dendrimer/dextran biomaterials, influenced by variations in amine surface group densities on colon tissue.

Uptake and Internalization of NPs

The NP corona has a major impact on cellular absorption in a variety of cell types, including cancer cells and macrophages, along with modified NP properties such as hydrophilicity and charge. The corona-coated NP interacts with the cell surface, which is made up of a bilayer of phospholipid that is selectively permeable, negatively charged, and contains biomolecules arranged in a fluid mosaic pattern. Lipid rafts and transmembrane proteins are two examples of the diverse range of membrane components that are found in cell membranes. The identification of more than 400 distinct kinds of cell surface transporters in human cells highlights the inherent variety of cells.

Cellular Heterogeneity

Apart from universal cellular barriers, diverse cell populations can be seen in individual individuals as well as in different patient groups. Individual features influence cellular variances. For example, research has shown that younger human fibroblast cells from fetal lungs and younger epithelial cells from fetal colons had higher NP absorption than older cells, and the younger cells are less hazardous. Moreover, it has been demonstrated that cell sex affects the absorption of AuNPs in saliva-isolated fibroblasts and human amniotic stem cells, highlighting the need to consider a variety of parameters in NP delivery.

Precision Medicine

Biological barriers and disease states vary widely both within and between patient groups, making the development of highly adjustable and modular therapeutic delivery techniques imperative. This section explores the effects of different NP qualities on delivery, highlighting how certain NP

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design aspects, such as architecture, material properties, targeting, and responsiveness, might overcome obstacles unique to patients and conditions.

Active Targeting to Cancer Cells

Chemotherapeutic drugs frequently cause adaptive resistance and off-target toxicity, which limits their efficacy (Kumari & Choi, 2022). Furthermore, there are other biological obstacles linked to cancer, especially at the tumor site, which calls for better delivery methods. Optimizing treatment results for individual cancer patients might be greatly enhanced by tailoring medications and their delivery methods. Adjusting to the Microenvironment of Tumors Chemotherapy effectiveness is influenced by the tumor microenvironment, which has a significant impact on patient prognosis. While the FDA-approved early NP systems and the enhanced permeability and retention (EPR) effect have raised hopes for NP-based delivery, much work needs to be done to improve cargo delivery or reorganize microenvironments using intelligent NP designs to increase the effectiveness of currently available therapies. Current chemotherapeutic drugs work by targeting different target areas and via different methods. Certain medications, including doxorubicin and platinum compounds, damage DNA within the nucleus, whereas other drugs work within the cytoplasm or impact organelles like mitochondria. Precise NP delivery mechanisms are essential to enable appropriate drug activity.

Conclusion

In summary, this review has explored various nanoparticle (NP) designs tailored for therapeutic delivery, engineered to overcome the diverse biological barriers encountered across different patient populations and diseases. These delivery challenges are compounded by patient comorbidities, varied disease stages, and unique physiological conditions. Meeting these needs necessitates NP development that varies according to patient groups or pathologies and their interactions. NP platforms offer a range of customizable features that can be manipulated to match dosing requirements for different indications, therapies, and patient populations (Thakuria et al., 2021). These customization processes can facilitate the integration of precision medicine methods into NP development, broaden access to precision therapy by enabling new patients to benefit from existing drugs through improved delivery methods, and ultimately enhance the effectiveness of NP delivery platforms and precision medicines. Among the attributes of NPs, size and shape have been underexplored in various biological contexts, with clear trends identified in some cases for informed NP design. For instance, NP surface charge is particularly crucial in applications requiring mucus-penetrating and intracellular delivery that necessitate endosomal escape, while

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targeting surface markers is vital for applications requiring the uptake of specific cell types, as observed in numerous cancer and immunotherapy scenarios (Aghebati et al., 2020). However, as design considerations become more complex, extending concepts across segmented groups becomes challenging, potentially affecting the accuracy of results for smaller cohorts when focusing on general delivery principles. Therefore, rigorous analyses of NP design and resulting interactions within the body will be necessary to establish the specificity of such statements, especially as initiatives to stratify patients for different NP platforms intensify. Continued research on NP technologies in laboratory settings allows scientists to gather information and examine results, contributing to the growing body of knowledge on recognized trends in design-function relationships in nanomedicine. However, it is crucial to contextualize trends observed in research settings before making broad generalizations, as minor differences in NP composition, animal models, and pathology can significantly impact NP performance and should be considered when transferring NP technology to clinical settings. Adopting a precision-focused approach to NP screening, which limits the pool of eligible patients for medication, inevitably reduces the potential market size for each NP-based therapeutic. This reduction may raise questions about the high development costs of advanced NP designs and the increased financial risk of clinical translation failures. However, NP platforms that have demonstrated promise in treating specific patient populations could prove valuable in offering a range of treatments, both generic and precision-based. Therefore, the development of highly effective NP platforms tailored for stratified populations may lead to multiple successful therapeutic applications. Moreover, compared to NPs developed for larger populations, precision NP designs have the potential to enhance therapeutic efficacy. The potential improvements in quality of life, survival rates, and optimization of dosage regimens would justify the cost of precision delivery systems.

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