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HIGHLIGHT

Future prospects in clinical translation of inorganic nanoparticles

KEY WORDS

Inorganic nanotherapeutics;
Black phosphorus nanosheet

Inorganic nanomaterials, as prospective members of the nanomedicine family, have shone brightly in the biomedical field because of their unique physicochemical properties such as a high surface-area-to-volume ratio, superior optical, magnetic, and electronic properties, and biocompatibility. Inorganic nanomaterials can serve as premier platforms for drug delivery, disease diagnosis and treatment, bioimaging, and biosensing through meticulous designs and functional modifications to overcome the limitations inherent in conventional therapy[1-5].

Within the category of disease diagnostics, inorganic nanomaterials, such as gold nanoparticles (AuNPs) and quantum dots, have garnered significant attention because of their unique fluorescence and surface plasmon resonance effects[1]. Early detection and precise diagnosis of diseases can be facilitated by high-resolution imaging and ultrasensitive detection of biomarkers such as proteins, DNA, and cells. Magnetic nanomaterials, such as iron oxide nanoparticles (IONPs), are instrumental in enhancing magnetic resonance images by markedly improving the image contrast, which helps delineate and confirm lesions more accurately. Additionally, IONPs magnetically guide drug delivery and cell separation, thereby minimizing collateral damage to healthy tissues and maximizing therapeutic efficacy.

During the course of disease therapy, inorganic nanomaterials have become pivotal in the advancement of precision medicine owing to their multifunctionalities and targeting capabilities that improve therapeutic efficiency and substantially reduce adverse effects[2-5]. Carbonaceous nanomaterials, such as carbon nanotubes, not only significantly boost the solubility and stability of therapeutic agents, but also achieve precise delivery to specific pathological regions[6]. Upon activation by external light or magnetic stimuli, AuNPs and IONPs can transduce energy into localized thermal effects, facilitating the site-specific clearance of diseased tissue without compromising adjacent healthy structures. In practical therapeutic applications, the properties of these nanomaterials can be engineered to meet specific treatment requirements. Taking antitumor therapy as an example, modulating the size, shape, and surface chemistry of nanomaterials can optimize their distribution and residence time within the tumor microenvironment, thereby amplifying treatment efficacy. For infectious diseases, the fine design of the antimicrobial activity of nanomaterials can ensure effective pathogen inhibition while avoiding excessive immune system activation. Notably, a pioneering study published in *Nature Nanotechnology*, reported the development of a targeted peptide-modified nanotherapeutic agent with dual inflammation-resolving and antioxidative effects for the treatment of atherosclerosis. This agent was comprised of PEGylated black phosphorus nanosheets (BPNSs@PEG), an S2P targeting peptide, and resolvin D1 (RvD1)[7] (Fig. 1). This investigation marks a significant milestone in nanomedicine, offering novel insights into the application of inorganic nanomaterials in biomedicine and demonstrating how an innovative design can overcome existing challenges and promote the broader application of inorganic nanomaterials in clinical practice.

Despite this advance, it is imperative to acknowledge that, while inorganic nanomaterials have demonstrated substantial potential in biomedicine, challenges pertaining to complex synthesis procedures, efficacy validation, *in vivo* accumulation efficiency, and biosafety concerns continue to impede their translation from the laboratory to the clinic. The *in vivo* fate of inorganic nanomaterials, including their absorption, distribution, metabolism, and excretion, is critical for their application. The physicochemical properties of nanomaterials, including particle size, morphology, structure, surface interface, and composition, dictate their interaction patterns with biomolecules, significantly affecting their ability to traverse various biological barriers, and directly

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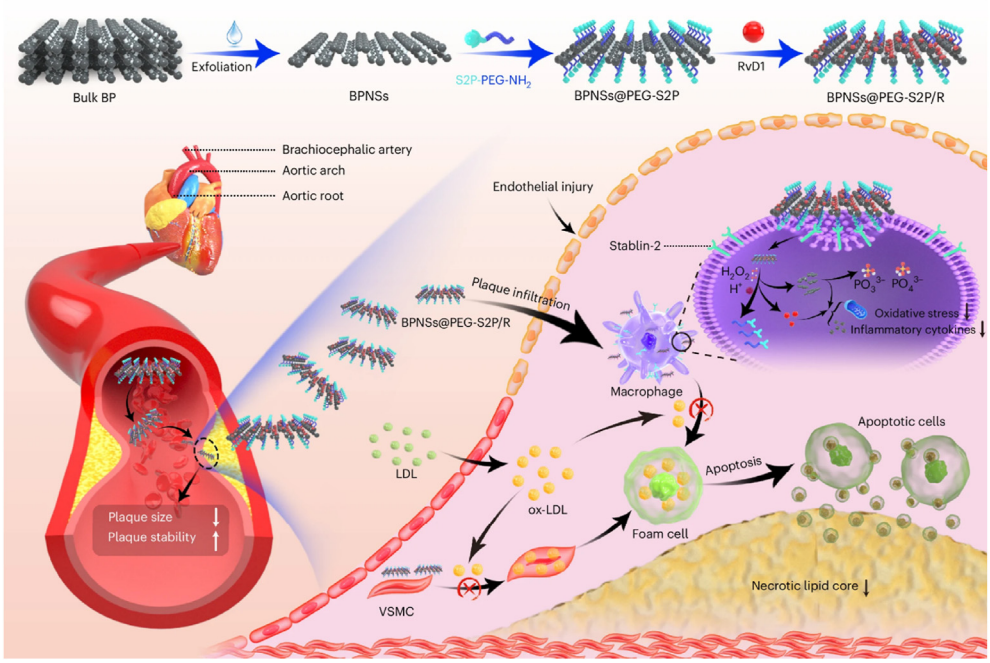

Figure 1 Schematic of the synthesis strategy and anti-atherosclerotic mechanism of BPNSs@PEG-S2P/R. Reprinted with the permission from Ref. 7. Copyright © 2024 Springer Nature.

influencing their safety and potential toxicity. It should be noted that, upon entering a biological system, inorganic nanomaterials initially interact with proteins, forming a "protein corona" that significantly alters their *in vivo* behavior and biodistribution patterns. Concurrently, the liver and kidney, as primary sites of nanomaterial clearance, are at risk of accumulating these particles, potentially leading to chronic toxicity and functional impairment. Fortunately, through surface modification and functionalization strategies, the nonspecific binding of inorganic nanomaterials to proteins, as well as their toxicity, can be significantly reduced, further enhancing their therapeutic efficacy and biosafety[8]. Therefore, future research should be dedicated to elucidating the underlying mechanisms governing these interactions to provide a theoretical foundation for the optimization of therapeutic strategies involving inorganic nanomaterials. Such a foundation will foster the development of inorganic nanomaterials with excellent biocompatibility and low toxicity.

Recently, nanomaterials containing essential trace elements for humans, or capable of being degraded by microorganisms or enzymes in the body, have received increasing attention owing to their ability to maintain functionality while reducing potential biological risks. Molybdenum disulfide nanoparticles (MoS_2) exhibit this trend, as they are capable of undergoing a protein corona-bridged transport-transformation-bioavailability chain *in vivo*. Upon degradation, the oxidized components from MoS_2 degradation are incorporated into molybdenum enzymes in the liver, thereby enhancing hepatic molybdenum enzyme activity and modulating liver metabolic functions. This suggests that nanomaterials consisting of essential trace elements may be converted into active biological molecules that organisms can exploit[9].

The development of highly sensitive and specific advanced tracing technologies has proven invaluable in ensuring the safe application of inorganic nanomaterials and reducing potential health hazards. These methodologies can assist researchers in determining the precise localization and accumulation of nanomaterials *in vivo* by furnishing high-resolution images of nanomaterials across various organs and tissues. Furthermore, they facilitate cellular-level investigations by delineating intracellular uptake and distribution patterns that help reveal metabolic transformation pathways and excretory routes of nanomaterials within the body. This comprehensive understanding is crucial for evaluating biocompatibility and pharmacological efficacy[10]. However, this also requires scientists to collaborate across disciplines and integrate knowledge from materials science, biology, medicine, and engineering to conduct comprehensive risk assessments and develop effective risk management strategies for nanomaterials.

Considerable research efforts on inorganic nanomaterials still predominantly focus on murine models and lack validation in higher-level animal models or humans. Thus, their clinical application may be accompanied by unforeseen toxicological effects, and it is crucial to conduct additional long-term safety and efficacy evaluations of inorganic nanomaterials in more preclinical animal models, and even clinical trials, to establish standardized nanotherapeutic platforms. Similarly, the inherent complexity of the fabrication processes of nanopreparations presents a challenging barrier to the scale-up of production and quality control of inorganic nanomaterials, critically impeding their clinical translation. Achieving large-scale production while ensuring stable product quality requires immediate resolution. Future research should be directed towards optimizing synthetic processes, enhancing production efficiency, and reducing costs, all of which are conducive to establishing standardized quality control systems.

Owing to the above factors, the rapid advancement of inorganic nanomaterials is posing unprecedented challenges to regulatory frameworks worldwide. Currently, regulatory bodies, including the United States Food and Drug Administration, European Medicines Agency, and China's National Medical Products Administration, are actively constructing guidelines suitable for

the unique attributes of nanotechnology, focusing on detailed characterization, toxicological assessments, and biocompatibility testing of nanomaterials, including strict preclinical and clinical trial requirements. Despite the gradual refinement of regulatory frameworks, the inherent complexity of nanomaterials and their unpredictable behavior in biological environments are pushing existing regulations into a state of continuous evolution, wherein safety assessment remains the primary challenge. Given the size-dependent effects of nanomaterials that lead to distinct *in vivo* behaviors compared to conventional drugs, it is essential to develop novel assessment tools and standards. Furthermore, in the absence of unified international standards and testing methodologies, the standardization and accurate characterization of nanomaterials face significant challenges, considerably increasing the difficulty of product development. The complexity of intellectual property protection, data sharing, and insufficient international collaboration are hindering scientific progress and the establishment of unified regulatory standards. Regulatory bodies must maintain flexibility, continuously update regulations to keep pace with technological advancements and foster the development of international standards. This will ensure the safe, effective, and responsible application of inorganic nanomaterials in the biopharmaceutical domain.

In summary, inorganic nanomaterials have demonstrated distinct advantages in antitumor therapy, infectious disease treatment, cardiovascular disease management, and medical imaging. The utilization of inorganic nanomaterials within biomedical applications is replete with opportunities but is not devoid of challenges. Collaboration between the scientific community, industry, and regulatory authorities is pivotal for promoting the healthy development of this domain and harnessing its potential to benefit humanity.

Author contributions

Ke Xu: Writing − original draft. Ying Liu: Writing − review & editing. Chunying Chen: Writing − review & editing.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Ke Xu[a,b], Ying Liu[a,*], Chunying Chen[a,b,*]

[a]*CAS Key Laboratory for Biomedical Effects of Nanomaterials and Nanosafety & CAS Center for Excellence in Nanoscience, National Center for Nanoscience and Technology of China, Beijing 100190, China*

[b]*University of Chinese Academy of Sciences, Beijing 100049, China*

*Corresponding authors.

E-mail addresses: liuy@nanoctr.cn (Ying Liu), chenchy@nanoctr.cn (Chunying Chen)

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