

Gold Nanoparticles in Cancer Theranostics: Existing Challenges and Future Perspectives

Xi Tang

Department of Chemical Engineering, The University of Manchester, Manchester, UK

xi.tang@student.manchester.ac.uk

Abstract. Conventional methods for cancer diagnosis and therapy currently face significant limitations. The primary treatment modalities are surgery, chemotherapy, and radiation therapy, which are usually compromised by major challenges such as multidrug resistance (MDR), lack of targeting, and severe damage to healthy tissues. Thus, it is essential to develop alternative and more effective therapeutic strategies. Nanomedicine has emerged as a promising field that provides innovative and improved options for cancer diagnosis and theranostics. Gold nanoparticles (AuNPs) stand out as one of the most popular nanomaterials, with extensive applications across multiple areas in oncology, including diagnostic imaging, targeted drug delivery, and AuNPs-mediated therapeutic techniques. This review comprehensively examines the properties of AuNPs and their corresponding advantages in cancer diagnosis and treatment, while also summarizing the current status of the development of AuNPs in cancer research. It briefly discusses potential mechanisms of AuNP toxicity in vivo and several common synthesis routes. Furthermore, the article provides a detailed analysis of the existing challenges hindering large-scale application and commercialization of AuNPs, including toxicity and safety concerns, as well as challenges in mass production and quality control. Finally, the review offers insights into future perspectives such as green synthesis, theranostics, personalized and precision nanomedicine.

Keywords: Gold nanoparticles, cancer, challenges, perspectives.

1. Introduction

Cancer remains one of the leading causes of death worldwide, posing a serious threat to global health and human lives [1]. The International Agency for Research on Cancer (IARC) estimates indicated that globally, 2022 saw roughly 20 million new cancer cases and 9.7 million fatalities from the disease. Demographic-based predictions further indicate that the number of new cancer cases is expected to rise to 35 million by 2050, representing a 77% increase compared to the 2022 estimate [2]. However, current cancer treatment primarily entails surgery, chemotherapy, and radiation therapy. While these modalities are effective at killing tumor cells, they also cause severe damage to healthy cells and tissues, resulting in significant adverse effects, particularly from chemotherapy and radiation, including but not limited to anemia, fatigue, hair loss, nausea, pain, appetite loss, diarrhea, and delirium [1]. Hence, there is an urgent demand for developing noninvasive and selective therapeutic technologies for cancer therapy [3]. Nanotechnology, which is defined as the study and application of materials at the scale of 1 to 100 nanometers, has huge potential in the field of medicine. Since the colloidal nature of gold-based nanoparticles was first demonstrated as the cause of their red color by Michael Faraday in 1857, AuNPs have promised to be highly biocompatible nanoparticles for applications in medical treatment and diagnostics [4]. Compared to the conventional cancer treatment modalities, nanomedicine based on AuNPs demonstrates numerous advantages, such as high selectivity, minimal damage to the body, and the ability to be surface-functionalized with specific targeting ligands [5].

2. Properties of AuNPs

The remarkable advantages are due to the unique properties of AuNPs. Firstly, as a noble metal, gold possesses remarkable chemical inertness, resulting in high stability. It also exhibits excellent biocompatibility and relatively low inherent toxicity compared to conventional chemotherapeutic

agents. All of these advantageous properties make AuNPs an ideal platform for cancer theranostics. In addition, the high surface-to-volume ratio of AuNPs provides ample sites for functionalization, enabling their surface to be easily modified with targeting ligands and drug molecules, thus enhancing their aqueous dispersibility, biocompatibility, and targeting efficacy to achieve selective drug delivery [5, 6]. Moreover, the localized surface plasmon resonance (LSPR) property of AuNPs enables their broad application in early cancer detection and photothermal therapy. Table 1 summarizes various nanostructures of AuNPs, highlighting their key characteristics, advantages, and drawbacks [4].

Table 1. Classification of gold nanostructures and their properties [4]

Nanostructure	Characteristics and Advantages	Shortcomings
Gold nanotube	Tunability of plasmonic resonances in the near-infrared (NIR) region; Larger active areas and more electroactive sites for biomolecule stabilization; high scattering contrast and sensitivity	Cytotoxicity risk associated with chemical synthesis
Gold nanorod	Dual-tunable NIR LSPR peaks; Easy surface modification; High sensitivity; Antimicrobial mechanism; Strong saturable absorption Enhanced NIR absorption;	In vivo hepatotoxicity; Hepatic accumulation; low photostability
Gold nanocage	Hollow porous nanostructure; Exceptional scattering and absorption cross-sections	Melting point at a power density
Gold nanoshell	Tunability of plasmonic resonances in the NIR region; Highly effective for Photothermal therapy (PTT)PTT and surface-enhanced raman scattering (SERS) Single LSPR peak;	Weak non-linear response
Gold nanosphere	Minimal specific surface area; High cellular internalization; Highest colloidal stability; Easy and available synthesis methods; Easy Surface Modification	Cytotoxicity; In vivo multi-organ accumulation

3. Synthesis Methods of AuNPs

Gold nanoparticles, also referred to as gold colloids, exhibit a wide spectrum of morphological configurations, including nanospheres, nanorods, nanoshells, and nanocages [1]. The synthesis of AuNPs can be categorized into two primary types: the top-down approach, such as mechanical milling, and the bottom-up approach which involves chemical reduction, is the most common method of synthesis [7].

In the top-down method, nanoparticles are synthesized by breaking down suitable bulk materials using various lithographic and mechanical techniques, such as milling, grinding, aerosol technology, ion sputtering, thermal and laser ablation [7].

The bottom-up methods, which include chemical (e.g., chemical reduction) and biological methods (using plants or microorganisms), rely on the formation of new nuclei via the reduction and self-assembly of atoms, which subsequently grow into nanoscale particles [8]. Among these, chemical reduction is the most common and widely used bottom-up method. The synthesis of AuNPs through chemical reduction involves two key steps. The first step is the use of reducing agents, including citric and oxalic acids, hydrogen peroxide, and sulfites. The role of these reducing agents is to supply

electrons to reduce the gold ions (Au^{3+} and Au^+) to their zero-valent metallic state (Au^0) [9]. Following reduction, stabilizing agents such as trisodium citrate dihydrate, sulfur ligands (mostly thiolates), and surfactants (e.g., cetyltrimethylammonium bromide, CTAB), are introduced to stabilize the resulting nanoparticles against aggregation by imparting interparticle repulsive forces, which in turn determine the final particle size, growth rate, and morphology. It is noteworthy that the stabilizing agent can, in some cases, be identical to the reducing agent [9].

4. Existing Challenges

The 5 key stages in drug development are: Discovery Development, Preclinical Research, Clinical Research, Data review, and Post-Market Monitoring. A new technology typically requires 10 to 15 years to progress [10]. Currently, the research directions of AuNPs in cancer biomedical applications primarily focus on drug delivery, biological imaging probes, cancer diagnostics, and therapeutic modalities, including photodynamic and photothermal therapy [9]. While there are numerous ongoing research studies working on the AuNPs applications in cancer theranostics, and many of them have shown favourable results on in vitro and animal studies, the majority of them still remain at the preclinical stage. Moreover, only a small fraction of AuNPs-related clinical trials obtaining approval by the US Food and Drug Administration (FDA) [6]. To date, Aurolase® Therapy is the only gold nanoshell-based photothermal therapy that has entered human clinical trials for cancer treatment [3].

4.1. Toxicity and Safety issues

4.1.1 Toxicity mechanisms

The formation of reactive oxygen species (ROS) is considered to be one key toxicological mechanism of nanoparticles, which could further cause inhibition of antioxidants and oxidative stress, resulting in inflammation and damage to molecules and cell membranes [11]. Studies have found that ROS production increases significantly with rising concentrations of AuNPs (from $1\mu\text{g/mL}$ to $100\mu\text{g/mL}$) [12]. In conclusion, oxidative stress is the primary mechanism underlying nanoparticles-induced cytotoxicity and apoptosis [11].

In addition to oxidative stress, AuNPs toxicity also involves non-oxidative mechanisms. According to the study done by Ji et al., mitochondrial toxicity was identified as a main cause of cytotoxicity that disrupts metabolic processes and affects amino-acid synthesis [11]. Beyond metabolic disruption, AuNPs could also cause genotoxicity. Cardoso et al. demonstrated in vivo DNA damage in Wistar rats as a non-oxidative mechanism of AuNP toxicity. Importantly, as shown by Abdelhady et al., this DNA damage can occur independently of ROS [11].

4.1.2 Potential safety issues

Despite the promising preclinical results, there are various challenges in transitioning from preclinical studies to widespread clinical adoption. First of all, the most important and the most widely concerning challenge is toxicity and safety. The poor biodegradability of AuNPs in vivo makes them difficult to be quickly excreted by the body, and may accumulate in major organs [13]. AuNPs primarily accumulate in the liver and kidney, which are the main pathways for nanoparticle metabolism and clearance. Studies have shown that smaller particles ($< 6\text{ nm}$) are cleared through the renal pathway owing to the size constraints of glomerular pores during renal filtration, where larger nanoparticles ($>10\text{ nm}$) are cleared through the hepatic pathways [6]. Evidence from mouse studies showed that only 9% of intravenously administered 40-nm AuNPs were cleared from the liver over 6 months. Furthermore, other preclinical research indicated that the quantity of 155-nm AuNPs retained in the body shows no significant reduction 1 year after administration [13]. Nevertheless, one key strategy to overcome the challenges of non-biodegradable AuNPs is the manipulation of their surface chemistry, which could bias the AuNPs to particular cell types and in vivo clearance pathways, thereby enhancing the therapeutic potential and clinical viability of non-biodegradable platforms [6].

Additionally, emerging evidence indicates that nanomaterials (e.g., TiO₂, SiO₂, Au, Ag) can induce nanomaterial-induced endothelial leakiness (NanoEL), which could facilitate the intravasation and subsequent extravasation of cancer cells, thereby potentially accelerating metastatic [6]. Therefore, NanoEL is considered a double-edged sword, which can enhance drug delivery to tumors but could also promote cancer cell spread [6].

A key limitation in the current researches is the dominance of short-term and in vitro analyses. Although these studies have provided crucial insights into direct effects and potential toxicological mechanisms, the comprehensive understanding of the long-term impacts and in vivo behaviour of AuNPs is still lacking [11]. In short, results from simple in vitro studies may fail to recapitulate the complexity of in vivo systems [14]. Therefore, further studies are imperative to fully understand the long-term effects and in vivo pharmacokinetics of AuNPs.

4.2. Mass-Production and Quality Control

Scaling up has consistently been a significant challenge during the transition from laboratory-scale synthesis to industrial-scale production. The final performance of the product and the production yield would be hugely affected by the synthesis process chosen [14]. Moreover, many of the synthesis approaches are constrained by limitations such as low yield and poor reproducibility [14]. The synthesis of AuNPs typically results in a broad distribution of particle sizes [13]. Particle size is one of the factors that will affect the toxicity of AuNPs, along with their shape, surface charge, and coating [11]; hence, batch consistency remains a critical challenge for the large-scale manufacturing of AuNPs. According to the study by Enea et al. in 2021, which evaluated the toxicity of AuNPs of various sizes and shapes in human HepaRG cells and primary rat hepatocytes (PRH), the 15-nm spherical particles exhibited the highest toxicity among all tested samples, surpassing even that of the 60-nm AuNPs [15]. Therefore, it is essential to develop simpler and more efficient synthesis methods to achieve uniform particle size distribution.

Furthermore, the use of toxic agents during the synthesis can cause serious damage to human health and ecological systems [1]. Meanwhile, cost is another crucial factor that must be considered. Developing cleaner, cheaper, and more economical fabrication routes would significantly advance the commercialization of AuNPs-based technologies.

5. Future perspectives

5.1. Green Synthesis

As a solution to the aforementioned limitations and risks of conventional chemical reduction methods, a recently developed method, green synthesis, offers a pathway to produce AuNPs in a more sustainable and environmentally friendly manner. Like chemical reduction, green synthesis is a bottom-up approach. The key difference between conventional chemical reduction and the green synthesis is that the reducing agents used in green synthesis are derived from biological sources, including extracts of plants, microorganisms, fungi, algae, and mammalian cell lines [8]. Many reducing agents used in the green synthesis of AuNPs also act as stabilizing agents, providing dual functions of reduction and stabilization against aggregation [11]. Figure 1 illustrates the process of green synthesis of AuNPs [8].

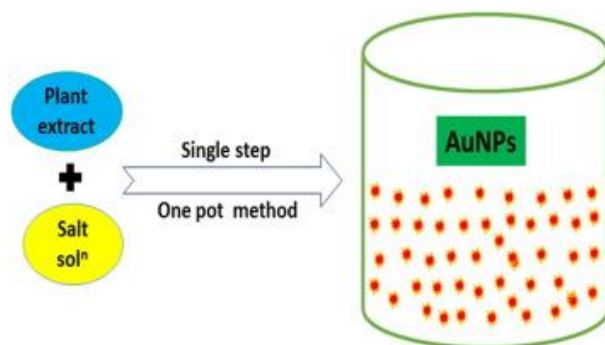


Figure 1. Single-step synthesis of gold nanoparticles mediated by plant extract [8]

The first significant advantage of green synthesis is that the nanoparticles are free from toxic byproducts that are adsorbed during chemical synthesis [8]. The natural compounds utilized in green synthesis are able to stabilize the particles when they approach the surface, which eliminates the requirement for toxic stabilizing agents [1], particularly CTAB, which has been defined as extremely cytotoxic [14]. Furthermore, green synthesis is simpler, single-stepped, and more cost-effective compared to conventional chemical synthesis [8]. For these reasons, the adoption of green synthesis for AuNPs production has been steadily increasing in recent years. This rapidly advancing field holds significant potential for innovating eco-friendly nanomaterials, which are critical for developing sustainable solutions to pressing global challenges in environmental and public health [11].

5.2. Theranostics

Theranostics refers to a unified system designed to simultaneously perform diagnosis and therapy, which heavily relies on advanced structural integration nanotechnology [16]. This can be achieved by conjugating therapeutic compounds onto the imaging agents through both covalent and non-covalent interactions [7], since their surface can be modified with diverse targeting ligands [17]. The three fundamental properties defining AuNPs are their LSPR, surface multivalent coordination, and structural flexibility. These properties enable the rational design of nanostructures to achieve enhanced NIR scattering and absorption, modulated drug release, drug targeting delivery, and combination of multiple functions. This engineering capability aims to improve therapeutic and imaging performance, often through complementary multimodal strategies [16]. Figure 2 illustrates the modification of AuNPs with diverse functional compounds [7].

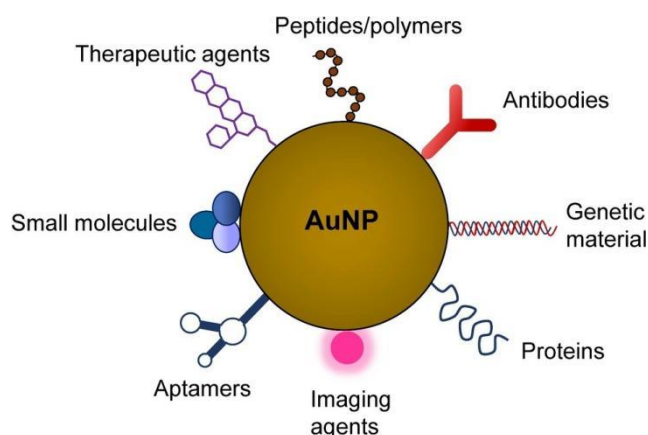


Figure 2. Multifunctional AuNPs platforms for cancer theranostics [7]

Theranostics platforms could offer an enhanced performance in cancer theranostics [16]. However, challenges related to safety concerns and immunogenic issues still remain [7]. Thus, advanced structural engineering of AuNPs is critical to simultaneously enable lower toxicity and greater therapeutic efficacy [16].

5.3. Personalized and Precision Nanomedicine

Cancer is often perceived as a single disease, but it in fact comprises a multitude of complex subtypes, each requiring distinct therapeutic strategies [18]. The concept of “personalized” and “disease-specific” was first introduced by Mahmoudi, who showed that exposing nanoparticles to plasma from healthy individuals and patients with various diseases results in significantly different protein adsorption patterns [19]. Personalized and precision nanomedicine, as a breakthrough in healthcare, seeks to provide tailored therapy according to the unique genetic, biological, and clinical characteristics of the patients. Following in vivo administration, the surface of nanoparticles will be coated with a layer of adsorbed biomolecules from biological fluids, a phenomenon known as the “personalized protein corona”, which is predominantly composed of proteins. The subsequent analysis of the protein corona proteome can enable the discovery of patient-specific biomarkers [20]. It has been proven that the presence of disease-specific biomarkers in human blood allows for the early detection of various illnesses. However, the concentration of cancer biomarkers is extremely low in the early stages, which presents significant challenges for early cancer detection [20]. In this case, AuNPs can function as a “nanoaccumulator” to adsorb and enrich cancer biomarkers from blood plasma [19], thereby facilitating their early detection. Figure 3 illustrates the flow diagram of early cancer detection using AuNPs [19].

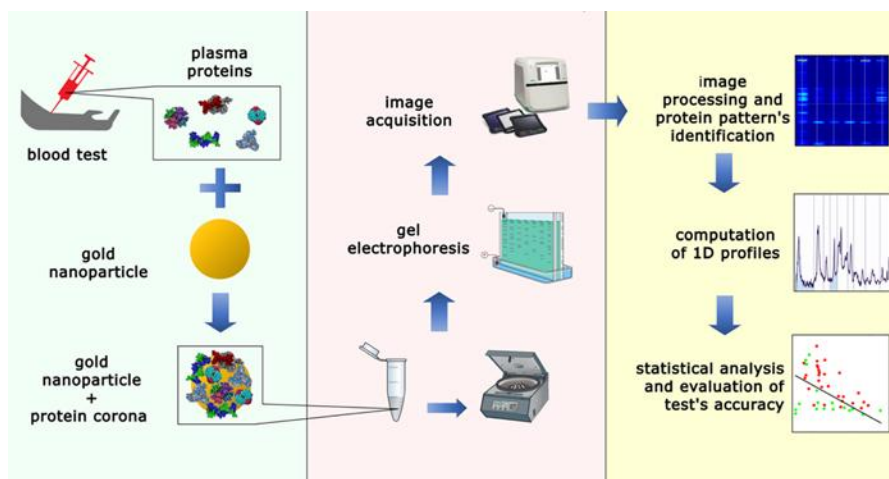


Figure 3. Flow diagram of gold NP-enabled blood (NEB) tests [19]

This targeted approach leads to a significant improvement in patient outcomes, a marked reduction of negative side effects, and increased patient confidence in treatment plans [21]. Furthermore, the ability to diagnose cancer in its initial phases and introduce the treatment before it progresses could dramatically enhance patient survival and quality of life for affected individuals and their families [19].

Personalized cancer is an absolute trend for future direction. Future patients are able to receive precision subtyping diagnosis and optimal personalized regimens. Ultimately, the future of medicine will evolve into an information science, where doctors could offer tailored medicines to individual patients based on their genomic profiles. Over the next decade, the accumulation of vast, personalized datasets will enable information technology (IT) systems to transform raw data into specific, actionable hypotheses about individual patients [21].

6. Conclusion

The immense potential of AuNPs in cancer diagnostics and therapeutics is undeniable. Gold-based nanomedicine, as a leading multifunctional approach in future cancer theranostics, can contribute to improving therapeutic efficacy and reducing harm to healthy tissues. However, significant challenges must be overcome before this potential can be fully realized. While the short-term toxicity of AuNPs has been verified as safe, their toxicological mechanisms and long-term accumulation effects remain

undetermined. Furthermore, toxicity concerns associated with high dosage regimens or particular surface chemistries have led to uncertainties concerning their long-term safety. These concerns necessitate a comprehensive human and environmental safety evaluation. Additionally, the size of nanoparticles is critical for their therapeutic efficacy. Existing synthesis methods are plagued by inherent limitations, including environmental and biological toxicity, unsatisfactory production yields, the lack of scalable production capabilities, and poor control over the size distribution of the final product. To address these environmental concerns, it is essential to explore sustainable manufacturing methods. It may take decades to address these challenges before AuNPs can be widely applied and commercialized. Green synthesis, as one of the potential future techniques, represents a viable solution to address the aforementioned challenges. Moreover, future theranostics platforms hold promise for combining diagnostic and therapeutic functions within a single system, thereby achieving more efficient and simplified cancer treatment protocols. Looking forward, the future prospects for personalized and precision cancer nanomedicine are encouraging. By leveraging individual patients' genetic profiles, the efficacy of cancer treatment is expected to be greatly enhanced, offering a brighter future in cancer treatments and saving countless lives afflicted by cancer.

References

- [1] Karen Magaly Soto, Sandra Mendoza, Jose M López-Romero, et al. Gold nanoparticles: synthesis, application in colon cancer therapy and new approaches - review. *Green Chemistry Letters and Reviews*, 2021, 14 (4): 665-678.
- [2] Freddie Bray, Mathieu Laversanne, Hyuna Sung, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, 2024, 74 (3): 229-263.
- [3] Jonathan Buiel, Jordan Robert, Dikran Mekhjian, et al. Photothermal Therapy: From Encouraging Lab Results to Lackluster Clinical Translation. *Advanced Therapeutics*, 2025, 8 (3): 2400347.
- [4] Qinyue Gao, Jingjing Zhang, Jie Gao, et al. Gold Nanoparticles in Cancer Theranostics. *Front. Bioeng. Biotechnol.*, 2021, 9.
- [5] Anjali Yadav, Ruchi Bharti. Gold Nanoparticles in Cancer Treatment and Diagnostics: A Review of Emerging Trends and Therapeutic Potential. *Orbital: The Electronic Journal of Chemistry*, 2024, 16 (3): 205-219.
- [6] Xue Li, Bing Wang, Shuang Zhou, et al. Surface chemistry governs the sub-organ transfer, clearance and toxicity of functional gold nanoparticles in the liver and kidney. *Journal of Nanobiotechnology*, 2020, 18 (1): 45.
- [7] Donald A Fernandes. Multifunctional gold nanoparticles for cancer theranostics. *3 Biotech*, 2024, 14 (11): 267.
- [8] Shakeel Ahmed, Annu, Saiqa Ikram, et al. Biosynthesis of gold nanoparticles: A green approach. *Journal of Photochemistry and Photobiology B: Biology*, 2016, 161141-153.
- [9] Carla Daruich De Souza, Beatriz Ribeiro Nogueira, Maria Elisa CM Rostelato. Review of the methodologies used in the synthesis gold nanoparticles by chemical reduction. *Journal of Alloys and Compounds*, 2019, 798714-740.
- [10] Discovery Phase in Drug Development. *BioAgilytix*.
- [11] Łukasz Niżnik, Maciej Noga, Damian Kobylarz, et al. Gold Nanoparticles (AuNPs)—Toxicity, Safety and Green Synthesis: A Critical Review. *International Journal of Molecular Sciences*, 2024, 25 (7): 4057.
- [12] Ilyas Ozcicek, Nese Aysit, Cagri Cakici, et al. The effects of surface functionality and size of gold nanoparticles on neuronal toxicity, apoptosis, ROS production and cellular/suborgan biodistribution. *Materials Science and Engineering: C*, 2021, 128112308.
- [13] Wenjuan He, Fuyuan Yang, Keming Chen, et al. Targeted gold nanoparticles for ovarian cancer (Review). *Oncology Letters*, 2024, 28 (6): 1AL-1AL.
- [14] Maria Mendes, Antonella Barone, João Sousa, et al. Gold Nanorods as Theranostic Nanoparticles for Cancer Therapy. *Nanotheranostics: Applications and Limitations*, 2019, 363-404.

- [15] Maria Enea, Eulália Pereira, Joana Costa, et al. Cellular uptake and toxicity of gold nanoparticles on two distinct hepatic cell models. *Toxicology in Vitro*, 2021, 70105046.
- [16] Wenwen Chen, Shaohua Zhang, Yangyang Yu, et al. Structural-Engineering Rationales of Gold Nanoparticles for Cancer Theranostics. *Advanced Materials*, 2016, 28 (39): 8567-8585.
- [17] Patrícia Figueiredo, Tomás Bauleth-Ramos, Jouni Hirvonen, et al. Chapter 1 - The Emerging Role of Multifunctional Theranostic Materials in Cancer Nanomedicine. *Handbook of Nanomaterials for Cancer Theranostics*, 2018, 1-31.
- [18] Kevin M Koo, Eugene JH Wee, Paul N Mainwaring, et al. Toward Precision Medicine: A Cancer Molecular Subtyping Nano-Strategy for RNA Biomarkers in Tumor and Urine. *Small*, 2016, 12 (45): 6233-6242.
- [19] Luca Digiacomio, Damiano Caputo, Roberto Coppola, et al. Efficient pancreatic cancer detection through personalized protein corona of gold nanoparticles. *Biointerphases*, 2021, 16 (1): 011010.
- [20] Jiayu Ren, Rong Cai, Jing Wang, et al. Precision Nanomedicine Development Based on Specific Opsonization of Human Cancer Patient-Personalized Protein Coronas. *Nano Lett.*, 2019, 19 (7): 4692-4701.
- [21] Hamid Ashraf, Ahmad Alam, Rizwan Ahmad. *Personalised Medicine. Personalized and Precision Nanomedicine for Cancer Treatment*, 2024, 5-13.