Journal of Pharmaceutical Analysis 14 (2024) 100964

Contents lists available at ScienceDirect

Journal of Pharmaceutical Analysis

journal homepage: www.elsevier.com/locate/jpa

Review paper

Progress and application of intelligent nanomedicine in urinary system tumors

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ARTICLE INFO

Article history:
Received 28 November 2023
Received in revised form
25 February 2024
Accepted 11 March 2024
Available online 12 March 2024

Keywords:
Intelligent nanomedicine
Urinary system tumors
Drug delivery
Biological barriers

ABSTRACT

Urinary system tumors include malignancies of the bladder, kidney, and prostate, and present considerable challenges in diagnosis and treatment. The conventional therapeutic approaches against urinary tumors are limited by the lack of targeted drug delivery and significant adverse effects, thereby necessitating novel solutions. Intelligent nanomedicine has emerged as a promising therapeutic alternative for cancer in recent years, and uses nanoscale materials to overcome the inherent biological barriers of tumors, and enhance diagnostic and therapeutic accuracy. In this review, we have explored the recent advances and applications of intelligent nanomedicine for the diagnosis, imaging, and treatment of urinary tumors. The principles of nanomedicine design pertaining to drug encapsulation, targeting and controlled release have been discussed, with emphasis on the strategies for overcoming renal clearance and tumor heterogeneity. Furthermore, the therapeutic applications of intelligent nanomedicine, its advantages over traditional chemotherapy, and the challenges currently facing clinical translation of nanomedicine, such as safety, regulation and scalability, have also been reviewed. Finally, we have assessed the potential of intelligent nanomedicine in the management of urinary system tumors, emphasizing emerging trends such as personalized nanomedicine and combination therapies. This comprehensive review underscores the substantial contributions of nanomedicine to the field of oncology and offers a promising outlook for more effective and precise treatment strategies for urinary system tumors.

1. Introduction

Urinary tumors include neoplasms of the bladder, kidney and prostate, and pose a significant challenge to healthcare systems worldwide due to their high incidence rates [1,2]. The invasive nature of these malignancies, and the resource-intensive conventional therapeutic approaches have spurred the development of intelligent nanomedicine-based strategies, which offer targeted pharmaceutical delivery, enhanced diagnostic precision, and improved tolerability [3,4]. Nanomedicine utilizes nanoscale materials, typically 1–100 nm in size, to develop precise, targeted, and highly efficient therapeutic and diagnostic platforms [5,6]. Furthermore, the physical, chemical, and biological characteristics of nanomaterials can be manipulated according to the unique tumor characteristics [7,8], thereby offering unprecedented opportunities to enhance treatment efficacy while minimizing negative effects on healthy tissues.

In this review, we have discussed the intricate landscape of urinary tumors and the limitations of current treatment modalities. Furthermore, the principles of nanomedicine design in the context of targeted drug delivery and the ability to overcome the biological barriers of urinary tumors have also been reviewed. Our objective is to provide critical insights into the future trajectory of intelligent nanomedicine in achieving highly precise, effective, and patient-centered treatment of urinary system tumors.

2. Urinary tumors and current treatment challenges

2.1. Types of urinary tumors and challenges

Urinary system tumors have a complex clinical landscape that present significant challenges for their diagnosis and treatment. For

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https://doi.org/10.1016/j.jpha.2024.100964

instance, most diagnostic methodologies for urinary malignancies entail invasive and discomforting procedures such as cystoscopy and biopsies, which warrants novel strategies with greater diagnostic precision and minimal invasiveness. Furthermore, the high rates of recurrence of these malignancies necessitate effective strategies to predict disease progression and ensure timely intervention. Urinary tumors can also develop resistance to conventional chemotherapy drugs over time. Finally, the inherent biological barriers presented by the microenvironment of these tumors, such as renal clearance, tumor heterogeneity, and immune evasion, impair delivery of therapeutic agents to the neoplastic cells.

Bladder cancer is one of the most common malignancies of the urinary system, and is characterized by frequent recurrence and invasive phenotypes [9–11]. It currently ranks 10th in terms of global cancer prevalence, with approximately 573,000 newly diagnosed cases and over 200,000 deaths recorded annually [12–14]. Bladder cancer is particularly prevalent in developed countries, and correlates with tobacco consumption and occupational exposure to carcinogens. Furthermore, the protracted and resource-intensive management of recurrent bladder cancer places considerable pressure on public health systems [15,16]. The diagnosis of bladder cancer largely depends on cystoscopy, which causes discomfort and requires technical expertise. The early stages of bladder cancer are non-invasive, and primarily treated by intravesical chemotherapy, wherein the drugs are directly injected into the inner lining of the bladder. However, this approach has several side effects, such as irritation and burning sensation in the bladder, and is unable to achieve sustained and targeted drug delivery [17]. Consequently, there is an urgent need to develop strategies for the early detection and targeted ablation of bladder cancer.

Kidney cancer, typified by renal cell carcinoma (RCC), is another common malignancy of the urinary system that presents a distinctive set of challenges [18]. Over 400,000 cases of RCC are diagnosed annually worldwide, and the incidence of RCC is steadily increasing [19,20]. It is asymptomatic in the nascent stages and often discovered incidentally during routine medical imaging. The diagnosis of RCC mainly relies on radiographic and histopathological assessments. Furthermore, RCC cells are highly recalcitrant to conventional chemotherapy and radiation therapy regimens, and targeted therapies have shown promise but are limited by the development of resistance. Therefore, surgical intervention is the primary therapeutic approach against RCC, although it is not universally applicable. Overall, the management of advanced-stage kidney cancer and its comorbidities entail significant financial burden [21], thereby warranting novel drug delivery strategies.

Prostate cancer is the most frequently diagnosed cancer in men, and is often difficult to diagnose due to its heterogeneous spectrum, ranging from slow-growing to highly aggressive forms [22]. The risk factors of prostate cancer are advanced age, genetic predisposition, and hormonal imbalances. The annual caseload of prostate cancer is 1.4 million, which presents significant challenges to public health systems worldwide [22,23]. Furthermore, prostate cancer entails substantial economic burden due to the high costs of early detection, active surveillance, and therapeutic interventions [24]. Early detection primarily relies on prostate-specific antigen (PSA) testing, which unfortunately has low specificity [25]. Therapeutic options include surgical intervention, radiation therapy, and androgen-deprivation therapy. The current challenges to the management of prostate cancer are the delineation between aggressive and indolent cases, and treatment-related sequelae, including hormonal perturbations [26].

2.2. Limitations of conventional treatment methods

Urinary tumors are currently treated by chemotherapy and radiation therapy, which inevitably affect the healthy adjacent tissues due to lack of tumor specificity [27–29], resulting in adverse events that significantly worsen patients' quality of life. For instance, radiation therapy often results in urinary and sexual dysfunction in prostate cancer patients [22,24,30]. Furthermore, bladder cancer has a high rate of recurrence, which is attributed to the poor penetration of chemotherapy drugs into the bladder wall [31,32]. Intravesical chemotherapy, the standard intervention for bladder cancer, often requires frequent and uncomfortable instillations due to the inability to maintain therapeutically relevant concentrations of the drug within the bladder. On the other hand, RCC is inherently recalcitrant to conventional chemotherapy agents [33,34], and the tumor cells infiltrate into the contiguous anatomical structures as the disease progresses to advanced stages. The diagnosis and monitoring of urinary system tumors often entail invasive procedures, including cystoscopy, biopsies, or prostate biopsies, which are not only uncomfortable but also increase the risk of potential complications. Furthermore, the current diagnostic methods cannot effectively distinguish between aggressive and indolent variants of bladder cancer, which is of profound significance in terms of therapeutic interventions. Conventional therapeutic modalities are inherently less effective against recurrent neoplasms, necessitating multiple treatment cycles and vigilant surveillance. In addition, cancer cells frequently develop resistance to chemotherapeutic drugs, which is particularly evident in RCC cases, and the survival of drug-resistant clones leads to recurrence and treatment failure.

Intelligent nanomedicine tailored to the unique complexities of each urinary tumor subtype can obviate the above limitations by facilitating precise drug delivery, improving diagnostic precision, and circumventing biological impediments, offering a patient-centric approach to urinary system tumor management [35].

3. Nanomedicine: A new era in the management urinary system tumors

3.1. The potential of nanomedicine in cancer diagnosis and therapy

Nanomedicine harnesses nanoscale materials, typically measuring 1–100 nm, to engineer diagnostic and therapeutic platforms. Liposomes were introduced as carriers for anti-cancer drugs in the 1960s and 1970s [36,37], marking the advent of nanomedicine in cancer treatment. Doxil, a liposomal formulation of the chemotherapeutic drug doxorubicin, was approved in 1995, exemplifying the potential of nanomedicine to enhance drug efficacy while mitigating side effects [38]. Since then, a diverse array of nanoparticle-based drug delivery systems have been developed, including polymeric nanoparticles, dendrimers, and quantum dots [39–41], which can be engineered to perform specific functions based on the distinct tumor characteristics. Moreover, intelligent nanomedicine with stimuli-responsive properties and targeted drug delivery has ushered in a new era of precision cancer therapy.

Traditional chemotherapy, though effective in eliminating tumor cells, often lacks specificity, resulting in collateral damage to the non-target tissues [7,42]. Nanocarriers functionalized with ligands, antibodies, or peptides can selectively target cancer cells or specific tumor microenvironments, thus mitigating harm to normal tissues and diminishing systemic toxicity (Fig. 1) [8,42–44]. The targeting ability of nanomedicine also preserves the physiological functions of the organ systems and therefore maintains patients' quality of life [45]. Moreover, nanoparticles with surface modifications and stimuli-responsive attributes can enhance drug retention within

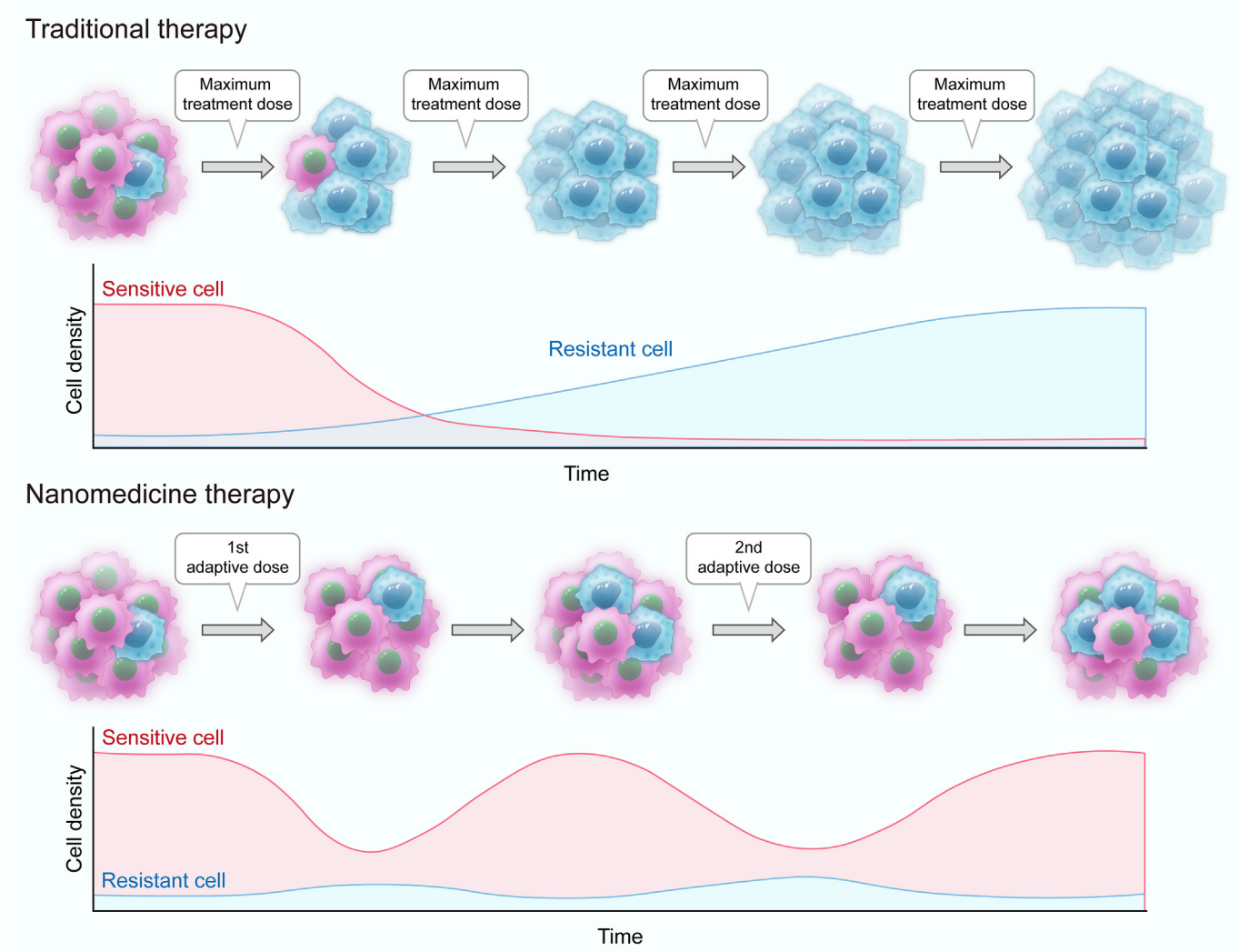

Fig. 1. Comparison of conventional cancer therapies and nanomedicine-based therapies. Chemotherapy, radiation therapy and surgery affect both diseased and healthy tissues, leading to side effects. Nanoparticles loaded with drugs or other therapeutic agents are designed to deliver the payload to specific disease sites, which not only enhances treatment efficacy but also reduces systemic toxicity. Nanomedicine strategies can be adapted to individual patient profiles and optimize therapeutic outcomes. Thus, nanomedicine offers for more targeted, efficient, and patient-centered treatments.

tumor tissues and promote a more uniform distribution within tumor lesions [46], thereby circumventing rapid clearance and tumor heterogeneity [47,48], and eventually improving the therapeutic outcomes [49].

In addition to therapeutic applications, nanomedicine has also been employed in advanced imaging and diagnostics. Several nanomaterials can function as contrast agents and enhance the accuracy of magnetic resonance imaging (MRI) and computed tomography (CT) scans [50–53]. Nanomedicine-based imaging augments early tumor detection and allows precise disease characterization. Furthermore, nanomedicine can be easily integrated into personalized medicine which is tailored to the individual patients based on their unique genetic profiles and disease attributes. Overall, the adaptability and customizability of nanomedicine can transform the current landscape of cancer therapy to more patient-centric approaches, and even aid in the management of distinct tumor subtypes.

3.2. Application of nanomedicine in urinary system tumors

As discussed the previous section, drug-loaded nanoparticles with surface modifications, such as ligands or antibodies, can selectively target cancer cells and obviate the off-target toxicity and side effects of conventional chemotherapy drugs [7,54,55]. This is particularly crucial for the treatment of urinary system tumors, where preserving healthy bladder or kidney tissue is paramount. Nevertheless, urinary system tumors present several biological barriers that hinder effective drug delivery. For instance, renal clearance rapidly eliminates drugs from the body and reduces their levels in the tumor lesions. Encapsulation of drugs in nanoparticles can prevent renal clearance, prolong circulation and enhance intra-tumoral retention [6,56–58]. Furthermore, the heterogeneity of urinary tumors, especially kidney cancer, can impede uniform drug distribution. Nanocarriers designed with stimuli-responsive properties can overcome this barrier by releasing drugs in a controlled and targeted manner.

Nanomedicine also aligns seamlessly with the principles of personalized medicine, enabling tailored therapies based on the unique genetic profiles and disease characteristics of individual patients. This not only optimizes treatment outcomes but also minimizes the risk of adverse effects. Nanomedicine-based personalized therapies can be valuable in prostate cancer management, especially in distinguishing the aggressive tumors from

the indolent forms. Drug resistance is a recurring issue in the treatment of urinary tumors, notably kidney cancer. Nanomedicine can counter the adaptive mechanisms employed by cancer cells and combat treatment resistance by enabling sustained and controlled release of therapeutic agents. Furthermore, recent studies have shown that contrast agents based on nanoparticles can enhance the accuracy of diagnostic tools like MRI and CT scans, facilitating early tumor detection and precise disease characterization [59–61]. Early diagnosis can significantly impact treatment outcomes, particularly for urinary system tumors.

In conclusion, nanomedicine holds immense potential for the management of urinary system tumors in terms of precise drug delivery, personalized medicine, enhanced diagnostic accuracy, and combating drug resistance and inherent biological barriers.

4. Intelligent nanomedicine design for urinary system tumors

4.1. Principles of intelligent nanomedicine design

Intelligent nanomedicine design encompasses drug encapsulation, targeting, and controlled release [62,63]. Encapsulation of therapeutic agents within nanoscale carriers, primarily nanoparticles or liposomes, serves multiple purposes. Firstly, it shields the drugs from premature degradation, ensuring their stability during transit through the bloodstream. Secondly, it can modify the pharmacokinetic properties of the drugs, resulting in prolonged circulation and enhanced bioavailability. Surface modifications of nanoparticles or liposomes with ligands, antibodies, or peptides enable them to recognize and bind to receptors or antigens overexpressed on the surface of cancer cells, ensuring the precise delivery of the therapeutic payload to the tumor site and minimizing off-target effects [3,64]. Controlled release mechanisms constitute a pivotal aspect of intelligent nanomedicine design [65]. Stimuli-responsive nanocarriers, activated by changes in pH or temperature for instance, can release the encapsulated drugs gradually and selectively in the tumor microenvironment in response to the specific conditions, resulting in optimal therapeutic effects [66–69].

The combination of drug protection, precise targeting, and controlled release ensures that therapeutic agents reach their intended destination with maximal potency while minimizing systemic side effects [70,71]. Intelligent nanomedicine design can revolutionize the management of urinary system tumors, offering hope for more effective, personalized, and patient-centric treatments.

4.2. Tailoring nanomedicines to urinary system tumors

Urinary system tumors present a diverse array of challenges due to their distinct characteristics. Nanomedicines tailor-made for these unique features can potentially improve therapeutic outcomes.

Bladder cancer is characterized by frequent recurrence and the risk of progression to invasive forms [46,72]. Nanoparticles designed to adhere to the bladder lining can deliver the drug cargo directly to the bladder wall in a sustained manner [48,73], thereby reducing the likelihood of recurrence and minimizing the need for frequent, uncomfortable intravenous instillations. Additionally, nanodrugs functionalized with stimuli-responsive ligands/antibodies can precisely target tumor sites and release drugs upon encountering specific conditions within the bladder. Likewise, nanodrugs incorporating ligands specific for the receptors overexpressed on RCC cells can selectively enhance drug uptake and minimize off-target effects, which may counteract the recalcitrance of RCC to conventional chemotherapy and radiotherapy [47,74]. Moreover, the controlled release of drugs from nanoparticles can be adjusted to address the slow-growing nature of certain RCC subtypes, and optimize drug delivery over an extended period [75,76]. Functionalized nanoparticles carrying contrast agents for imaging can be used to distinguish between the aggressive and indolent forms of prostate cancer [77]. This can guide treatment decisions, ensuring that aggressive forms receive timely intervention while sparing patients with indolent disease from unnecessary treatments [78,79]. Finally, nanomedicines can be designed with surface modifications that allow them to evade renal clearance, thereby extending their circulation time and increasing the likelihood of reaching the urinary tumor sites [80–82].

Taken together, intelligent nanomedicine not only optimizes drug delivery and minimizes side effects but also offers opportunities for personalized therapies that consider the specific subtype and stage of the cancer. Given the continuing advances in this field, intelligent nanomedicine offers a promising avenue for improved outcomes and quality of life for patients with urinary system tumors.

5. Intelligent nanomedicine for diagnosis and imaging of urinary system tumors

Early detection and accurate imaging play pivotal roles in enhancing the prognosis and management of urinary system tumors [83,84]. Intelligent nanomedicine enables highly sensitive detection of early stage urinary tumors through nanoparticles that target tumor-specific biomarkers [85,86]. For instance, nanoparticles designed to target prostate-specific membrane antigen (PSMA) receptors, which are often overexpressed on prostate cancer cells, enable early tumor detection through advanced imaging techniques like positron emission tomography (PET) [87–90]. Furthermore, nanoparticle-based contrast agents have the advantages of improved signal-to-noise ratios and prolonged circulation times, which can significantly enhance the visibility of tumors. For example, superparamagnetic iron oxide nanoparticles (SPIONs) can significantly enhance the precision of MRI in differentiating between benign and malignant renal masses (Fig. 2A) [50,91,92].

Integration of multimodal imaging agents, such as fluorescent dyes for optical imaging and radiotracers for PET imaging, into a single nanoplatform can further improve diagnostic precision and allow comprehensive tumor evaluation (Fig. 2B) [93,94]. Furthermore, Theranostic nanomedicine is a pioneering concept combining both therapeutic and diagnostic functions within a single platform. Nanocarriers loaded with both imaging agents and therapeutic drugs not only enable precise tumor imaging, but also facilitate real-time monitoring of treatment responses, thereby streamlining tailored therapies and allowing timely adjustments. In addition, nanoparticles incorporating fluorescent dyes can facilitate image-guided tumor surgical resection. Precise visualization of tumor margins using an imaging agent ensures complete resection and significantly diminishes the risk of residual cancer cells.

Liquid biopsies have emerged as a non-invasive method for detecting urinary and other cancers through the identification of circulating tumor cells or tumor-specific nucleic acids [95,96]. Nanoparticle-based capture and detection systems can significantly improve the sensitivity and specificity of liquid biopsies, thereby offering a promising approach for early tumor detection and real-time monitoring of treatment responses. Furthermore, nanoparticles conjugated to radiolabeled PSMA-targeted ligands can detect early prostate cancer lesions, even in cases of biochemical recurrence, and monitor disease progression with high specificity through PET imaging [97,98]. Likewise, SPION-enhanced MRI can accurately distinguish between benign and malignant renal masses since owing to the differential accumulation of these nanoparticles in benign and malignant tissues [99–101].

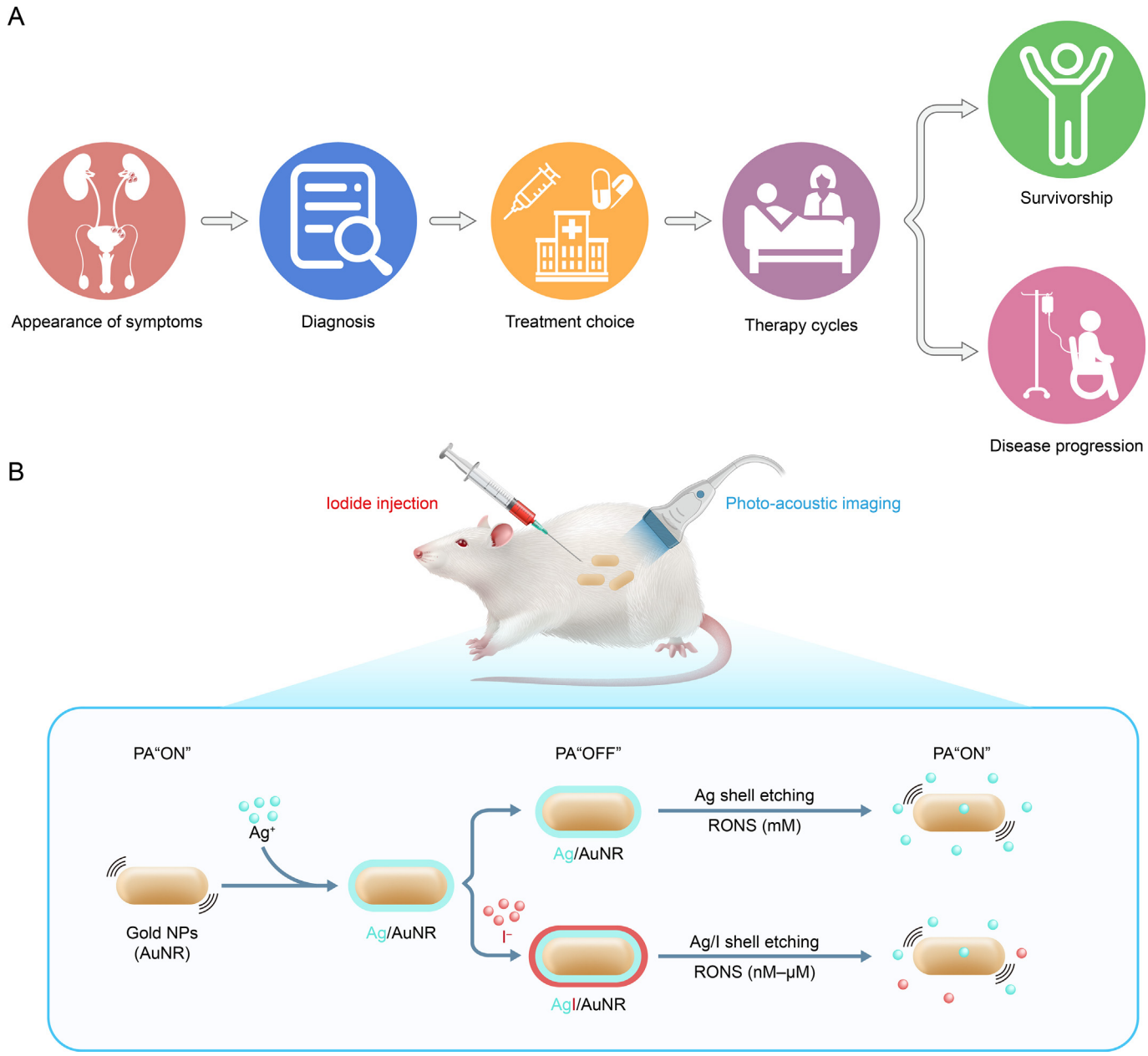

Fig. 2. Intelligent nanomedicine for early tumor diagnosis. (A) Nanoparticles (NPs) engineered as contrast agents enhance the sensitivity and specificity of magnetic resonance imaging (MRI) for earlier and more accurate disease detection, monitoring of treatment responses, and visualization of intricate anatomical structures. (B) Iodide-doped gold nanoparticles can measure oxidative stress levels through non-invasive, high-resolution photo-acoustic imaging (PA), thus showing potential for early disease detection and treatment monitoring. NR: Nanorod.

Taken together, intelligent nanomedicine holds immense promise in the diagnosis and imaging of urinary system tumors, which highlights the potential for more finely tuned therapeutic strategies and improved patient outcomes.

6. Therapeutic applications of intelligent nanomedicine

6.1. Intelligent nanomedicine for targeted drug delivery

Intelligent nanomedicine capitalizes on a diverse repertoire of targeting mechanisms to enhance the specificity of drug delivery (Fig. 3). Surface modifications with ligands, antibodies, or peptides allow nanoparticles to recognize and bind to receptors or antigens that are overexpressed on cancer cells, thus ensuring the targeted delivery of the therapeutic payloads. Encapsulating drugs within nanoparticles circumvents the off-target effects and systemic toxicity associated with chemotherapy [102], ultimately improving patient tolerance and overall quality of life during treatment.

Urinary system tumors present some inherent barriers, including renal clearance, tumor heterogeneity, and immune evasion, which limit the efficacy of therapeutic agents. Nanoparticles can be designed to avoid renal clearance, thus prolonging the circulation of drugs and improving access to tumor sites. Moreover, nanoparticles imbued with stimuli-responsive attributes can overcome tumor heterogeneity by specifically releasing drugs within the tumor microenvironment.

Urinary system tumors also manifest substantial inter-patient heterogeneity, necessitating a personalized approach to treatment.

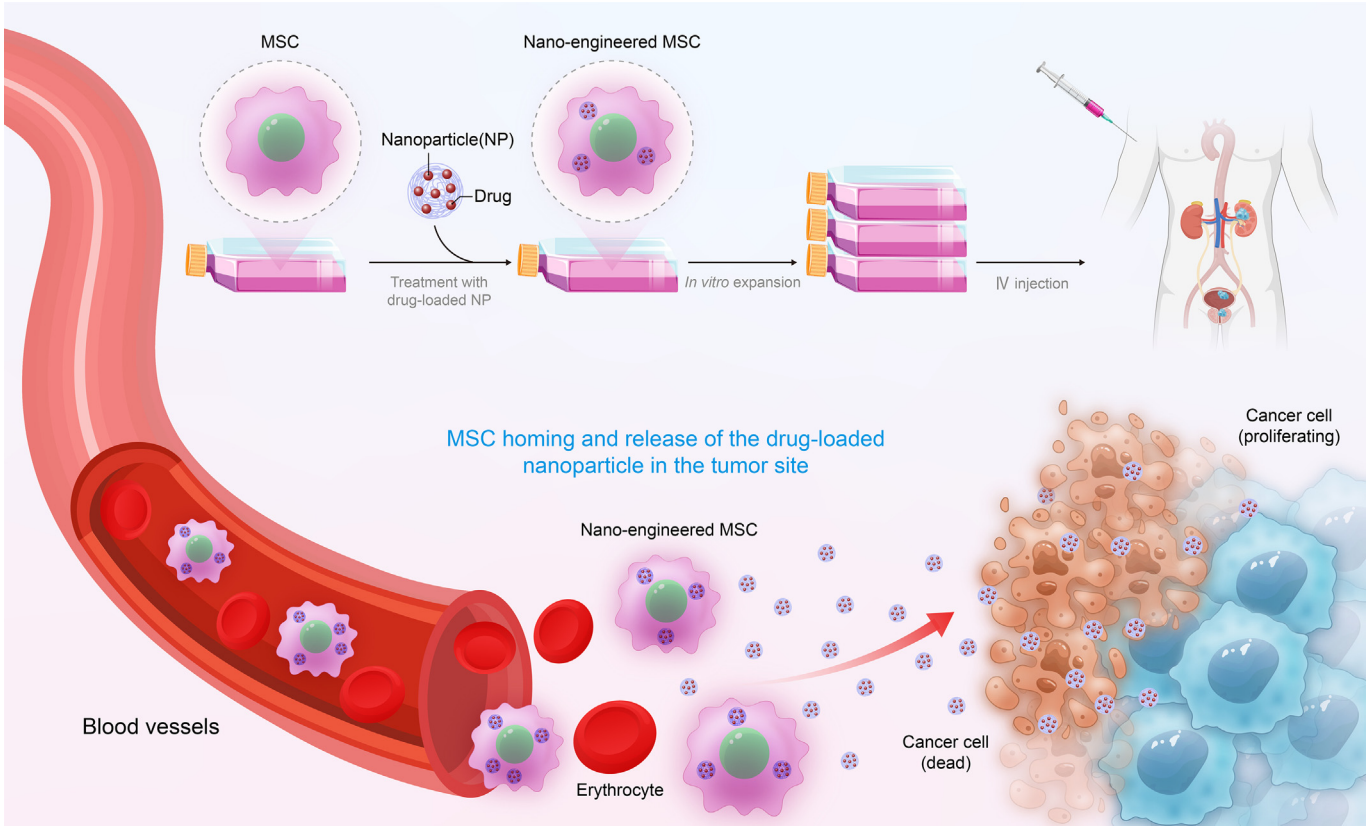

Fig. 3. Mesenchymal stem cells (MSCs) can home to tumor sites and deliver drug-loaded nanoparticles to the target cells. Once loaded with drug-loaded nanoparticles, MSCs can navigate the complex urinary system and reach the intended target. This targeted approach minimizes off-target effects on healthy tissues, significantly reducing side effects and enhancing patient tolerability. Upon reaching the tumor microenvironment, these drug-loaded nanoparticles can be released in a controlled manner, thereby optimizing therapeutic outcomes.

Intelligent nanomedicine can facilitate treatment customization based on individual patient profiles through tailormade drugs, targeting ligands, and release mechanisms. Furthermore, nanoparticles incorporating imaging agents can be used to visualize tumor sites in real time through MRI, CT, or ultrasound [94,103,104], and release the drug cargo with high precision in response to imaging cues. Image-guided drug delivery not only maximizes therapeutic efficacy but also diminishes harm to healthy tissues.

In conclusion, intelligent nanomedicine can achieve targeted drug delivery, mitigate systemic toxicity, overcome biological barriers, align with personalized medicine, and accommodate image-guided therapy, which can contribute to better patient outcomes and quality of life.

6.2. Advantages of nanomedicine over traditional chemotherapy

Foremost among the merits of nanomedicine is its exceptional precision in drug delivery. In stark contrast to traditional chemotherapy, which lacks specificity and impacts both malignant and healthy cells indiscriminately, nanocarriers can be engineered to target markers or receptors that are overexpressed on the surfaces of urinary system tumor cells. This unparalleled selectivity effectively curtails collateral harm to healthy tissues, thereby diminishing side effects and markedly enhancing the patient's overall quality of life. It is noteworthy that a significant proportion of chemotherapeutic agents grapple with limited solubility, a predicament that can significantly impede their therapeutic efficacy [105]. Nanomedicine adroitly tackles this quandary by encapsulating drugs within nanoparticles, thereby augmenting their solubility and bioavailability. This strategic intervention guarantees that a higher proportion of the drug reaches the intended tumor site, ultimately optimizing therapeutic outcomes.

Urinary system tumors will encounter problems such as distinctive biological barriers, renal clearance, and tumor heterogeneity, among others during treatment. Nanomedicine offers tailored solutions to these formidable challenges. Notably, nanoparticles can be strategically designed to elude renal clearance, ensuring the persistence of drugs within the bloodstream and their efficacious delivery to tumor sites [106,107]. Furthermore, nanoparticles fortified with stimuli-responsive attributes have the capability to bypass tumor heterogeneity by releasing drugs with surgical precision at specific sites in the tumor microenvironment where their action is needed.

Conventional chemotherapy often causes systemic toxicity, triggering a series of adverse effects that can severely debilitate patients. In stark contrast, nanomedicine reduces this toxicity by enclosing drugs within nanoparticles, thus protecting healthy tissues from the harmful effects of the therapeutic agent until it reaches its intended target site. This strategic encapsulation significantly heightens patient tolerability throughout the course of treatment. The considerable heterogeneity observed among patients afflicted with urinary system tumors necessitates the pursuit of personalized therapeutic approaches. Nanomedicine, by dint of its adaptability and multifaceted customization potential, aligns seamlessly with the fundamental tenets of personalized medicine. The intricate customization of drugs, targeting ligands, and release mechanisms ensures that therapeutic regimens are meticulously tailored to harmonize with the unique

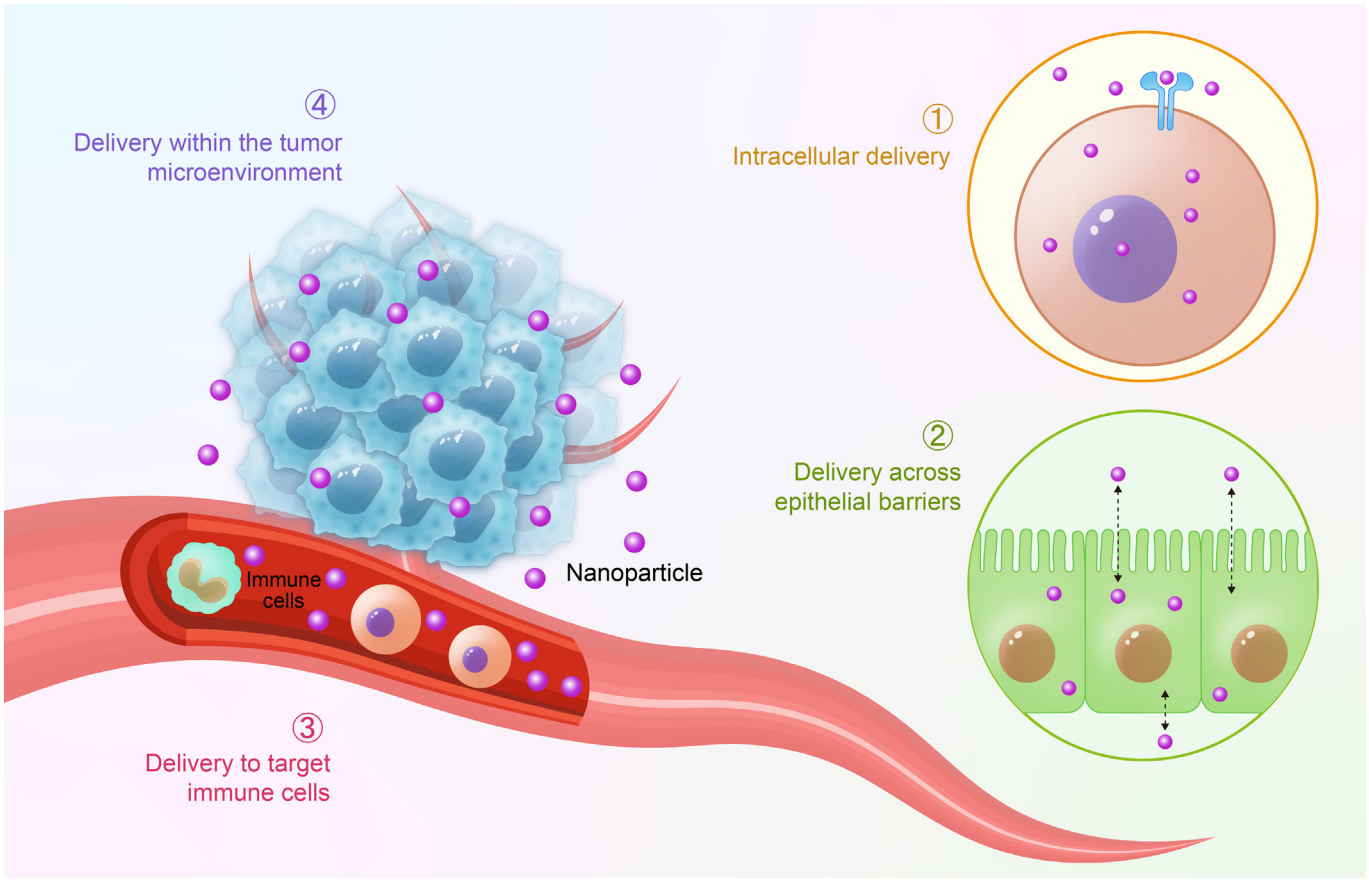

Fig. 4. Conquering biological barriers with nanoparticles. The urinary tumor microenvironment poses challenges related to drug delivery, immune evasion, and tissue penetration. Innovative nanoparticles have been engineered to evade immune detection, enhance drug solubility, and deliver therapeutic payloads with precision. Their adaptability allows them to navigate the intricate biological landscape of urinary tumors, thereby optimizing treatment outcomes and reducing side effects.

attributes characterizing each patient's tumor. Furthermore, the integration of imaging modalities into the realm of nanomedicine furnishes a real-time monitoring framework for drug delivery and therapeutic response assessment. This image-guided approach empowers clinicians with the capacity to visualize tumor sites, gauge the effectiveness of treatments, and make timely adjustments, thereby augmenting treatment precision to unprecedented levels.

In summary, nanomedicine offers numerous advantages over traditional chemotherapy, such as for the treatment of urinary system tumors. Nanomedicine's precision, ability to enhance drug solubility, capacity to overcome biological barriers, reduction of toxicity, alignment with personalized medicine principles, and facilitation of image-guided therapy combine to make it a transformative approach with the potential to significantly improve patient outcomes and redefine the established standards for managing these malignancies.

7. Designing nanoparticles that adapt to the urinary tumor microenvironment

Although nanomedicine has emerged as a promising option for treating urinary system tumors, rapid renal clearance and tumor heterogeneity can diminish therapeutic efficacy by reducing the circulatory half-life and tumor retention of the nanoparticles. Therefore, tailoring nanoparticles according to the unique urinary microenvironment can optimize drug delivery [108,109]. The kidneys are the major excretory organs of the body, and orchestrate the filtration of diverse substances, including nanoparticles, from the circulation [68,110]. Nanoparticles with augmented dimensions or surface modifications can elude renal clearance. Notably, polyethylene glycol coating, also known as PEGylation, can prolong the circulation of nanoparticles, thereby increasing their likelihood of homing to the tumor site.

The microenvironment of urinary tumors is highly complex owing to the diverse cell populations, dynamic extracellular matrix, and a fluctuating blood supply. In addition, urinary system tumors exhibit considerable heterogeneity, which poses a formidable challenge pertaining to the uniform distribution of therapeutic agents. Stimuli-responsive nanoparticles have been designed that release therapeutic agents in a precise and targeted manner in response to the specific conditions in distinct tumor regions [111]. Notably, several studies have shown that pH-responsive polymeric nanoparticles can selectively release encapsulated drugs in the characteristically acidic tumor niche following low pH-induced conformational changes [112].

Furthermore, stimuli-responsive nanocarriers can also acclimatize to the ever-evolving conditions within the urinary system and tumor microenvironment (Fig. 4) [113,114], which ensures that the therapeutic payloads are delivered to the specific locations. For instance, temperature-sensitive liposomes have been designed that disintegrate when exposed to hyperthermic conditions and release the encapsulated drugs, and are inducible by external stimuli such as focused ultrasound or radiofrequency ablation [115,116]. This strategy also ensures that the therapeutic agents homogenously diffused throughout the tumor subregions [117]. Furthermore,

enzyme-responsive nanoparticles have been tailored that release their cargo in direct response to the presence of specific enzymes in the tumor microenvironment, which enhances drug distribution and therapeutic outcomes.

The immune system is also a key factor that determines the circulatory lifespan and distribution of nanoparticles. Stimuli-responsive nanocarriers coated with immune-evasion molecules can escape recognition by immune cells, resulting in extended circulation. *In vivo* studies have clearly demonstrated increased retention and tumor-specific accumulation of nanoparticles with immune-evasion coating.

Taken together, stimuli-responsive nanocarriers can adapt to the unique microenvironment of urinary tumors and circumvent the intricate biological barriers of the urinary system, which translates to increased therapeutic precision and efficacy.

8. Clinical translation of intelligent nanomedicine and challenges

8.1. Research status of intelligent nanomedicine for urinary system tumors

The domain of intelligent nanomedicine geared towards the management of urinary system tumors has witnessed substantial advancements in recent years, marked notably by the initiation of several auspicious therapies undergoing rigorous clinical scrutiny. These clinical investigations furnish indispensable insights into the veracity and efficacy of nanomedicine-based strategies when applied within the realm of real-world patient cohorts. From a vantage point grounded in professionalism and academia, an appreciation of the contemporary status of these clinical trials assumes pivotal importance, serving as a linchpin for the evaluation of the translational potential inherent to intelligent nanomedicine as a modality for the management of urinary system tumors.

Clinical trials germane to nanomedicine in the context of bladder cancer have predominantly gravitated towards intravesical therapeutic modalities [118,119]. A prevailing paradigm within these trials is the utilization of nanoparticles as vehicles for the direct bestowal of therapeutic agents into the bladder milieu, thereby effectuating a judicious mitigation of systemic drug exposure. The therapeutic agents under scrutiny encompass a gamut spanning immunomodulators to chemotherapeutic agents. The auspicious outcomes gleaned from preliminary forays into this domain have catalyzed the inception of large-scale investigations aimed at scrutinizing the efficacy of these interventions, with a focal emphasis on their potential to curtail tumor recurrence and progression, all the while enhancing patient tolerability.

Within the sphere of kidney cancer, clinical trials have unfurled an expansive vista characterized by the exploration of nanoparticle-facilitated drug delivery systems designed to augment the bioavailability of targeted therapeutic regimens. This augmentation is predicated on the encapsulation of therapeutic agents within nanoparticles in pursuit of the twin objectives of potentiated drug delivery to renal tumor foci and the amelioration of systemic adverse effects. The overarching strategy in these endeavors encompasses the amalgamation of image-guided methodologies and biomarker-driven targeting, thereby engendering a heightened precision in therapeutic interventions. This rich tapestry of clinical trials is presently in progress, with the collective aim of ascertaining the clinical merits of these approaches in patients afflicted with renal cell carcinoma.

Clinical trials in the milieu of prostate cancer have adroitly harnessed the intrinsic imaging prowess of nanoparticles to propel a dual-pronged mission: one characterized by the amalgamation of contrast agents with therapeutic payloads to enable both precise diagnostic delineation and efficacious treatment. The indispensable tools at the disposal of these trials encompass MRI and PET, standing as the vanguard of diagnostic imaging modalities [87]. These clinical endeavors are diligently scrutinizing the diagnostic fidelity, the monitoring of treatment responses, and the therapeutic dividends that can be realized through the judicious incorporation of nanomedicine-based interventions into the management of prostate cancer [120]. These trials are notable not only for their focus on localized therapies but also for the strategic exploration of liquid biopsies employing nanoparticles as instrumental agents. These liquid biopsies are designed with the overarching goal of detecting urinary system tumors by analyzing the microscopic realm of circulating tumor cells, nucleic acids, or proteins. Furthermore, the realm of biomarker research, centered on nanomedicine-based diagnostics, is rapidly pushing the boundaries of personalized medicine for urinary system tumors.

While the clinical trials supporting advanced nanomedicine for the management of urinary system tumors are spread across different stages of development, they collectively represent a growing recognition of the inherent potential of nanomedicine. As these trials unfold and accumulate empirical data, they are poised to transform the landscape of urinary system tumor management, ushering in a new era characterized by increased precision, enhanced efficacy, and the customized provision of therapeutic options for the well-being of affected patients.

8.2. Safety, regulatory approval, and scalability of intelligent nanomedicine

While intelligent nanomedicine holds vast potential for the treatment of urinary system tumors, it is still beset with challenges concerning safety, regulatory validation, and scalability. For instance, certain nanoparticles may exhibit toxicity or immunogenicity, potentially leading to adverse effects [121,122]. Therefore, rigorous preclinical toxicity evaluation is crucial to gauge the safety profiles of both nanocarriers and therapeutic payloads. Moreover, the long-term effects of nanomedicine also warrant thorough investigation, given the potential necessity for repeated administrations in the treatment of urinary system tumors. Thus, multidisciplinary studies integrating clinical practice, toxicology, and nanotechnology are needed to identify and mitigate potential safety risks of nanomedicine.

Given the distinctive attributes and dynamic evolution of nanomedicines, it is often difficult to secure regulatory approval. The guidelines of national regulatory bodies, such as the Food and Drug Administration (FDA) in the United States or the European Medicines Agency (EMA) in Europe, mandate rigorous evaluation of the physicochemical attributes, stability profiles, and toxicity footprints of nanoparticles. Researchers and pharmaceutical developers face considerable challenges in translating intelligent nanomedicine therapies into clinical practice. Hence, the collaborative efforts of academia, industry stakeholders, and regulatory agencies will be decisive in expediting and streamlining the regulatory clearance process of nanomedicine.

The extensive clinical utilization of nanomedicine formulations hinges on the feasibility of manufacturing nanoparticles on a scale commensurate with large-scale clinical trials and commercial production. Furthermore, preservation of batch-to-batch consistency, quality control, and cost-effectiveness are key concerns regarding scalability. To this end, researchers are diligently exploring a spectrum of manufacturing methodologies, spanning from microfluidics to continuous flow processes, to bridge the gap between laboratory-scale experimentation and large-scale commercial production. Variations in particle size, drug loading, and

surface properties can have a significant impact on the therapeutic efficacy and safety profiles of nanomedicine formulations. Therefore, it is crucial to establish standardized protocols for the synthesis, characterization, and quality control of nanomedicines in order to ensure reproducibility and uniformity.

In summary, the full potential of nanomedicine can only be realized by addressing the safety concerns, navigating regulatory guidelines, and achieving scalability milestones. There is an urgent need for more extensive collaboration between academia, pharmaceutical industry, regulatory agencies, and healthcare practitioners in order to expedite the clinical translation of nanomedicine for urinary system tumor management.

9. Future directions and emerging trends in intelligent nanomedicine

Intelligent nanomedicine holds immense potential for enhancing therapeutic outcomes and the quality of life of cancer patients. In this section, we have summarized the current and prospective trends in the nanomedicine-based therapies for urinary system tumors.

Greater customization of nanomedicine-based therapies can be expected in the foreseeable future due to continuing advances in genomics, proteomics and biomarker research. Nanocarriers, therapeutic payloads, and treatment regimens tailormade to the intricate genetic and molecular profiles of individual tumors can optimize therapeutic responses while simultaneously minimizing side effects. As molecular profiling becomes more accessible and cost-effective, personalized nanomedicine is poised to become the standard for urinary system tumor management. Furthermore, there is considerable interest in combining nanomedicine with immunotherapy for the treatment of bladder cancer and RCC. Various immunomodulatory agents, including immune checkpoint inhibitors, cytokines, and antigens, can be seamlessly incorporated into nanocarriers. The targeted delivery of these immunotherapeutic drugs to the tumor microenvironment can bolster the immune system's capacity to identify and eliminate malignant cells, and synergistically augment the therapeutic effects.

Theranostic nanomedicine combines therapeutic and diagnostic agents into a single nanoplatform, and offers the possibility of simultaneously delivering therapeutic agents to the tumor site, and providing real-time monitoring of treatment responses through advanced imaging modalities or biomarker sensing. Therefore, theranostic nanomedicine can facilitate timely adjustments to treatment strategies via immediate assessment of therapeutic efficacy. Likewise, amalgamation of diverse therapeutic modalities within a singular nanomedicine platform enables concurrent chemotherapy, targeted therapy, immunotherapy, and radiation therapy, resulting in synergistic therapeutic effects. The intelligent design of the nanoparticles further allows precise control over the release kinetics of multiple therapeutic agents. Combination therapeutic approaches are of particular interest in advanced kidney cancer or recurrent bladder cancer, which frequently exhibit treatment recalcitrance.

Minimally invasive drug administration is a significant concern for urinary system tumors, especially bladder cancer. Techniques such as intra-tumoral injection or endoscopic instillation can minimize patient discomfort and concomitantly enhance the precision of drug delivery. Moreover, liquid biopsies employing nanomedicine-based technologies can revolutionize urinary system tumor diagnostics. Liquid biopsies offer a non-invasive strategy for early cancer detection, ongoing treatment monitoring, and the identification of minimal residual disease based on circulating tumor cells, cell-free DNA, or tumor-derived exosomes. Nanoparticles endowed with specialized capture and detection systems can further enhance the diagnostic precision of liquid biopsies.

Integration of nanomedicine with cutting-edge imaging technologies can facilitate precise tumor detection, along with real-time tracking of nanomedicine distribution within the urinary system, as well as real-time image-guided therapeutic interventions. Nanoparticles functioning as contrast agents, or incorporating quantum dots and advanced MRI contrast agents, enable high-resolution tumor visualization that can enhance the precision of tumor resection, particularly for bladder and prostate cancers.

To summarize, personalized nanomedicine, combination therapies, immunomodulation, liquid biopsies, and image-guided therapies are the emergent trends in intelligent nanomedicine within the landscape of urological tumors. These advances can potentially augment treatment outcomes, minimize deleterious side effects, and offer a repertoire of therapeutic options for individualized, patient-centric care.

10. Conclusion

In this review, we have explored the applications, current research status and future prospects of intelligent nanomedicine within the landscape of urological tumors. Intelligent nanoparticles can orchestrate precise drug delivery to the tumor sites via targeting ligands, which not only improves therapeutic efficacy but also minimizes off-target effects. Furthermore, stimuli-responsive nanocarriers can evade renal clearance, adapt to the tumor heterogeneity, and respond to the ever-fluctuating tumor microenvironment.

Advances in genomics and biomarker research have brought personalized nanomedicine to the forefront. Nanoparticles tailormade to the unique characteristics to individual patient profiles can optimize drug delivery, augment treatment efficacy and mitigate side effects. Furthermore, targeted delivery of immunomodulatory agents into the tumor microenvironment via nanocarrier can synergistically enhance treatment outcomes by stimulating anti-tumor immune responses. Integration of multiple therapeutic agents within a single nanocarrier is also a promising strategy for achieving synergistic therapeutic effects against urinary system tumors, especially advanced kidney cancer or recurrent bladder cancer. Furthermore, nanomedicine technologies can be employed to retrieve liquid biopsies for the detection of circulating tumor cells and cancer biomarkers, thereby allowing early detection, treatment monitoring, and identification of minimal residual disease. Finally, nanomedicine has revolutionized cancer diagnostics by using nanoparticles as contrast agents or integrating imaging probes techniques.

In conclusion, nanoscale technologies can potentially transform cancer diagnostics and treatment through precise drug targeting, controlled release, and improved imaging. While challenges like safety and scalability remain, clinical translation is in progress. The future of intelligent nanomedicine in urinary system tumor management is promising, especially with personalized approaches and combination therapies.

CRediT authorship contribution statement

Yingming Xiao: Conceptualization, Writing – Original Draft, Visualization, Figure Preparation; **Lei Zhong:** Investigation, Writing – Review & Editing, Visualization; **Jinpeng Liu:** Investigation, Writing – Review & Editing, Visualization; **Li Chen:** Writing – Review & Editing, Supervision; **Yi Wu:** Writing – Review & Editing, Supervision; **Ge Li:** Conceptualization, Visualization, Resources, Writing – Review & Editing, Supervision.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

Acknowledgments

Thanks to Bioinfo Composer and Beijing Xinshi for their language polish services.

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