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REVIEW

Nanoreagents Against the Blood-Testis Barrier: A Strategy for Diagnosing and Treating Male Reproductive System Diseases

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Abstract: Male reproductive health represents a critical yet challenging area of medical science, where conventional diagnostics and therapies are often limited by physiological barriers—particularly the blood-testis barrier (BTB)—and the complex etiology of disorders such as infertility, prostate cancer, and erectile dysfunction. In recent years, nanoreagents has emerged as a transformative tool, enabling unprecedented advances in drug delivery, imaging, and therapeutic precision. This review systematically examines the application of diverse nanomaterials—including metal nanoparticles, lipid-based systems, polymeric carriers, and natural derivatives such as nanobodies, extracellular vesicles, and cell membrane-coated nanoparticles—in the context of male reproductive medicine. These platforms facilitate targeted drug delivery across the BTB, enhance local drug bioavailability, minimize systemic toxicity, and support sustained release profiles. In diagnostic imaging, nanotechnology augments modalities such as MRI, PET, and photoacoustic imaging. Furthermore, natural biomaterials offer biocompatible and immunologically inert strategies for drug encapsulation and targeted transport, improving both efficacy and safety. Despite these promising developments, challenges remain in standardization, long-term biosafety, and scalable synthesis. Nevertheless, the integration of nanotechnology in male reproductive health is poised to redefine treatment paradigms, offering personalized, efficient, and minimally invasive solutions. As research progresses, nano-based approaches hold significant potential to address unmet clinical needs and improve reproductive outcomes worldwide.

Keywords: nanoparticle, blood-testis barrier, reproductive system diseases, drug delivery, biomaterials

Introduction

Reproduction is a critical priority for all human populations, with men playing an essential role. According to global surveys conducted by the World Health Organization, one in seven couples of reproductive age worldwide experiences infertility,[1] and male factors account for approximately 50% of these cases. The rising incidence of male infertility has attracted increasing attention worldwide, prompting extensive research into the physiological functions and pathological mechanisms of the male reproductive system. Male reproductive system diseases pose serious threats to men's health. Conditions such as sperm abnormalities, sexual dysfunction, reproductive tract infections, and tumors not only impair physical and psychological well-being but are also major contributors to male infertility. Male reproductive disorders

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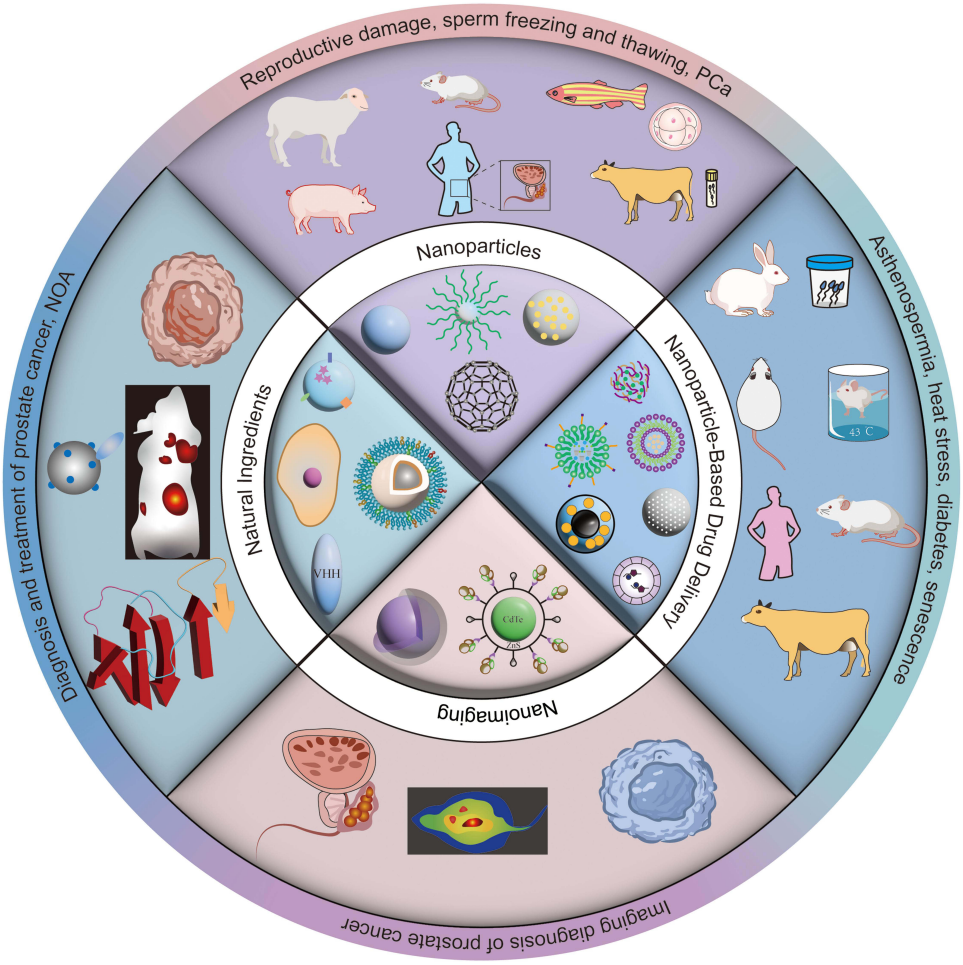
Graphical Abstract



constitute a complex spectrum of conditions with multifactorial etiology. A prominent example is asthenozoospermia, characterized by reduced sperm motility and associated with impaired fertilization potential.[2,3] The pathophysiology of this condition—linked to genetic predisposition, oxidative stress, inflammation, and immune dysregulation—remains incompletely elucidated.[4] Current management includes oral hormone therapy, antioxidant regimens, and traditional Chinese medicine.[5] Oxidative stress represents another major contributor to male infertility, inducing sperm membrane lipid peroxidation and DNA damage.[6,7] These alterations have been associated not only with subfertility, but also with adverse outcomes such as miscarriage, genetic disorders, and childhood malignancies.[8] Clinically, oral antioxidants including vitamin C, vitamin E, carnitine, and zinc are commonly used to mitigate such reproductive damage.[9] Erectile dysfunction (ED), another prevalent condition, arises from diverse risk factors such as diabetes, obesity, psychological disturbances, and age-related testosterone decline.[10–13] Its pathogenesis frequently involves oxidative stress pathways,[14] making phosphodiesterase-5 (PDE-5) inhibitors a first-line treatment. However, their efficacy can be limited by side effects and food interactions.[12,15] A common challenge across these disorders is the inability of conventional oral drugs to achieve site-specific delivery within the reproductive system. This often results in prolonged therapy, suboptimal efficacy, and systemic side effects. There is a clear clinical need for more precise and targeted treatment strategies to overcome these limitations.

Oral drug administration remains a primary treatment strategy for these conditions. However, its efficacy is limited by issues related to dosing regimen, timing, and bioavailability, and is further compromised by first-pass metabolism.[16] Moreover, many therapeutic agents are unable to effectively cross the blood-testis barrier due to their molecular weight or solubility, hindering their action on the germinal epithelium. In the case of chronic bacterial prostatitis (CBP), prolonged antibiotic therapy is required, and its success largely depends on achieving adequate drug concentrations at the infection site within the prostate.[17] For prostate cancer (PCa), localized treatment has emerged as a promising strategy to minimize damage to healthy glandular tissue. These challenges highlight the urgent need for drug delivery systems that enable precise targeting, sustained release, and enhanced penetration of physiological barriers. To address these complex issues, this article proposes an innovative strategy: the protective use of nanoreagents, which offers a novel and promising direction for the treatment of male reproductive system diseases. Experimental evidence clearly demonstrates the impediment of the blood-testis barrier to drug delivery: analysis of biological samples from gossypol-treated rats revealed that the drug concentration in the seminiferous tubule fluid was significantly lower than that in plasma.[18] However, when gossypol was encapsulated in liposomes, this nano-formulation exhibited a enhanced ability to penetrate the blood-testis barrier without altering its systemic pharmacokinetics, thereby providing a robust strategy for achieving precise drug delivery to the testicular site.[19]

After years of advances, nanotechnology has achieved breakthroughs and found applications across multiple disciplines. It has become a vital area of development in biomedicine, particularly in early tumor diagnosis, drug encapsulation and delivery, and tissue engineering.[20–22] In the field of reproductive health, nanotechnology is increasingly recognized by physicians and biologists. For example, in 2014, Barkalina et al investigated mesoporous silica nanoparticles as targeted carriers for reproductive medicine and evaluated their effects on in vitro sperm function.[23,24] In 2018, Lloyd-Parry et al reviewed the applications of nanomedicine in women's health, spanning reproductive medicine, mental health, and sexual health.[25] That same year, Remião et al summarized potential uses of nanotechnology in assisted reproductive technology (ART) and outlined emerging prospects for its application.[26] More recently, in 2021, Silva et al discussed the role of nanotechnology in ART—particularly for delivering hormones and antioxidants to embryos and oocytes—while also highlighting the challenges in the application of nanotechnology.[27]

Given this context, the emergence of nanomaterials and nanotechnology in healthcare is highly promising. Programmable nanomodulators offer new opportunities to address challenges once considered insurmountable The unique physiological structure of the male reproductive system provides an ideal platform for the application and development of nanotechnology. A growing body of research has documented the use of nanotechnology in managing various male reproductive disorders, including ED, prostatitis, reproductive tract damage, oxidative stress, asthenospermia, and reproductive tumors, as well as in sperm cryopreservation and artificial insemination. Nonetheless, a systematic review that offers detailed and comprehensive guidance for researchers in this field remains lacking. Therefore, this article aims to explore the convergence of nanomedicine with the diagnosis and treatment of male reproductive system diseases, focusing on advances in various nanoparticle-based strategies—including metal nanoparticles. We also evaluate the beneficial effects and significant potential of programmable nanoreagents constructed from polymer-based, metal-based, and lipid-based nanocarriers in treating these conditions. The emergence of naturally derived nanomaterials with better biocompatibility, enhanced cellular penetration, and higher bioavailability indicates that the vision of a widespread intersection between nanomedicine and reproductive system disease diagnosis and treatment is on the verge of becoming a reality. Although the full clinical translation of nanotechnology has yet to be realized, this work will provide valuable insights and support to advance its biomedical applications.

Physiological Architecture and Importance of the Male Reproductive System

The male reproductive system comprises both external and internal organs. The external structures include the penis and scrotum, while the internal components consist of the testes, epididymis, vas deferens, ejaculatory ducts, seminal vesicles, and prostate, among others.[28] A central component of this system is the testes—ellipsoidal organs located bilaterally within the scrotum. Within the testicular interstitial tissue, Leydig cells are responsible for the secretion of androgens, primarily testosterone (T).[29,30]

Androgens, which include several types present in the human body, play a central role in regulating male reproductive health. Governed by the hypothalamic-pituitary-gonadal axis (HPG), the secretion of androgens is initiated by gonadotropin-releasing hormone (GnRH), stimulating the anterior pituitary to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These hormones act on the testes, promoting testosterone production and stimulating spermatogenesis.[31]

Androgens also play important roles beyond reproduction, participating in key metabolic processes such as protein synthesis, nitrogen balance regulation, calcium deposition in bone, skeletal muscle development, and erythrocyte production.[32,33] As central endocrine organs, the testes not only produce hormones but also provide essential structural and biochemical support for spermatogenesis—including specialized physiological barriers, nutrients, and growth factors.[34]

Spermatogenesis is a complex physiological process that takes place in the seminiferous tubules of the testes. It is tightly regulated by the HPG axis and key signaling pathways—including TGF-β/Smad, AMPK, and MAPK—and represents a fundamental aspect of male reproductive health,[35,36] A critical structure supporting this process is the BTB, a dynamic ultrastructure formed by Sertoli cells that maintains a stable microenvironment essential for spermatogenesis. However, under inflammatory or pathological conditions, the BTB impedes the passage of immune mediators and therapeutic agents, thereby complicating treatment approaches (Figure 1).[37] Furthermore, drug efflux transporters such as P-glycoprotein (P-gp) and breast cancer resistance protein, expressed at the BTB, limit the penetration of exogenous compounds and help protect developing germ cells from damage.[38]

Overcoming the BTB is essential for effective treatment of male reproductive system diseases. Conventional oral drug administration is substantially limited by such physiological obstacles, highlighting the urgent need for advanced delivery strategies or engineered carriers.

The prostate gland, a chestnut-shaped organ situated below the bladder, plays multiple essential roles in male reproductive physiology. Its functions encompass the secretion of prostatic fluid, containing enzymes vital for semen liquefaction and antimicrobial properties due to its high zinc concentration. Additionally, the prostate facilitates the conversion of testosterone to dihydrotestosterone (DHT), supporting the maturation of male reproductive organs. It is further involved in penile erection, ejaculation, urinary control, and overall reproductive function.[39] A detailed understanding of these physiological mechanisms provides the foundation for developing effective treatments for prostate-related disorders and advancing therapeutic interventions.

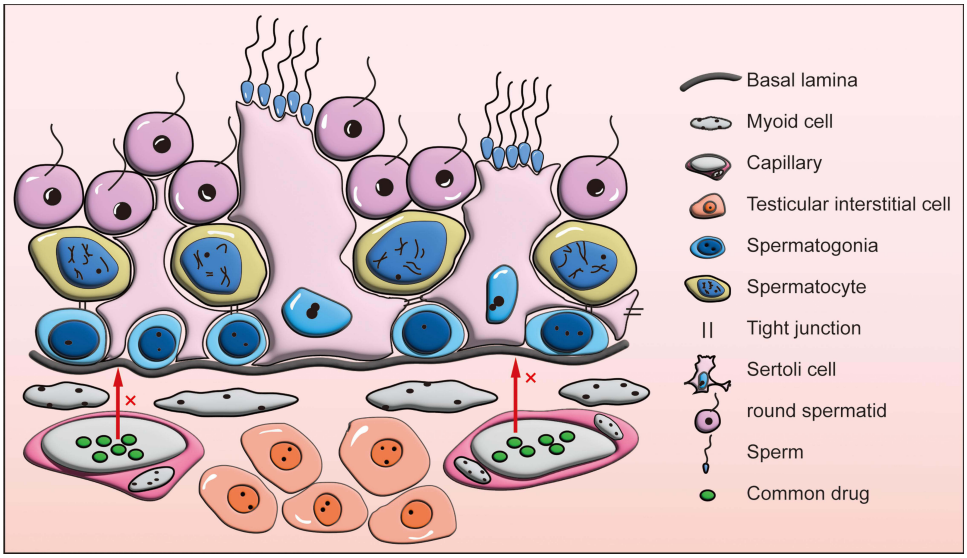


Figure 1 Traversing the blood-testis barrier poses a considerable challenge for common drugs. Red colored upward arrows and cross symbols indicate that common drugs cannot pass through BTB.

Nanotechnology - A New Dawn in the Diagnosis and Treatment of Male Reproductive System Diseases

The Enormous Potential of Nanotechnology for the Diagnosis and Treatment of Male Reproductive System Diseases

Nanotechnology is an interdisciplinary field focused on the study, fabrication, and application of materials at the nanometer scale (1–100 nm). It has been widely adopted across diverse disciplines—including materials science, engineering, chemistry, computer science, physics, and biology—unlocking a wide range of scientific and practical possibilities.[40] Nanomaterials, comprising nanoscale particles, can either exist naturally, like antibodies, cell membranes, and exosomes, or be synthetically engineered through nanotechnology, as seen with metal nanoparticles, quantum dots, and organic polymers. The ongoing advancement of nanotechnology has not only spurred the growth of high-tech industrial sectors but has also enabled transformative integration with conventional industries.

Nanomedicine represents a rapidly evolving frontier that is catalyzing transformative advances in medical science. This discipline utilizes materials and techniques at the nanoscale to significantly improve the diagnosis, treatment, and prevention of diseases. In biomedicine, nanotechnology plays a pivotal role in drug delivery, with liposomes and polymer nanoparticles among the most widely studied systems.[41] It also contributes substantially to oncology, enabling enhanced diagnostic and therapeutic outcomes through tools such as nanocoatings, nanosensors, quantum dots, metal nanoparticles, liposomes, dendrimers, DNA-based nanostructures, and extracellular vesicles.[20,42] These innovations improve accuracy and efficiency across multiple modalities—including endoscopy, tumor marker assays, medical imaging, intraoperative navigation, chemotherapy, phototherapy, and targeted drug delivery. To overcome limitations of conventional vaccines, nanoscale materials—including liposomes, polymers, and inorganic nanoparticles—have been employed as antigen carriers and adjuvants. Their tailored designs enhance immunogenicity, stability, and specificity through targeted delivery and controlled release.[43] Owing to their unique properties, such as targeting ability, radical scavenging, antioxidant activity, high biocompatibility, and anticancer or antibacterial effects, nanomaterials hold substantial promise in addressing male reproductive disorders. Nanomedicine has thus begun to integrate into the diagnosis and treatment of male reproductive system conditions—covering testicular and prostate diseases, fertility impairments, and other related disorders—which profoundly impact physical and psychological well-being. Faced with the constraints of conventional methods, there is a clear need for more innovative, precise, and personalized therapeutic strategies. Nanotechnology offers such an approach, providing improved diagnostic accuracy and refined drug delivery platforms that enhance treatment efficacy and patient quality of life. Currently, nanotechnology and nanomaterials are being applied across a spectrum of areas in male reproductive health, including disease treatment, drug delivery, tumor imaging, radiotherapy, sperm cryopreservation, and assisted reproductive technologies (Figure 2).

Within this comprehensive review, we embark on an exploration of how nanomedicine is transforming the diagnosis, treatment, and pioneering research surrounding male reproductive system disorders. We outline the core principles of nanomedicine, survey its current applications in male reproductive health, evaluate recent research advances, and identify promising future directions. The integration of nanomedicine not only offers new prospects for clinical management in this field but also establishes a foundation for transformative medical progress, with far-reaching implications for improving reproductive health outcomes.

Precision Treatment of Male Reproductive System Diseases - Nanosolutions

The rapid evolution of precision medicine has brought personalized treatment strategies to the forefront of modern healthcare. By tailoring therapies to both disease characteristics and individual patient profiles, precision medicine enables more customized interventions, improved clinical outcomes, reduced side effects, and enhanced quality of life.[44] This approach has been increasingly applied in the management of male reproductive disorders, including infertility, hypogonadism, erectile dysfunction, prostate cancer, and benign prostatic hyperplasia.[45] The emergence of nanomaterials and nanotechnology is now reshaping the paradigm of precision treatment for male reproductive system diseases. By harnessing the passive or active targeting abilities of nanoparticles and nano-delivery systems, nanomedicine

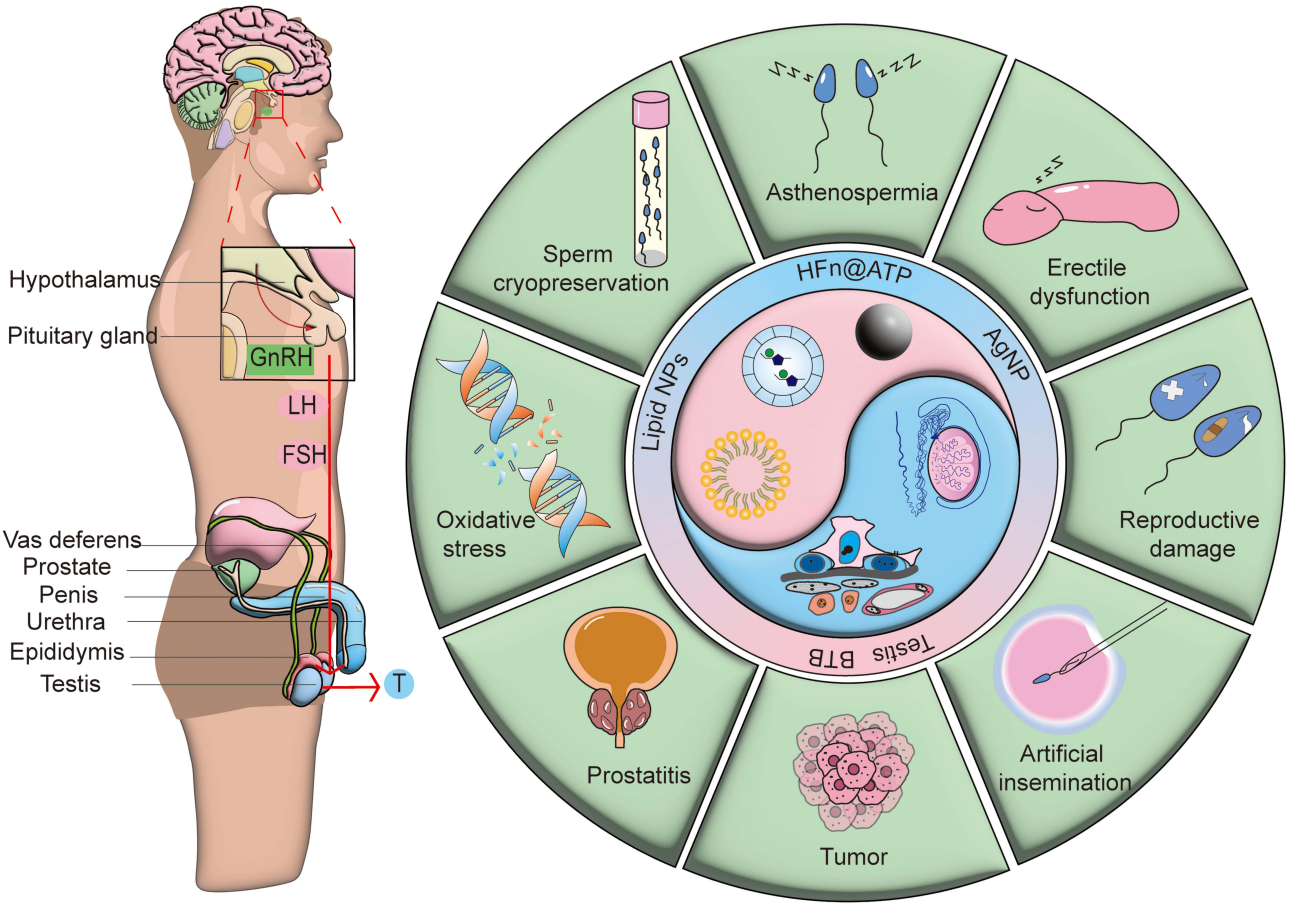


Figure 2 The utilization of nanoparticles in the diagnosis and treatment of male reproductive system diseases. The intricate process of spermatogenesis is intricately regulated by the Hypothalamus-Pituitary-Gonadal (HPG) axis. Red colored arrows: the GnRH, originating from the hypothalamus, stimulates the secretion of LH and FSH from the anterior pituitary gland. These hormones, in turn, act upon the testes, initiating the production of T and fostering spermatogenesis. Silver nanoparticles (AgNP), ATP-loaded h-ferritin nanoparticles (HFn@ATP), and solid lipid nanoparticles (Lipid NPs) exhibit the remarkable ability to penetrate the BTB and exert their effects on male reproductive system organs, including the testicles. These nanoparticles present promising prospects for the treatment of various male reproductive system diseases such as asthenospermia, ED, reproductive damage, prostatitis, reproductive tumors, and oxidative stress of the reproductive system. Moreover, their applications extend to diverse fields, including sperm cryopreservation and artificial insemination.

allows drugs to penetrate physiological barriers such as the blood-testis barrier with improved accuracy. This targeted approach enhances therapeutic efficacy while minimizing off-target effects and damage to healthy tissues.

The exceptional designability of nanoparticles enables their application in precision medicine, a principle powerfully demonstrated in subsequent chapters. For instance, gold-silica nanoshells (GSNs) integrate magnetic resonance imaging guidance with near-infrared photothermal ablation, achieving precise control and minimally invasive therapy for prostate cancer lesions.[46] Similarly, to address the challenge of poor targeting in stem cell therapy for erectile dysfunction, superparamagnetic iron oxide nanoparticles (SPIONs) facilitate the magnetic field-guided precise accumulation of adipose-derived stem cells (ADSCs) at target sites, substantially improving therapeutic outcomes.[47] These examples collectively underscore that tailoring nanomaterials based on specific clinical challenges and etiological insights is pivotal to advancing precision medicine in male reproductive health.

Nanomedicine in the Treatment of Male Reproductive System Disorders

Nanomedicine, characterized by the application of nanoscale materials and technologies, is emerging as a transformative approach for diagnosing and treating male reproductive system disorders. This comprehensive exploration into nanomedicine's role in treating male reproductive system disorders underscores its potential to usher in a new era of precision, effectiveness, and reduced side effects.

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Fusion of Nanoparticles in the Treatment of Male Reproductive System Disorders

The integration of nanoparticles offers a novel therapeutic pathway for addressing male reproductive conditions. This exploration into the fusion of nanoparticles in treating male reproductive system disorders unveils a transformative path forward. As we navigate this intersection of nanotechnology and male reproductive health, the synergy of nanoparticles offers unprecedented potential for tailored and effective therapeutic strategies, heralding a new era in advancing patient outcomes and overall quality of life.

Inorganic Nanoparticles

Metal and metal compound nanoparticles—including common metals (eg, zinc, iron), noble metals (eg, gold, silver), and rare metals—play an essential role in biomedical applications.[48] These nanoparticles often exhibit intrinsic anticancer activity, making them valuable in targeted drug delivery systems for chemotherapeutic agents. They can also enhance the efficacy of tumor radiotherapy and enable localized ablation of advanced tumors.[49] Furthermore, when employed as contrast agents, metal-based nanoparticles improve the diagnostic performance of in vivo imaging techniques (Figure 3).[50]

Beyond their established roles in cancer therapy, metal nanoparticles also demonstrate significant antiviral activity. They inhibit viral attachment and uncoating by directly binding to viral particles or by inducing oxidative denaturation of viral nucleic acids and proteins via reactive oxygen species (ROS) generation. Furthermore, they can disrupt disulfide bonds within viral structural proteins.[51]

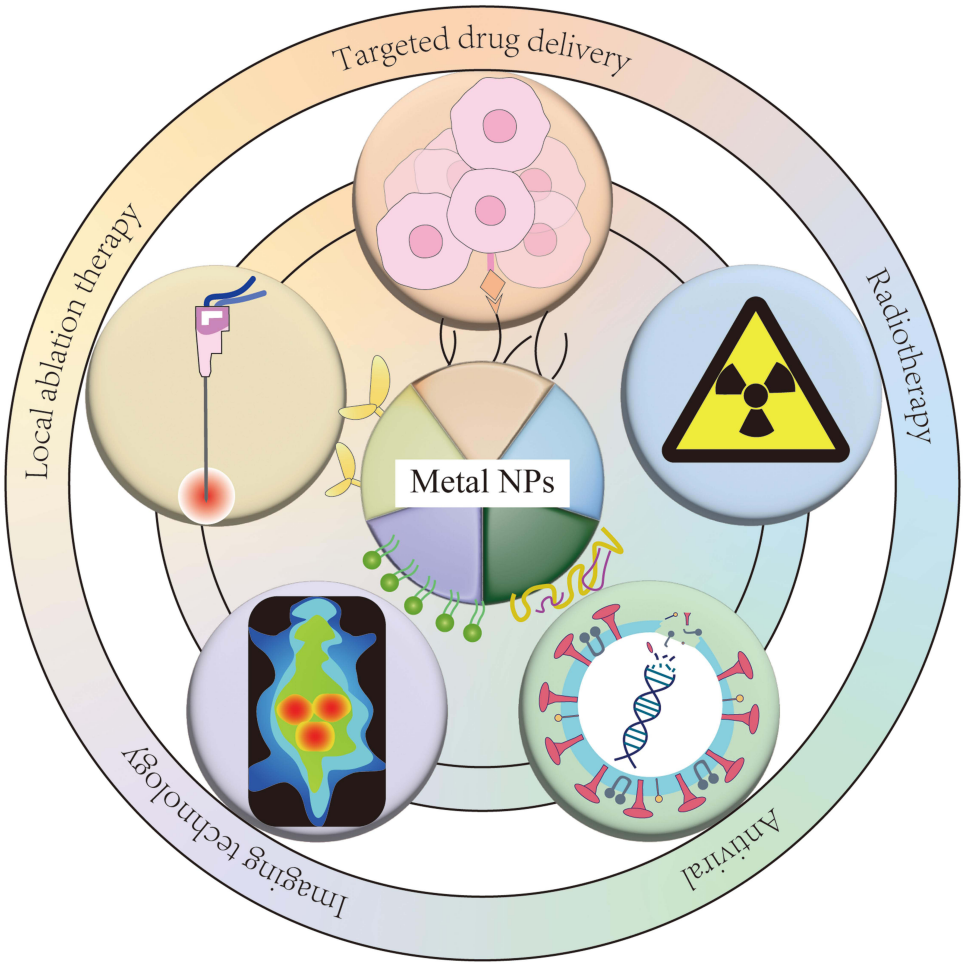

Figure 3 The utilization of metal nanoparticles in biomedical applications. NPs represent a sophis ticated tool in the realm of biomedicine. Their versatile applications extend to targeted drug delivery for anticancer agents, tumor radiotherapy, and the localized ablation of tumors. Additionally, they play a pivotal role in advancing in vivo imaging techniques and antiviral therapy, contributing to the forefront of biomedical innovation.

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In the context of the male reproductive system, metal nanoparticles offer broad applicability. In addition to conventional benefits such as targeted drug delivery, extended tissue retention, and enhanced therapeutic efficacy, they provide distinctive functional advantages tailored to reproductive medicine.

Zinc Nanoparticles (Zn-NPs) and Zinc Oxide Nanoparticles (ZnO-NPs)

Zinc nanoparticles[52] and zinc oxide nanoparticles exhibit notable antioxidant properties. ZnO-NPs, in particular, are characterized by excellent biocompatibility, cost-effectiveness, and low toxicity, rendering them highly promising for biomedical applications. ZnO-NPs are employed in diabetes management by preserving insulin activity, and their intrinsic toxicity is leveraged in anticancer and antibacterial therapies. Additionally, their luminescent properties make them suitable for bioimaging, while their use as drug carriers significantly enhances bioavailability.[53]

In the context of male reproductive health, zinc nanoparticles improve semen quality for in vitro fertilization and cryopreservation. Studies show that nano-zinc supplementation reduces lipid peroxidation damage without adversely affecting sperm concentration, viability, or fertilization capacity. This protective effect on sperm membrane integrity increases the number of functional mitochondria in bovine sperm. Furthermore, the inclusion of zinc nanoparticles in in vitro embryo culture systems enhances embryonic development rates.[54] Co-administration of 100 nm Zn-NPs effectively mitigated the reproductive toxicity induced by Ag-NPs. This protective effect was evidenced by increased sperm concentration, motility, and viability, elevated androgen levels, as well as a reduction in the number of sperm with abnormal morphology.[52]

ZnO-NPs have also been shown to alleviate cisplatin-induced reproductive toxicity in male rats by reducing oxidative stress and improving sperm antioxidant capacity and DNA integrity.[55] In streptozotocin (STZ)-induced diabetic male rats, ZnO-NPs mitigate testicular damage, supporting the recovery of stromal and seminiferous epithelial structure, steroidogenesis, and spermatogenesis.[56] Similarly, intraperitoneal injection of ZnO-NPs alleviates $AlCl_3$-induced reproductive toxicity in rats through antioxidative, anti-apoptotic, and anti-inflammatory mechanisms, along with the restoration of normal androgen levels.[57]

In summary, Zn NPs and ZnO-NPs demonstrate multifaceted protective effects in various models of male reproductive toxicity, predominantly attributed to their potent antioxidant properties. They not only significantly improve sperm quality and function under conditions of cryopreservation and stress, but also effectively protect testicular tissue and support embryonic development across diverse toxicity models (such as those induced by Ag NPs, cisplatin, and diabetes), revealing broad application prospects. Future research should focus on precisely defining their therapeutic window and elucidating their in vivo metabolic pathways to facilitate clinical translation.

Silver Nanoparticles (AgNPs) and Calcium Oxide Nanoparticles (CaO NPs)

Silver nanoparticles are among the most widely used nanomaterials in biomedicine, valued for their scalable production and potent antimicrobial activity.[58] They are employed in treating wound infections—particularly burns[59]—and serve as targeted carriers for retinal therapeutics.[59] When synthesized using borohydride and starch, AgNPs exhibit dual effects in zebrafish fertilized eggs, promoting growth at low concentrations.[60] Their antimicrobial mechanism involves disruption of membrane electron transport, induction of oxidative damage, and release of heavy metal ions.[61,62] In assisted reproduction, AgNPs help maintain semen sample sterility by inhibiting bacterial and fungal contamination without compromising sperm membrane integrity, morphology, or acrosome function. For instance, 10–20 nm AgNPs effectively suppress Staphylococcus aureus proliferation in boar semen.[63] However, AgNPs also demonstrate reproductive toxicity, making them suitable for modeling the biosafety of reproductive medical devices.[58] It is therefore essential to strictly control their dosage to minimize potential adverse effects.

Calcium oxide nanoparticles have been found to influence testosterone levels and testicular mass. Oral administration of low to moderate CaO NP doses significantly increases testicular weight and serum testosterone in male rats. However, high doses may cause testicular histopathological alterations and reduce testosterone production.[64]

The roles of AgNPs and CaO NPs in male reproductive health highlight the "double-edged sword" nature of nanomaterials. AgNPs exhibit a delicate balance between antibacterial efficacy and reproductive toxicity, while CaO NPs demonstrate typical dual dose-dependent effects: beneficial at low doses yet harmful at high doses. This clearly

demonstrates that the biological outcomes are fundamentally determined by precise dosage and specific nanomaterial properties. Future research must prioritize defining the safe therapeutic window for each material to enable the harnessing of their benefits while mitigating potential risks.

Selenium Nanoparticles (Se-NPs) and Cerium Oxide Nanoparticles (CeO_2 NPs)

Beyond conventional metal nanoparticles, rare metal nanoparticles such as selenium nanoparticles and cerium oxide nanoparticles play an important role in protecting sperm morphology and function. Research has demonstrated selenium's ability to alleviate testicular oxidative stress and germ cell apoptosis induced by heat stress in mice.[65] Compared to elemental selenium, Se-NPs exhibit higher bioavailability, greater surface activity, and lower toxicity. They protect testicular structure and function through multiple pathways, ultimately improving reproductive outcomes in male rats.[66] Notably, Se-NPs counteract aflatoxin B1 (AFB1)-induced reproductive toxicity in male mice by restoring spermatogenesis, reducing testicular damage, improving in vitro fertilization rates, and modulating testicular hormone synthesis. They also support normal embryonic development, reducing AFB1-induced cleavage abnormalities and embryonic arrest.[67] Through free radical scavenging, Se-NPs alleviate deltamethrin (DLM)-induced testicular oxidative stress in rats, enhance glutathione peroxidase activity and total antioxidant capacity (TAC), reduce sperm oxidative damage and death, and improve overall sperm quality.[68–71] Similarly, Se-NPs mitigate cisplatin (CIS)-induced reproductive toxicity in male rats, counteracting sperm and DNA damage, decreased peroxynitrite levels, and elevated serum testosterone.[72] In sexually maturing male goats, adequate Se-NPs supplementation increases testicular selenium levels, enhances glutathione peroxidase and ATPase activity in testicular tissue and semen, preserves sperm membrane integrity and mitochondrial architecture, and prevent the increase in abnormal sperm rates and abnormal sperm mitochondria associated with direct selenium addition.[73]

Cerium oxide nanoparticles, often referred to as nanoceria, are widely used in semiconductors and automotive applications. In biomedicine, their antioxidant and anti-inflammatory properties show promise in treating ocular diseases and protecting retinal neurons from damage.[74,75] Known for low synthesis cost, straightforward preparation, and stable catalytic activity under physiological conditions,[76] CeO_2 NPs also help maintain testicular function. Diabetes can damage the blood-testis barrier—essential for normal spermatogenesis—leading to impaired sperm quality and male infertility.[77] It also induces oxidative stress in germ cells by downregulating Nrf2, a central transcription factor in antioxidant defense.[78] Antioxidant therapies such as CeO_2 NPs, which scavenge free radicals and inhibit oxidative stress,[79] can alleviate diabetic symptoms and complications.[74] In diabetic male rats with reproductive injury, CeO_2 NPs upregulate Nrf2 expression, ameliorate testicular and sperm damage, and reduce sperm DNA fragmentation.[80] Furthermore, in pregnant mice treated with CeO_2 NPs, pro-apoptotic gene expression is downregulated in the testicular cells of male offspring, thereby enhancing their anti-apoptotic capacity.[81]

Owing to their exceptional antioxidant and antibacterial properties, metal nanoparticles are widely applicable across various aspects of male reproduction. Their favorable biocompatibility and cost-effectiveness further broaden their utility, representing a significant advance at the intersection of nanotechnology, energy, and biomedicine. As medical technology evolves and demand grows for precise, targeted therapies, metal nanoparticles are poised to play an increasingly important role in male reproductive medicine.

Lipid Nanoparticles

Beyond metal-based nanoparticles, a variety of other nanomaterial compositions are increasingly being applied in male reproductive medicine. One notable example is the use of nano-micelles, prepared from glycerophospholipids (GPL) and cholesterol-loaded cyclodextrin (CLC), through a technique termed Membrane Lipid Replacement (MLR). This approach has been successfully introduced into cryopreserved human semen samples, demonstrating considerable potential for improving sperm preservation.[82]

The MLR method, facilitated by these nano-micelles, has been shown to significantly improve post-thaw sperm motility and viability. It effectively inhibits sperm apoptosis, preserves acrosome integrity, and enhances mitochondrial function. The underlying mechanism involves the integration of nano-micelles into the mitochondrial membrane, where they facilitate the replacement of oxidized lipids. This process helps counteract the damaging effects of excessive ROS

generated during sperm cryopreservation. By reducing mitochondrial membrane potential, nano-micelles contribute to the recovery of mitochondrial structure and activity, thereby supporting overall sperm function.

This application underscores the potential of lipid-based nanotechnology to address key challenges in male reproductive health, pointing toward a promising direction for further research and clinical translation.

Other Nanoparticles

Hydrated C_{60} fullerene, encapsulated in chitosan–silicate nanoparticles, exhibits strong antioxidant activity. In a streptozotocin-induced diabetic model of male reproductive dysfunction, this formulation was shown to normalize testosterone levels, alleviate testicular structural damage, reduce germ cell apoptosis, and significantly recover sperm quality.[83]

For the treatment of multifocal and localized prostate cancer, focal laser ablation has emerged as an effective strategy.[84,85] Clinical studies combining magnetic resonance-guided focused ultrasound with GSNs have demonstrated precise lesion control without serious complications or harmful changes in urogenital system function, particularly in patients with low- to intermediate-risk disease. GSNs absorb near-infrared light and convert it into heat, enabling localized thermal ablation of tumor cells while sparing adjacent healthy tissues.[46]

A range of nanoparticle types—each leveraging distinct optical, thermal, and biological properties—plays an increasingly important role in diagnosing and treating male reproductive diseases (see Table 1). This is especially evident in imaging and targeted drug delivery. Beyond their intrinsic physicochemical features, nanoparticle-based carrier

Table 1 Integration of Nanoparticles with the Treatment of Male Reproductive System Diseases

Nanomaterials		Application	Advantage	Therapeutic Effect	References
Metal NPs	Zn-NPs	Cryopreserved and thawed bull semen model	Does not affect sperm concentration, vitality, fertilization rate, antioxidation	Number of viable sperm with well-functioning mitochondria↑, in vitro embryonic development rate↑	[54]
		Ag-NPs induced reproductive toxicity in a male rat model	Anti-inflammatory, antibacterial, anticancer, antidiabetic, maintenance of DNA replication, repair, and cell division, prevention of oxidative stress	Sperm concentration, vitality, motility, and levels of male hormones↑, Number of sperm with abnormal morphology↓	[52]
	ZnO-NPs	CIS-induced reproductive toxicity in juvenile male rat model.	Low toxicity, body barrier penetration, and cell targeting	Spermatogenesis↑, sperm quality↑, DNA integrity↑	[55]
		STZ-Induced diabetes model in male rats	Anti-diabetic, antioxidant, anti-inflammatory, low toxicity, cellular and molecular targeting	Steroids, sperm production↑	[56]
		Reproductive toxicity male rat model induced by $ALCL_3$	Low toxicity, cellular and molecular targeting, antioxidant, anti-inflammatory, anti-apoptotic	Antioxidant capacity↑, anti-apoptotic ability↑, anti-inflammatory ability↑, testosterone↑	[57]
	AgNPs	Porcine semen cryopreservation in vitro	No reproductive cell toxicity, maintaining sperm cell membrane integrity, and no impact on sperm morphology and acrosome reaction	Staphylococcus aureus growth↓	[63]
	CaO NPs	Normal male rat model	-	Androgens↑, testicular weight↑	[64]
	Se-NPs	Normal male rat model	Low toxicity	Testicular weight↑, sperm concentration, vitality↑	[66]
		Reproductive toxicity model of male mice induced by AFB1	High surface activity, high bioavailability, low toxicity	Spermatogenesis, androgen levels, in vitro fertilization rate↑; Cleavage rate, embryo arrest rate↓	[67]
		DLM-induced reproductive toxicity male rat model	Co-administration with vitamin E	Testicular weight, androgen levels, sperm count, motility↑, antioxidant capacity↑	[69–71]
		CIS-induced reproductive toxicity in male rat model	High bioavailability, low toxicity, potent antioxidant	Spermatogenesis, androgen levels, sperm quality↑; Sperm DNA damage↓	[72]
		Model of reduced reproductive capacity in male goats induced by low selenium diet	Low toxicity	Testis GSH-Px activity↑, sperm quality↑	[73]
	CNPs	STZ-induced diabetic rat model	Simple synthesis steps, low cost, low toxicity, antioxidant, stable catalytic activity	Nrf2↑, ROS, SDF↓	[80]

(*Continued*)

Table 1 (Continued).

Nanomaterials		Application	Advantage	Therapeutic Effect	References
Other NPs	Nano-micelles	Model of human sperm after cryopreservation and thawing	Large surface area, easy to be taken up by cells, and prone to binding with sperm plasma membrane and mitochondrial membrane.	Sperm motility and viability↑; Sperm apoptosis↓	[82]
	Hydrated C_{60} fullerene	STZ-induced diabetic rat model	Strong antioxidant and tissue protective agent	Androgens, sperm quality↑; Sperm apoptosis↓	[83]
	GSN	Prostate cancer patient model	Low side effects	Urinary incontinence rate, ED rate↓	[46]

Notes: ↑ indicates an increase; ↓ indicates a decrease.

systems have substantially advanced drug delivery strategies for male reproductive conditions, a topic explored in detail in the following subsection.

Nanoparticle-Based Drug Delivery in the Male Reproductive System

The male reproductive system exhibits a complex physiological architecture, characterized by intricate tissue organization and the presence of the blood-testis barrier. These features often hinder effective drug delivery using conventional methods. Nanoparticle-based systems can overcome these limitations by enabling targeted transport of therapeutic agents to specific reproductive tissues. This strategy enhances local drug concentrations, minimizes systemic exposure, and reduces off-target effects.

Furthermore, nanoparticle platforms offer versatile applications across multiple domains of male reproductive health, including disease treatment, diagnostic imaging, and fertility preservation. Nanocarriers such as liposomes, polymeric nanoparticles, and metal-based particles serve as key platforms for improving drug stability, bioavailability, and controlled release profiles.

This section examines the diverse applications of nanoparticle-mediated drug delivery in the male reproductive system. It addresses both the challenge of crossing the blood-testis barrier and the development of targeted therapies for specific reproductive disorders. The integration of nanotechnology with pharmaceutical delivery is offering novel opportunities for precision medicine in male reproductive health. By examining fundamental principles, current applications, and recent advances, this review highlights the transformative potential of nanoparticle-based strategies for treating male reproductive system diseases.

Precise in Organ-Targeted Drug Delivery

Nanomaterials used as drug carriers are broadly classified into three categories: polymeric, lipid-based, and metal/metallic compound nanoparticles.[86] Therapeutic agents can be loaded onto or encapsulated within these nanoparticles through noncovalent or covalent interactions.[87] Thanks to their tunable physicochemical properties, nanoparticle-based delivery systems have been widely adopted across multiple biomedical fields (Figure 4).

For example, in the central nervous system, certain nanoparticles can cross the blood–brain barrier to enable targeted therapy for neurological disorders.[88] Liposomes, dendrimers, and solid lipid nanoparticles are commonly used in ophthalmic drug delivery to improve bioavailability and prolong residence time.[89] In cardiovascular disease, nanoparticle-formulated statins offer potential for managing conditions such as coronary heart disease.[90] Similarly, nanoparticles serve as effective carriers for bone-targeting agents in orthopedic and dental applications, including osteoporosis treatment.[91]

In oncology, various nanoparticles are extensively used for targeted drug delivery in lung, breast, and brain cancers.[92] For infectious diseases, nanocarriers enhance the efficacy of antimicrobial agents and serve as platforms for vaccine development.[93] In autoimmune disorders such as rheumatoid arthritis, magnetic nanoparticles enable targeted drug delivery with reduced systemic side effects.[94] Within the female reproductive system, nanomedicine has been applied in pregnancy monitoring, diagnosis and treatment of vaginal and reproductive tract infections, and fetal congenital disease screening.[95] The targeting precision of nanoparticle delivery systems has thus demonstrated considerable value

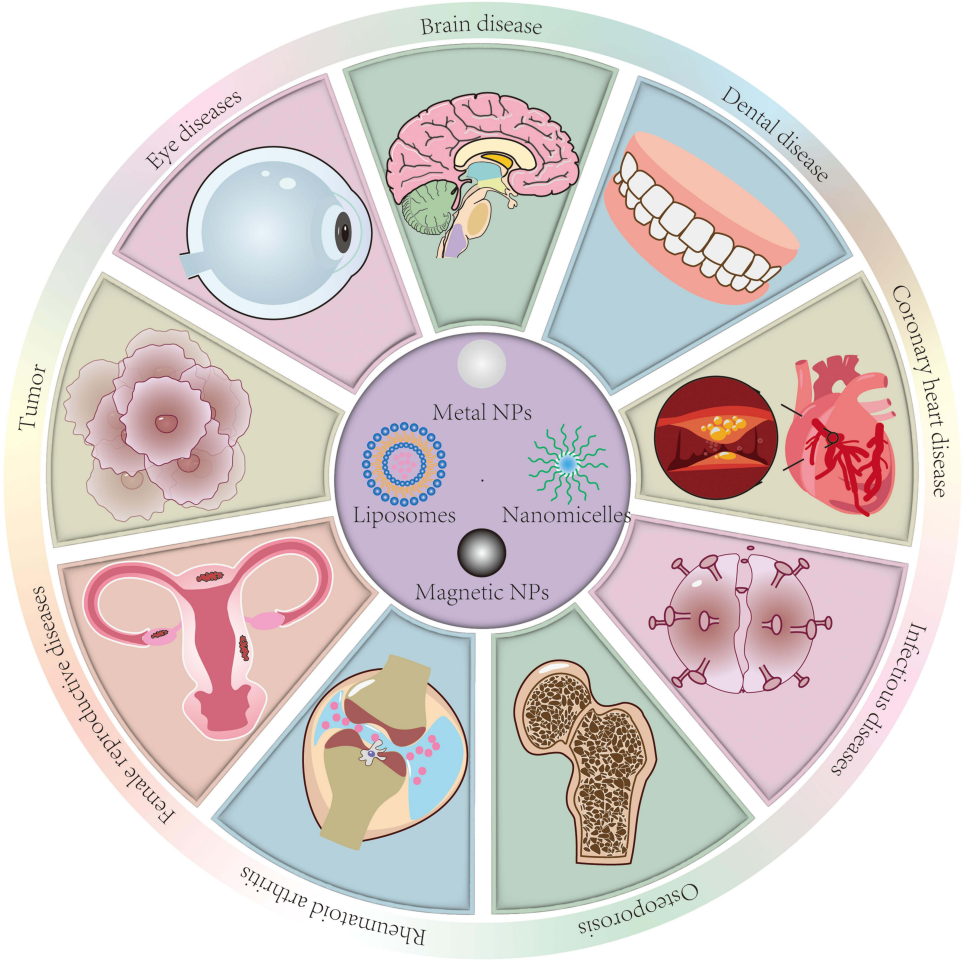

Figure 4 Application of nanocarrier drug delivery in various fields of life medicine. Polymer nanomaterials, metal and compound nanomaterials, lipid nanomaterials, and magnetic nanomaterials can be extensively employed as drug delivery carriers in various fields of life medicine, including brain diseases, eye diseases, coronary heart disease, osteoporosis, dental diseases, cancer, infectious diseases, rheumatoid arthritis, and diseases related to the female reproductive system.

across clinical specialties. In the male reproductive system, the unique physiological structure of the blood-testis barrier presents both a challenge and an opportunity for nanoparticle-based strategies. The following sections detail recent advances in nanocarrier applications within this specific biological context.

Nanoparticle-Based Nanoreagents in the Male Reproductive System

Nanoparticles represent a transformative platform for advancing male reproductive health. A diverse range of nanomaterials—including polymeric, metallic, and lipid-based nanoparticles—forms the foundation of these innovative strategies.[86] Through rational design, therapeutic agents can be attached to the surface or encapsulated within nanoparticles, enabling precise drug delivery via covalent or non-covalent interactions.[87] As summarized in Figure 4, nanoparticle-based delivery systems are being applied across numerous biomedical fields. Their targeting precision, tunable properties, and biocompatibility make them particularly promising for disease diagnosis and treatment in various clinical contexts. In the male reproductive system, the unique physiological structure of the blood-testis barrier further underscores the importance and potential of nanocarrier systems. In the subsequent discussion, we will delve into the current applications and recent breakthroughs of nanoreagents in the male reproductive system.

Polymer-Based Nanomaterials

Common polymeric nanoparticles include dendrimers, polylactic-co-glycolic acid (PLGA), polyethylene glycol (PEG), and chitosan. Among these, dendrimers offer multiple advantages for targeted drug delivery and have already entered

clinical use.[96] PLGA and PEG—the most widely employed synthetic polymers—are extensively utilized for tumor-targeted drug delivery.[97] Chitosan, a natural polysaccharide, is also frequently used in nanoparticle preparation due to the favorable stability, permeability, and bioactivity of chitosan-based nanocarriers.[98] Studies indicate that polymer nanoparticles play a protective role in sperm cryopreservation and can enhance drug bioavailability and release kinetics in the treatment of male reproductive disorders, thereby improving therapeutic outcomes.

Antrodia camphorata (AC), a medicinal mushroom native to Taiwan, exhibits anti-inflammatory and antioxidant properties with potential application in diabetes treatment. However, its bioactive components suffer from poor water solubility and low oral bioavailabilityt.[99] Recent research shows that chitosan–silicate nanoparticles loaded with ethanol extract of AC mycelium (nano-SAC) exert therapeutic effects in a diabetic rat model of reproductive dysfunction. Nano-SAC not only alleviates diabetic symptoms but also elevates superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities, thereby reducing oxidative stress, restoring sperm morphology and function, and normalizing testosterone levels. Compared with conventional SAC, nano-SAC demonstrates higher bioavailability and more effectively ameliorates diabetes-induced testicular abnormalities.[100] In another example, nanoparticles prepared from biodegradable chitosan and dextran sulfate preserve rabbit sperm quality and acrosome integrity during in vitro fertilization, while improving the bioavailability of loaded GnRH.[101] In ED treatment, topical application of nanoparticles encapsulating nitric oxide, sialorphin, or tadalafil improved symptoms in aged rats by enhancing drug efficacy and enabling controlled release, suggesting a safer and more efficient delivery strategy.[102] For CBP, antibiotic efficacy is limited by drug properties, prostate epithelium penetration, intraluminal accumulation, and bacterial resistance.[103] Since prostate inflammation involves macrophages expressing high levels of folate receptors (FRs),[104] researchers developed folate-modified, ROS-responsive nanoparticles loaded with cefpodoxime proxetil. In a CBP mouse model, this nanocarrier system successfully crossed the prostate epithelium, accumulated in glandular lumina, eliminated bacteria, reduced ROS levels, and alleviated inflammatory symptoms.[105]

In summary, polymer-based nanoparticles represent a highly versatile and promising platform for advancing targeted therapies in male reproductive medicine. Their utility extends beyond merely protective roles in sperm cryopreservation to enabling sophisticated drug delivery strategies. These systems overcome fundamental pharmacological barriers that plague conventional treatments, such as poor solubility, limited bioavailability, and inadequate tissue penetration. By ensuring precise, controlled delivery of active agents—whether antioxidants, hormones, or antibiotics—directly to pathological sites, polymer nanoparticles significantly enhance therapeutic efficacy while minimizing off-target effects. The future of this field lies in the rational design of next-generation "smart" polymers that demonstrate greater specificity and responsiveness to the unique pathophysiological microenvironment of reproductive organs, thereby translating this immense potential into tangible clinical solutions.

Metal and Its Compound Nanomaterials

Sperm motility is closely linked to cellular ATP levels, and external ATP supplementation has been shown to significantly enhance sperm vitality.[106,107] Human H-ferritin (HFn), an iron-storage protein, has been exploited not only for cancer diagnosis but also for its ability to cross physiological barriers such as the blood–brain and blood–testis barriers.[108–112] In a mouse model of gossypol-induced asthenozoospermia, ATP-loaded HFn nanoparticles traversed the blood–testis barrier and accumulated in the epididymal ducts via binding to HFn receptors on supporting cells. This enabled targeted ATP release into the acrosomal region of elongated sperm, resulting in a marked improvement in sperm motility (Figure 5). Exogenous ATP administration was also shown to enhance sperm function without adverse reproductive effects, supporting the potential of HFn@ATP as a therapeutic strategy, though the precise mechanism warrants further investigation.[112]

Curcumin, known for its anti-inflammatory and antioxidant properties, has shown promise in alleviating heat stress–induced testicular cell damage and apoptosis.[113,114] However, its clinical translation is hindered by poor aqueous solubility, low bioavailability, and structural instability.[115] A promising approach involves combining curcumin with SPIONs, which in one study substantially attenuated heat stress–induced testicular injury. This formulation reduced sperm oxidative stress, decreased sperm DNA fragmentation, and inhibited apoptosis, collectively improving sperm quality.[116] In a related study, curcumin combined with iron oxide nanoparticles (IONPs) ameliorated heat-induced sperm

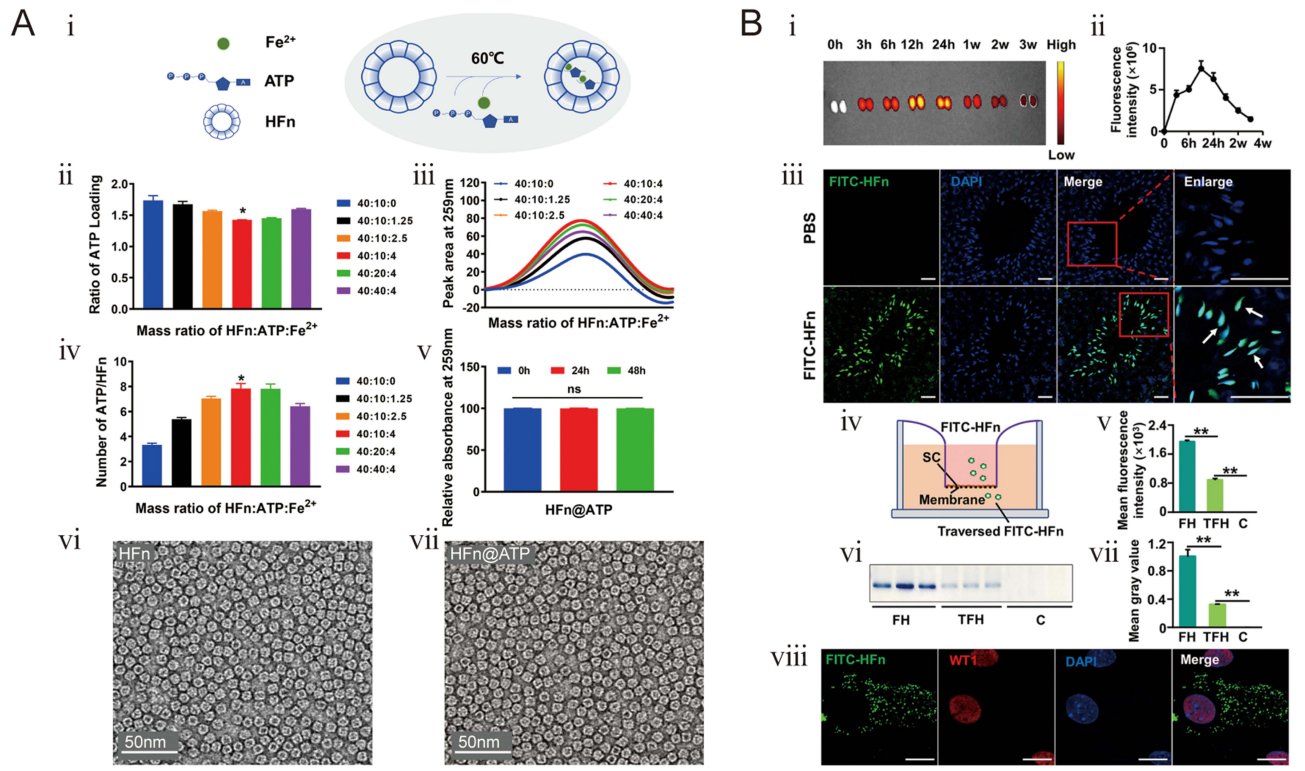

Figure 5 Enhancing sperm motility in asthenozoospermic mice through BTB with HFn@ATP.[112] (**A**) The preparation and characterization of HFn@ATP. (i) Schematic illustration of the preparation process of HFn@ATP. Panels (ii-v) highlight the optimal formula (HFn: ATP: Fe^{2+} = 40:10:4) and the stability of HFn@ATP for up to 48 hours. (vi-vii) The Transmission Electron Microscopy (TEM) image of HFn and HFn@ATP showcases the successful formulation. Scale bar = 50 nm. Values were presented as means ± SEM, *P < 0.05, ns: no significance. Moving to the in vitro BTB model, panels (**B**) vividly depict the journey of HFn as it traverses the BTB and selectively accumulates in the heads of elongated sperm. (i-ii) The time-dependent signal of HFn in the testicles, reaching its peak within 12 hours, further substantiates its efficient traversal through the BTB. (iii) HFn traversed the BTB and was specifically enriched in the heads of the elongated sperms. Scale bar = 20 μm. White arrow: elongated sperms. (iv) Illustration of the in vitro BTB model. SC: Sertoli cell. Notably, fluorescence intensity measurements in the medium from the lower chamber affirm the specific enrichment of HFn in elongated sperms' heads. The lower HFn protein levels in the medium from the lower chamber, compared to the upper chamber, and staining results indicating HFn's entry into Sertoli cells are presented in panels (v-vii). Scale bar = 20 μm. Values were presented as means ± SEM, **P < 0.01. This insightful illustration, reprinted with permission from ref.[112] published by the American Chemical Society in 2022, provides a comprehensive visual representation of the successful application and effectiveness of HFn@ATP in sperm motility enhancement through BTB.

damage. This treatment significantly improved testicular volume, seminiferous tubule length, sperm parameters, and stereological parameters. The underlying mechanism involves the upregulation of key spermatogenic genes such as C-kit, Stra8, and Pcna, which promotes spermatogonial proliferation and leads to increased serum testosterone levels.[117]

ADSCs have shown potential for treating type II diabetes–induced erectile dysfunction, but intracavernosal injection—the primary delivery route—is limited by short local retention and low engraftment rates.[118,119] To address this, ADSCs were combined with SPIONs, enabling magnetic field–guided targeted delivery. This approach extended local retention while maintaining stem cell viability, significantly improving therapeutic outcomes.[47]

From a broader perspective, these cases reveal that the true value of metal-based nanomaterials lies not merely in their material properties, but in their versatility as adaptable platforms that can be tailored to diverse therapeutic requirements—whether for small molecule delivery (ATP, curcumin) or cellular therapy (ADSCs). The consistent themes of enhanced targeting, improved pharmacokinetics, and multimodal therapeutic effects position these nanomaterials as foundational tools for precision medicine in male reproductive health.

Lipid Nanomaterials

Lipid nanoparticles (LNPs) offer stable drug loading, prolonged circulation half-life, reduced off-target effects, and efficient targeted delivery across biological barriers. These advantages have led to their widespread use in pharmaceuticals, drug delivery, hyperthermia, phototherapy, and bioimaging.[120,121] Within the male reproductive system, LNPs demonstrate significant antioxidant activity via multiple signaling pathways in models of human asthenozoospermia.

They also alleviate reproductive toxicity induced by certain chemotherapeutic agents and herbal medicines, such as tripterygium glycosides (TG).

Asthenozoospermia, a major cause of male infertility, has been treated using progesterone-derived solid lipid nanoparticles (SLNs) prepared by solvent emulsification-evaporation. These SLNs upregulate genes such as *P38MAPK, SPACA1, PKA*, and *PTK*, enhance TAC in semen, improve sperm membrane integrity, and restore sperm motility, capacitation rate, and acrosome reaction rate.[122] Ifosfamide (IFO), a common chemotherapeutic for pediatric osteosarcoma, can damage male germ cells and impair fertility, with potential transgenerational effects.[123–125] Studies show that Span 80 nanovesicles co-loaded with IFO and caffeine enhance antitumor efficacy in mouse osteosarcoma models without compromising fertility in male mice or their offspring. This may be due to the high tumor selectivity and membrane fusion propensity of Span 80 nanovesicles, which facilitate direct cytosolic drug delivery while minimizing impact on reproductive tissues.[126] TG, a widely used herbal anti-inflammatory and immunomodulatory agent, causes reproductive toxicity by downregulating anti-apoptotic genes, inducing testicular damage, and impairing spermatogenesis, potentially leading to infertility.[127–129] However, TG-loaded SLNs (TG-SLNs) mitigate these effects, prevent the decline in sperm motility seen with free TG, and preserve fertility in male rats. Testicular histology, sperm and mitochondrial morphology, and serum testosterone levels remained comparable to normal controls following TG-SLN treatment.[130] In antioxidant applications, GPx and vitamin E (α-tocopherol) have been widely studied. While lecithin nanoparticles improve rooster sperm motility, viability, and testosterone levels,[131,132] studies on bull sperm cryopreservation revealed that α-tocopherol combined with nano-lecithin showed effects similar to nano-lecithin alone. In contrast, the combination of GPx and nano-lecithin provided superior antioxidant protection, better maintained mitochondrial membrane potential and sperm survival, and led to higher fertilization and hatching rates compared to nano-lecithin alone.[133]

Leveraging their targeted delivery capability, LNPs demonstrate dual advantages in male reproductive medicine: they can act directly as therapeutic agents to improve sperm quality, and serve as protective agents to mitigate drug-induced reproductive toxicity while maintaining antitumor efficacy. This positions them as a promising platform for developing fertility-friendly therapies.

Other Nanomaterials

Curcumin exhibits diverse pharmacological activities with minimal toxicity, supporting its broad clinical application.[134,135] In male reproductive health, curcumin alleviates testicular damage, partially reverses the effects of aging on rooster reproduction, and improves sperm quality and fertility outcomes.[136,137] Its antioxidant properties also benefit semen cryopreservation by reducing oxidative stress, decreasing sperm abnormalities, and preserving membrane integrity.[138,139] Additionally, curcumin protects pancreatic β-cells in diabetes and, via the cGMP pathway, ameliorates diabetes-related erectile dysfunction.[140–142] However, curcumin's clinical utility is limited by poor aqueous solubility, low oral bioavailability, rapid metabolism, short half-life,[143] and interindividual variability in gut microbiota.[144] Nanoencapsulation strategies effectively overcome these limitations, enhancing curcumin's therapeutic potential.[145,146] Various nanocarriers have been designed to optimize its delivery for specific applications.[134] For instance, curcumin nanoemulsions reduce testicular DNA fragmentation, restore testosterone levels, and improve sperm motility in young rats fed a high-fat, high-sugar diet.[147] Similarly, porous silica-based curcumin nanoparticles (curc-np) ameliorate type 2 diabetes-associated ED, enhancing intracavernosal pressure and modulating inflammatory markers such as Nkap and HO-1 after topical administration.[148]

Beyond curcumin, other nanosystems show promise in reproductive medicine. BIO 300, a genistein nanosuspension with radioprotective properties,[149] improves bioavailability and preserves erectile function in rats following prostate radiotherapy without compromising anticancer efficacy.[150] Mitomycin C (MMC) is a widely used antitumor drug but possesses cytogenetic toxicity and teratogenic risks, severely impacting reproductive health.[151,152] Research indicates that active charcoal nanoparticles (ACNP) as a drug carrier for gastric cancer treatment significantly reduce the genetic toxicity of MMC, increasing its reproductive safety. The possible mechanism involves the relatively large particle diameter of ACNP (about 200 nm), limiting entry into larger lymphatic capillaries, reducing MMC concentration in the blood. This could alter MMC distribution in the body, thereby reducing drug concentration in reproductive organs. This approach, while alleviating chemotherapy pain in cancer patients, also lowers genetic and reproductive toxicity.[153]

In summary, nanocarrier-based drug delivery systems enable precise targeting, enhance bioavailability, and reduce toxicity in the treatment of male reproductive disorders (Table 2). Continued advancement in nanomedicine promises to further revolutionize therapeutic strategies for male reproductive health. Future research should focus on elucidating the detailed molecular mechanisms underlying these therapeutic effects, particularly the intracellular signaling pathways modulated by nanoparticle-delivered agents. Long-term biosafety studies and standardized assessment of potential nanotoxicity will be essential for clinical translation. As these technologies evolve, they promise to establish a new therapeutic arsenal for male reproductive disorders that are currently difficult to manage with conventional approaches.

Nanoimaging Technology for the Diagnosis of Male Reproductive System Diseases

Nanoimaging technology has significantly advanced the diagnosis of male reproductive system diseases by enabling visualization of cellular and molecular processes at nanoscale resolution. This approach provides detailed structural and functional information previously inaccessible through conventional imaging methods.

These techniques allow high-precision observation of cellular components, organelles, and biomolecules within male reproductive tissues. Such resolution is particularly valuable for diagnosing testicular disorders, prostate pathologies, and infertility-related conditions. By detecting subtle morphological and molecular alterations, nanoimaging facilitates early and accurate diagnosis, supporting timely clinical intervention.

A key application lies in elucidating spermatogenesis within seminiferous tubules. Nanoimaging reveals dynamic cellular interactions and microenvironmental factors influencing sperm development. It also enables detailed examination of the BTB, providing insights into its ultrastructure and regulatory mechanisms.

Furthermore, nanoimaging supports the detection of specific biomarkers associated with inflammation, oxidative stress, and genetic anomalies in reproductive tissues. The sensitivity of these tools allows identification of molecular-level changes, paving the way for personalized treatment strategies.

As nanoimaging technologies continue to develop, they offer great potential for non-invasive, high-resolution diagnostics in male reproductive medicine. Their integration into clinical practice represents a shift toward more precise and mechanism-based management of reproductive system diseases.

Nano-Imaging Technology in the Biomedical Field

Beyond its therapeutic uses, nanotechnology offers broad applications in medical imaging diagnostics. While conventional techniques such as X-ray and ultrasound remain fundamental, molecular imaging has emerged as a powerful complementary approach (Table 3). Molecular imaging enables noninvasive visualization and quantification of biological processes at molecular and cellular levels, providing insights beyond anatomical structure. The integration of nanotechnology with imaging systems enhances both targeting precision and contrast agent specificitys.[154,155] Current nanomaterial-based imaging platforms include magnetic resonance imaging (MRI), positron emission tomography (PET), computed tomography (CT), fluorescence imaging (FI), and photoacoustic imaging (PAI).[156]

MRI

Compared with CT, MRI provides superior soft tissue contrast and higher spatial resolution without employing ionizing radiation.[157] The technique operates on the principle that, under a strong external magnetic field, hydrogen nuclei in the body align with the field direction. When the field is removed, these nuclei return to their original state—a process termed relaxation. The resulting signals are collected and computationally reconstructed into anatomical images (Figure 6).[158] To improve image contrast and detection sensitivity, exogenous contrast agents are commonly administered. These are classified based on their predominant relaxation effects: T_1 (longitudinal) agents, T_2 (transverse) agents, or dual-mode agents. While traditional contrast agents are widely used, they often lack targeting specificity.[159]

Magnetic nanoparticles represent a promising class of MRI contrast agents due to their biocompatibility and safety profiles. Paramagnetic agents such as gadolinium-based compounds mainly affect T_1, whereas superparamagnetic nanoparticles—notably SPIONs—predominantly affect T_2 relaxation.[160,161] Nanoparticle-based contrast agents offer multiple advantages: they maintain stable physical properties, exhibit low toxicity, can be functionalized for specific

Table 2 Application of Nanocarrier Drug Delivery Technology in the Treatment of Male Reproductive System Diseases

Nanomaterials		Application	Advantage	Therapeutic Effect	References
Polymer Nanomaterials	Nano-SAC	STZ-induced diabetic rat model	Near-spherical, small particle size, controllable release, non-toxic	Levels of male hormones↑, sperm quality, quantity, and vitality↑	[100]
	NPs containing GnRH analogues in CS-DS	Incubation of rabbit sperm in vitro fertilization	Enhancing the Bioavailability of GnRH, Non-Toxic	Sperm Quality↑	[101]
	NPs encapsulating tadalafil, sialorphin, and nitric oxide	Male aging rat model	Small particle size, low toxicity	Erectile function↑	[102]
	ROS response NPs coated with CPD modified by FA	Male mouse model of chronic bacterial prostatitis	Cell targeted, controlled release	ROS, prostatitis↓	[105]
Metal and its compounds nanomaterials	HFn@ATP	Mouse model of asthenospermia induced by gossypol	Blood-testis barrier penetration, cell targeting, non-toxic	Sperm activity↑	[112]
	Curcumin-loaded SPIONs	Mouse testicular heat damage model	Good biocompatibility, non-toxicity	Semen quality↑; SDF, sperm apoptosis↓	[116]
	Curcumin-loaded IONPs	Mouse scrotal hyperthermia model	Small size, strong magnetism, low toxicity	Testicular volume, androgen, sperm production↑	[117]
	ADSC- SPIONs	STZ induced diabetic model in rats	Tissue targeting	Erectile function↑	[47]
Lipid nanomaterials	Progesterone -SLNs	Human asthenospermia semen model	High solubility, high effectiveness	Sperm motility↑, sperm energy yield↑, acrosome reaction rate↑	[122]
	Span 80 nm vesicles containing IFO and caffeine	IFO in the treatment of mouse osteosarcoma model	High mobility, high flexibility, high vascular permeability, high tumor selectivity	Spermatogenesis↑	[126]
	TG-SLNs	Reproductive toxicity induced by TG in rats	Hypotoxicity	Androgen level, sperm count, sperm motility↑	[130]
	GPx- nano-lecithin	A sperm model of a thawed bull	High effectiveness	Sperm quality, sperm motility↑, blastocyst formation rate↑	[133]
Other nanomaterials	Curcumin nanoemulsion	Rat model of sperm damage induced by high lipid and sugar	High absorptivity	Androgen level, sperm motility, viability, normal form sperm↑	[147]
	Curc-np	ED model of male rats with type 2 diabetes	High absorption rate, non-invasive	Erectile function↑; inflammation↓	[148]
	BIO 300	Male rat model of ED induced by radiation therapy	High bioavailability	Erectile function↑	[150]
	ACNP	MMC treatment of mouse gastric cancer model	The small size and regular shape avoid intestinal adhesion and abdominal irritation caused by ACP	Chromosomal aberration↓	[153]

Notes: ↑ indicates an increase; ↓ indicates a decrease.

Table 3 Comparison of Common Imaging Techniques and Nano-Imaging Techniques

Performance	Common Imaging Techniques	Nano-Imaging Techniques
Resolution	Low	High
Sensitivity	Low	High
Specific targeting	No	Yes
Non-specific binding	More	Less
Accuracy	Low	High
Safety	Low	High
Biocompatibility	Low	High
Image contrast	Weak	Strong
Adjustable duration of action	No	Yes
Local retention capacity	Low	High

targeting, and allow modulation of their in vivo residence time.[161] Among them, IONPs are extensively studied for their strong magnetic relaxivity and excellent biocompatibility.[162] For example, PEG-coated IONPs (OD15-P5) demonstrated no toxicity in vitro or in vivo and exhibited higher relaxivity than the commercial agent ferumoxytol (FMX), resulting in superior contrast in MRI. In a xenograft tumor model, OD15-P5 maintained localized accumulation at the injection site 24 hours post-administration, whereas FMX had diffused into surrounding tissues. This sustained retention suggests that OD15-P5 is suitable for longitudinal imaging studies and has potential as a platform for localized drug delivery in oncology.[163]

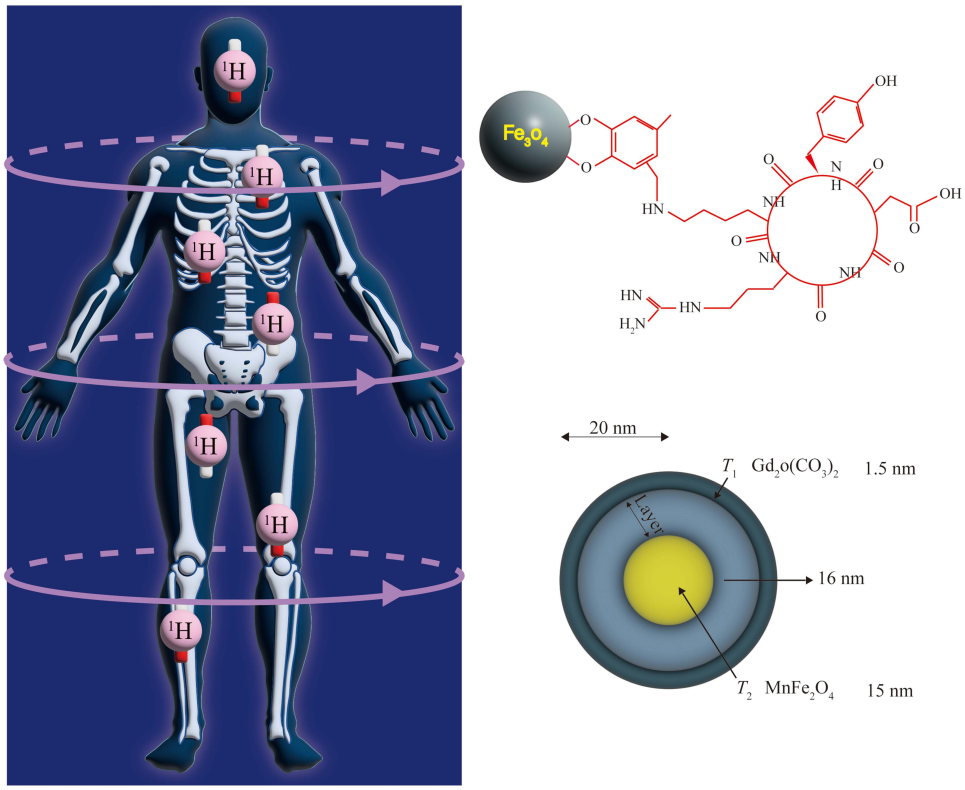

Figure 6 Magnetic Resonance Imaging. Hydrogen atoms moving disorderly within the body. After applying an external magnetic field, hydrogen atoms align and move according to the direction of the external magnetic field. Schematic representation of the structure of ultra-small superparamagnetic iron oxide nanoparticles coupled with cyclic arginine-glycine-aspartic acid through Mannich reaction for tumor-specific MRI.[159] Schematic image of a core–shell-type dual-mode nanoparticle contrast agent [MnFe2O4@SiO2@Gd2(CO3)2]. The T1 contrast material is positioned on the shell to have direct contact with water for high T1 contrast effects, while the superparamagnetic T2 contrast material is located at the core, inducing a long-range magnetic field for the relaxation of water.[159]

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PET Imaging

PET is a highly sensitive, non-invasive imaging technique based on positron-emitting radiotracers, with established applications in both clinical practice and scientific research.[164] Commonly used isotopes such as ^{11}C, ^{13}N, ^{15}O, and ^{18}F are incorporated into biologically active molecules for tracing metabolic and physiological processes—with ^{18}F-fluorodeoxyglucose (FDG) being a widely employed tracer.[165] PET is extensively utilized in cardiovascular, neurological, and oncological research for studying disease pathophysiology.[166] However, since PET primarily reveals the distribution and concentration of radiotracers without anatomical context, it is often combined with CT in hybrid PET/CT systems, improving diagnostic accuracy and specificity.[167] Various nanoparticles—including polymeric, magnetic mesoporous silica, gold, and melanin-based nanoparticles—have been integrated with radioisotopes for PET imaging.[168–171] For example, in monitoring cardiac allograft rejection, ^{64}Cu-labeled glucan nanoparticles (^{64}Cu-CLIO-VT680) enabled effective PET/CT imaging in a mouse model of heterotopic heart transplantation. The tracer signal in allografts was significantly higher than in controls, a finding validated by ex vivo analysis, and signal intensity decreased in response to therapeutic drugs.[172] Similarly, ^{64}Cu-labeled copper sulfide nanoparticles ([^{64}Cu]-CuS NPs) have been synthesized for tumor PET/CT imaging. These NPs exhibit straightforward preparation and high stability. In U87 glioma-bearing mice, PEG-coated [^{64}Cu]-CuS NPs accumulated passively in tumors, enabling clear fusion imaging with both PET and CT.[173] The small size and high surface area of nanoparticles enhance tracer delivery and retention, improving PET imaging sensitivity and resolution. Furthermore, the use of nanoparticles aids in achieving specific targeted aggregation of tracers at the intended site, thereby improving imaging effectiveness.

Other Imaging Techniques

CT generates high-resolution whole-body images by detecting differential X-ray absorption across tissues. While valued for its rapid acquisition, accessibility, and cost efficiency, CT has limited soft-tissue contrast, uses ionizing radiation, and exhibits relatively low sensitivity.[174] To address these limitations, nanoparticle-based contrast agents have been developed, including gold nanoparticles (AuNPs), metal sulfide nanoparticles, and iodinated bovine serum albumin nanoparticles. AuNPs provide stronger X-ray attenuation than conventional iodine-based agents, with improved targeting and biocompatibility. Metal sulfide nanoparticles offer tunable X-ray absorption, multifunctional imaging capacity, and targeting potential. Iodinated albumin nanoparticles demonstrate higher attenuation coefficients and better stability than small-molecule iodinated agents.[175–177] FI detects light emitted by fluorescent probes after excitation, enabling highly sensitive and specific visualization. Nanoparticles play an essential role in improving FI performance,[178] with commonly used agents including polymer nanoparticles, quantum dots (QDs), and dye-doped nanoparticles. Nanoencapsulation enhances the stability of fluorescent probes, improving sensitivity, photostability, and imaging resolution. These nanomaterials often exhibit unique optical properties that support high-contrast biological imaging.[179,180] PAI is an emerging hybrid modality that combines optical excitation with acoustic detection, offering high spatial resolution and rich optical contrast. It has been applied in cardiovascular, inflammatory, and cancer imaging.[181] To improve PAI performance, exogenous contrast agents such as metal sulfide and carbon-based nanomaterials have been developed. These agents exhibit strong near-infrared absorption, efficiently converting light into acoustic waves to enhance contrast and spatial resolution. Many also display photothermal conversion capabilities, enabling combined imaging and photothermal therapy. Through passive accumulation or active targeting via surface ligands, these nanoparticles improve imaging specificity and therapeutic potential.[182,183] Figure 7 summarizes the working principles and representative applications of nanoparticle-enhanced CT, FI, and PAI.

Nanotechnology in the Diagnosis of Male Reproductive System Diseases

Early diagnosis plays a critical role in cancer management. Although serum tumor marker detection is widely used for this purpose, it often lacks sufficient accuracy and requires invasive sampling.[155] The integration of PET and MRI has emerged as a powerful approach for diagnosing various malignancies, including prostate cancer. In one representative study, iron oxide nanoparticles were functionalized with amphiphilic molecules containing the chelator DOTA, PEG, and prostate-specific membrane antigen (PSMA) targeting ligands, forming DOTA-IO-GUL nanoparticles. These were subsequently labeled with the radiotracer ^{68}Ga. Both in vitro and in vivo experiments confirmed specific binding to

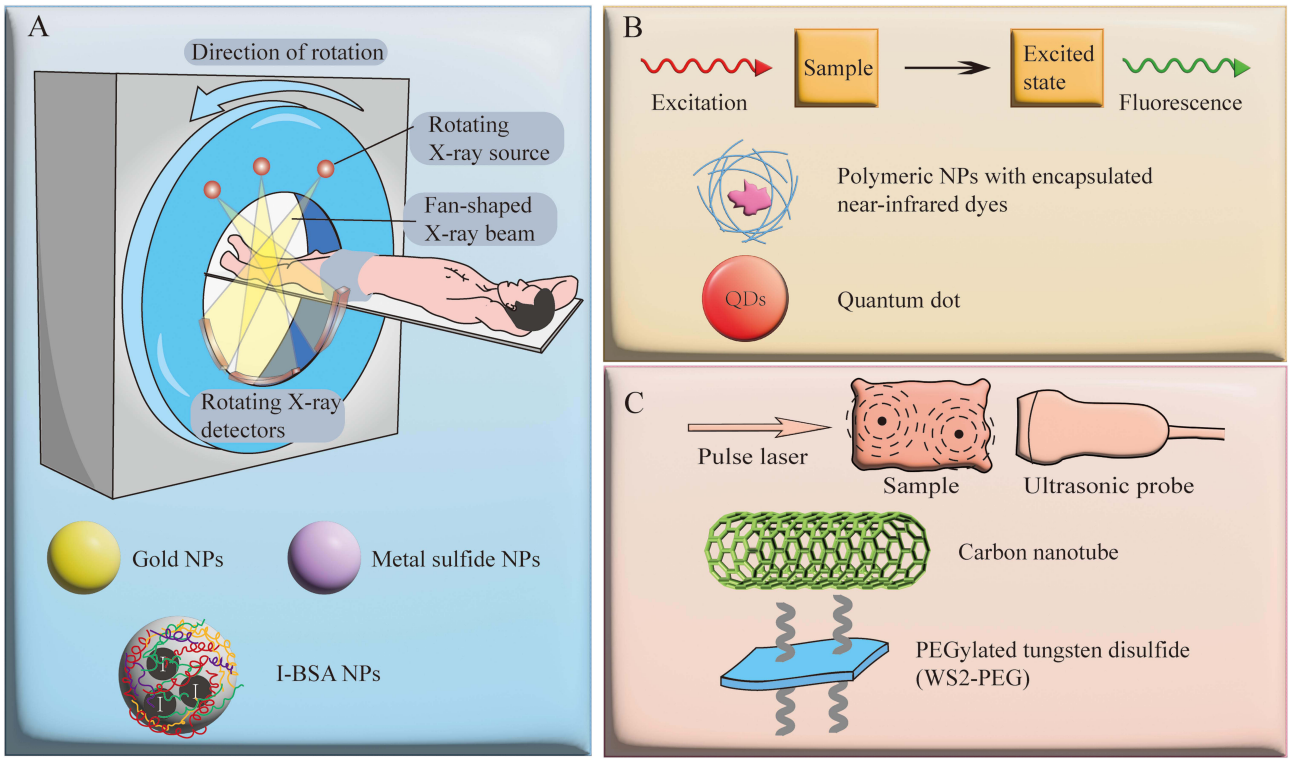

Figure 7 The fusion of nanoparticles with traditional imaging methods. (**A**) Schematic diagram of CT principle and nanoparticles. (**B**) Schematic diagram of FI principle and nanoparticles. (**C**) Schematic diagram of PAI principle and nanoparticles.

PSMA-expressing tumor cells. While MRI provided high-resolution anatomical localization, PET offered quantitative data on tumor uptake, demonstrating the complementary strengths of this bimodal imaging strategy (Figure 8).[184]

In another approach, semiconductor QDs were modified with β-Glu-RGD-BBN peptides to improve biocompatibility and aqueous solubility. After radiolabeling with ^{18}F, the resulting ^{18}F-FP-QD-RGD-BBN probe was evaluated for dual-modality PET and near-infrared fluorescence (NIRF) imaging. In vitro assays confirmed low cytotoxicity and specific binding to PC-3 prostate cancer cells. In mouse models, the probe showed enhanced tumor accumulation and targeting efficiency, supporting its potential as a dual-targeting, dual-modality imaging agent for prostate cancer detection (Figure 9).[185]

These advances highlight how nanotechnology can enhance diagnostic precision through targeted contrast agents and multimodal imaging, offering more accurate and less invasive options for detecting male reproductive system cancers.

Leveraging Natural Ingredients for Male Reproductive System Disorders

Natural ingredients have gained increasing attention as promising candidates for managing male reproductive system disorders. Unlike conventional pharmaceutical approaches, these compounds often provide a safer, more holistic therapeutic profile. Their multi-targeted actions—including antioxidant, anti-inflammatory, and hormone-regulating effects—align well with the complex pathophysiology of many reproductive conditions, offering a comprehensive strategy for treatment and prevention.

Fusion of Natural Materials with Nanomedicine

Nanocarrier-mediated drug delivery offers distinct physical and physiological advantages in biomedical applications. However, synthetic nanocarriers often face rapid clearance, immune recognition, and limited biocompatibility in the complex in vivo environment. While surface modifications such as PEGylation can enhance stability and targeting,[186] repeated administration of PEGylated systems may trigger anti-PEG immune responses, accelerating clearance and reducing long-term efficacy.[187] To address these limitations, researchers are increasingly turning to natural-derived

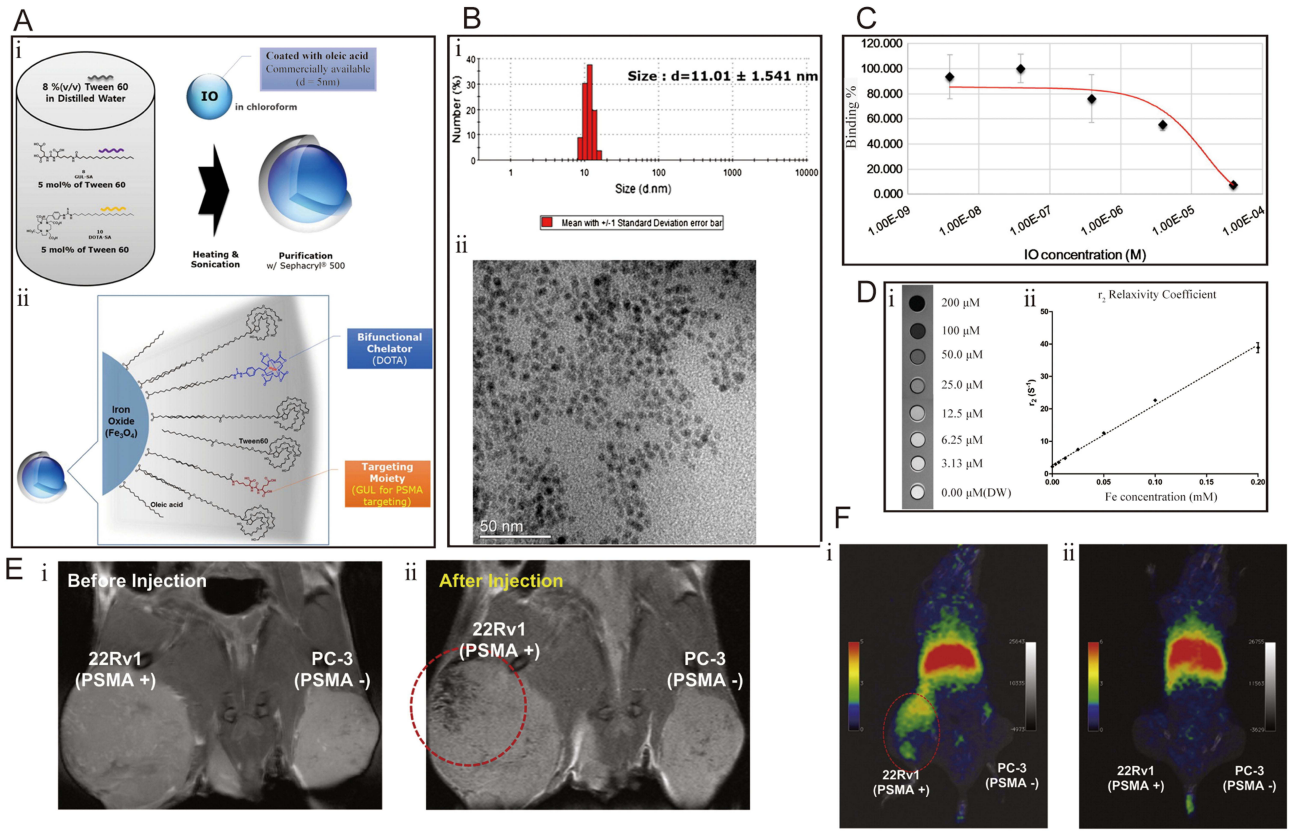

Figure 8 A complementary PET/MR dual-modal imaging probe for targeting PSMA.[184] (**A**) Synthesis of DOTA-IO-GUL. (i) Encapsulation of NPs with specific amphiphiles. (ii) Diagram of encapsulated DOTA-IO-GUL. (**B**) Size determination of DOTA-IO-GUL. (i) DLS data of DOTA-IO-GUL (d = 11.01 ± 1.541 nm). (i) TEM image of DOTA-IO-GUL. Scale bar = 50 nm. (**C**) In vitro cell binding assay result. Bound radioactivity of ^{125}I-MIP-1072, a PSMA-inhibitor, to the PSMA-positive cells, LNCaP, showed a dose-dependent decrease by addition of DOTA-IO-GUL. (**D**) MRI phantom study for the determination of DOTA-IO-GUL injection concentration. (i) MR image was obtained from serially diluted DOTA-IO-GUL from 200 μM Fe^{3+} concentration. (ii) Calculation of r2 relaxivity coefficient value of DOTA-IO-GUL. (**E**) In vivo micro-MRI image results. (i) Before injection, control image; (ii) after injection of DOTA-IO-GUL through the tail vein (1 h). Left tumor is PSMA positive (22Rv1) and right tumor is PSMA-negative (PC-3). Red circle demonstrates the selective uptake of DOTA-IO-GUL to the positive tumor. The block dots within the red circles indicate a decrease in MR signal in the 22Rv1 tumor, suggesting increased uptake of IONPs. (**F**) In vivo PET result. (i) PSMA-selective uptake results in micro-PET imaging. Red circle: PSMA-positive. (ii) Blocking study result with co-injection of MIP-1072.

materials as alternative platforms for nanocarrier design. The key advantages of natural nanoparticles over most of their synthetic counterparts lie in their superior biological properties. These include exceptional biocompatibility and biodegradability, inherent low immunogenicity and prolonged circulation half-life, intrinsic targeting capabilities, and significant potential as gene delivery vectors.[188] Collectively, these attributes underscore the promise of natural nanoparticles for circumventing the common reproductive toxicity associated with synthetic nanoparticles and for enabling precise diagnosis and therapy. Furthermore, given that thorough toxicological evaluation is a cornerstone of the clinical translation of nanomedicines,[189] the favorable biological profile of natural nanoparticles may facilitate a more streamlined path to clinical trials and, consequently, earlier integration into medical practice compared to synthetic alternatives.

This section highlights several promising classes of natural-source nanomaterials, including nanobodies (Nbs), cell membrane-based nanomaterials, and DNA-based nanomaterials, which together represent a new frontier in targeted and responsive therapeutic delivery.

Nanobodie

Nbs are single-domain antibodies naturally occurring in camelids, consisting solely of a variable heavy-chain domain without a light chain.[190] Compared with conventional antibodies, they offer distinct advantages including smaller size, stronger antigen binding, high stability, excellent water solubility, enhanced tissue penetration, and simplified production (Table 4). These properties have enabled their broad application in molecular imaging, disease diagnosis, and targeted

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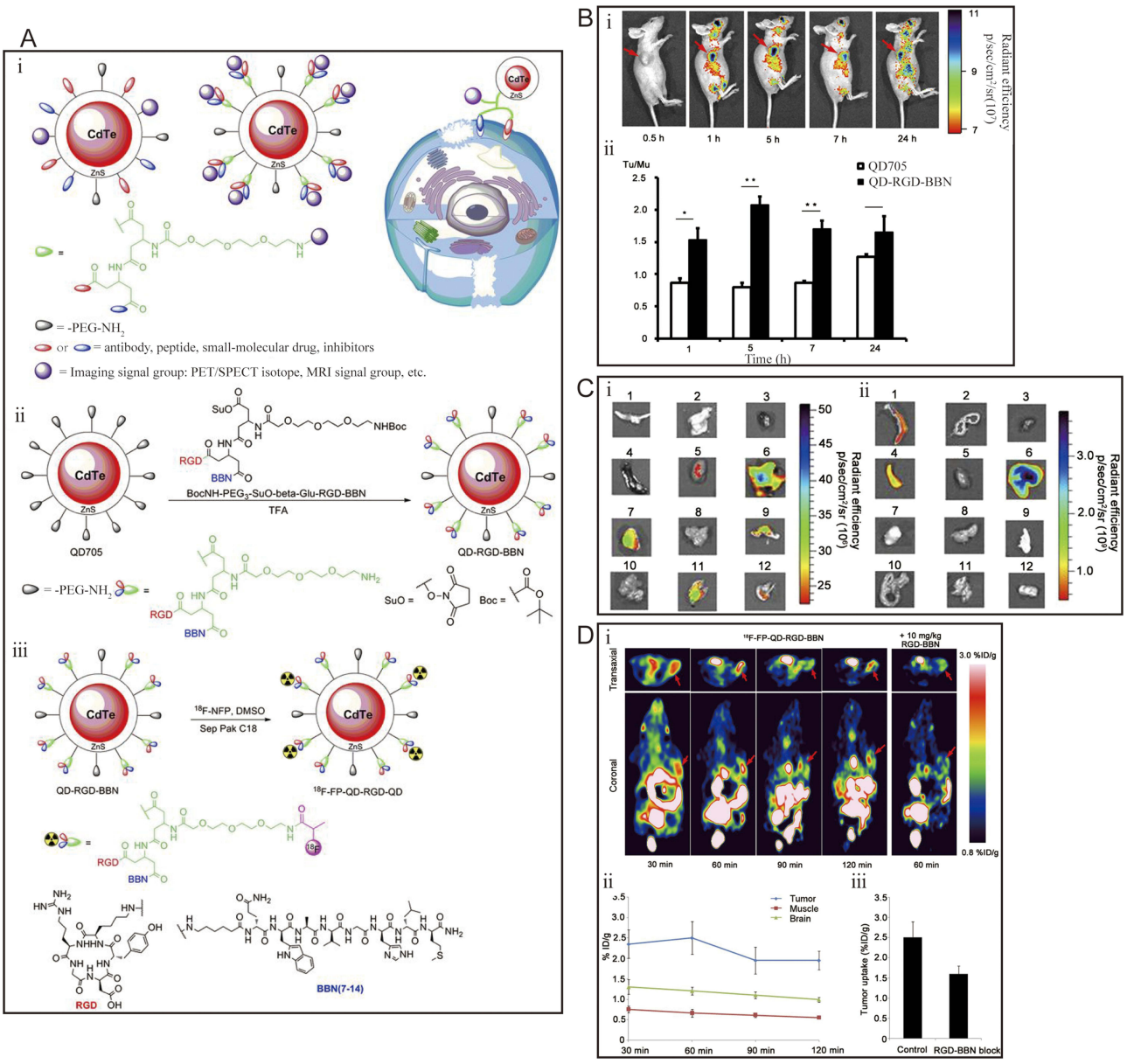

Figure 9 In vivo dual-modality PET/NIRF imaging of prostate tumor-bearing mice was investigated using functionalized QD probes.[185] (**A**) Functionalized QD probe for in vivo cancer dual-targeting and dual-modality imaging. (i) Schematic illustration of QD probe. (ii) Synthesis of QD-RGD-BBN. (iii) Synthesis of dual receptor–targeting dual-modality PET probe ^{18}F-FP-QD-RGD-BBN. (**B**) The optical imaging of the animal models with the QD conjugate probe. (i) In vivo NIRF imaging of PC-3 tumor–bearing mice at 0.5, 1, 5, 7, and 24 h after injection of QD-RGD-BBN. Red arrows: tumor. (ii) Tumor-to-muscle uptake ratios of mice injected with QD705 and QD-RGD-BBN. Data are mean ± SD. *P < 0.05, as compared with mice injected with QD705, 1-tailed paired Student *t* test (n = 3). **P < 0.01. (**C**) Ex vivo NIRF imaging. (**i**) NIRF image of harvested major organs at 5 h after injection of QD-RGD-BBN. (ii) NIRF image of harvested major organs at 5 h after injection of QD705. 1 = bone, 2 = brain, 3 = heart, 4 =spleen, 5 = kidney, 6 = liver, 7 = tumor, 8 = muscle, 9 = skin, 10 = intestine, 11 = lung, 12 = stomach. (**D**) PET imaging of PC-3 tumor–bearing mice with targeting dual-receptor PET/NIRF probe. (i) PET images of same mouse at 30, 60, 90, and 120 min after injection of ^{18}F-FP-QD-RGD-BBN and in presence of blocking agent RGD-BBN. Red arrows: tumor. (ii) Uptake of ^{18}F-FP-QD-RGD-BBN in tumor, muscle, and brain over time, as quantified by ROI analysis of small-animal PET scans. (iii) Tumor uptake of ^{18}F-FP-QD-RGD-BBN at 60 min after injection in absence of blocking agent (control) and in presence of RGD-BBN, as quantified by ROI analysis of small-animal PET scans.

therapy (Figure 10).[191] In oncological diagnostics, nanobodies enable highly sensitive tumor detection. For example, a ^{68}Ga-labeled anti-epidermal growth factor receptor (EGFR) nanobody combined with PET imaging showed excellent tumor targeting and visualization in xenograft mouse models.[192] Similarly, a ^{99}mTc-8B6-labeled nanobody allowed specific SPECT imaging of EGFR-overexpressing tumors.[193] When conjugated with near-infrared fluorescent dyes, anti-EGFR nanobodies enabled rapid optical imaging with shorter acquisition times and higher tumor uptake than conventional antibodies, benefiting from their superior penetration and targeting capabilities.[194] In cancer treatment, the anti-PD-

Table 4 Nanobodies versus Conventional Antibodies and Cell Membrane Nanomaterials versus Regular Nanomaterials

Performances	Conventional Antibodies	Nb	Performances	Regular Nanomaterials	Cell Membrane Nanomaterials
Molecule size	About 150–200kDa.	About 15–20kDa	Source	Synthetic	Cell membrane
Contains light chains or not	Yes	No	Ingredient	Proteins, polysaccharides, and other biomolecules	Polymers, metals, oxides, etc.
Antigen-binding capacity	Strong	Stronger	Biocompatibility	Poor	Good
Idiosyncrasy	Strong	Stronger	Biological toxicity	High	Low
Immunogenicity	Strong	Weak	Immunogenicity	Strong	Weak
Preparation process	Intricate	Simpler	Bioactivity	No	Yes
Stability	Poor	Good	Cell penetration	Weak	Strong
Biological barrier crossing capacity	Weak	Strong	Targeting capability	Limited target identification	Recognizes and binds to specific cells

L1 nanobody KN035 enhanced T cell-mediated antitumor immunity when combined with immune checkpoint blockade, effectively suppressing tumor growth in mice.[195] Nanobodies can also be functionalized on nanocarriers: anti-EGFR nanobodies conjugated to drug-loaded liposomes improved tumor-specific delivery and significantly inhibited cancer cell proliferation.[196] Beyond therapy, nanobodies serve as sensitive detection tools. A tetravalent nanobody cocktail targeting tumor-associated glycoprotein 72 (TAG-72) demonstrated high specificity, affinity, and multi-epitope binding, potentially improving current monoclonal antibody-based diagnostics.[197]

In neurological infections, nervous necrosis virus (NNV)-specific nanobodies coupled with antiviral drugs and nanocarriers crossed biological barriers, enhancing drug distribution and antiviral activity at infection sites while prolonging therapeutic efficacy.[200]

Cell Membrane-Based Nanomaterials

Beyond nanobodies, natural cell membranes have emerged as another promising platform for functionalizing nanomaterials (Table 4). Cell membrane-based nanoparticles generally fall into two categories: vesicles derived directly from native cell membranes, and synthetic nanoparticles coated with membrane components (Figure 10).[198] Exosomes—a type of extracellular vesicle—serve as effective drug carriers capable of delivering nucleic acids, proteins, and small molecules with low immunogenicity and high biocompatibility. Their similarity to endogenous vesicles enables efficient cellular uptake, enhanced bioavailability, and the ability to cross biological barriers such as the blood–brain barrier (BBB).[199] For example, brain endothelial cell-derived exosomes loaded with doxorubicin or paclitaxel successfully traversed the BBB in zebrafish models and significantly inhibited the growth of U-87MG glioblastoma cells, outperforming free doxorubicin.[201] A wide range of cell sources—including erythrocytes, leukocytes, endothelial cells, and stem cells—can be used to produce membrane-coated nanoparticles.[198] These cell membrane-based nanoparticles (CMBNPs) combine the biological functions of native membranes with the tunable properties of synthetic cores,[202,203] improving targeting and reducing immune clearance.[204] For instance, coating PLGA nanoparticles with red blood cell membranes prolongs their circulation half-life and enhances serum stability.[202] Similarly, leukocyte membrane-coated mesoporous silica particles evade immune recognition and leverage receptor–ligand interactions to enable targeted delivery and extended circulation.[205]

DNA-Based Nanomaterials

DNA-based nanomaterials can be engineered into diverse architectures—including DNA tetrahedra, DNA origami, DNA nanotubes, and aptamer-based structures—that have been utilized for tumor cell detection, real-time imaging, photodynamic therapy, and targeted drug delivery.[206] These nanostructures exhibit high biocompatibility, structural programmability, and low cytotoxicity. A distinctive advantage is their ability to be internalized by cells without the need for transfection agents, positioning them as promising candidates for biomedical applications. However, several challenges currently limit the clinical translation of DNA-based nanomaterials. First, endogenous nucleases can degrade DNA

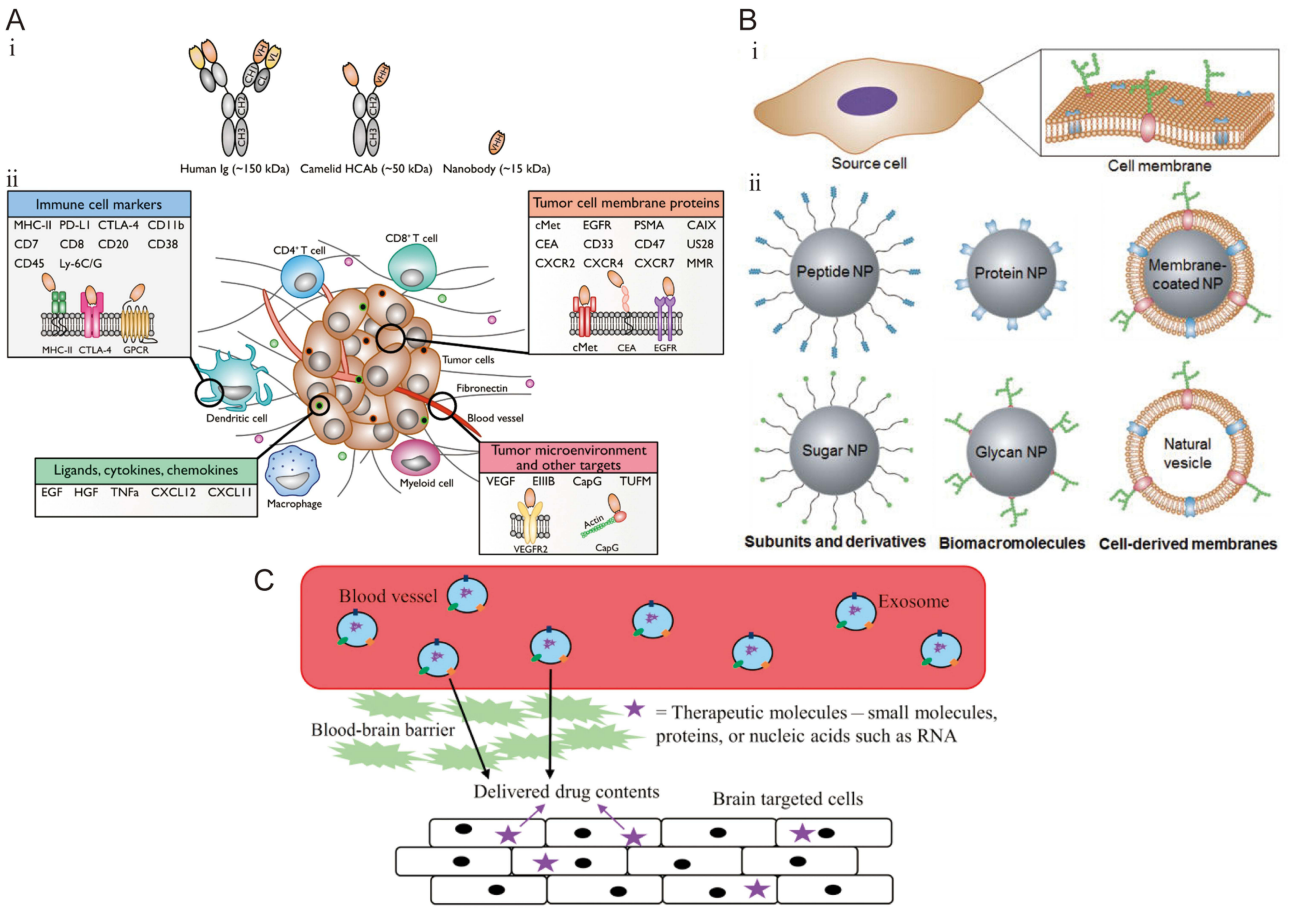

Figure 10 Biomimetic nanomaterials for nanomedicine. (**A**) Nanobodies and their targets in relation to the tumor. (i) Schematic representation of a conventional human Ig, camelid HCab, and a nanobody. (ii) Schematic overview of the tumor-associated targets for which nanobodies have currently been established.[191] (**B**) Cell membrane-based strategies for nanoparticle functionalization. (i) Many cellular properties are determined by membrane composition, including the different proteins and glycan structures that are present. (ii) Examples of different cell membrane-based design strategies for fabricating biomimetic nanoparticles.[198] (**C**) Ability of exosome and its drug contents to cross the blood–brain barrier.[199]

nanostructures, potentially compromising structural integrity and therapeutic efficacy. Second, the pharmacokinetic profiles of these materials remain insufficiently characterized, hindering comprehensive safety and efficacy evaluation. Finally, high synthesis costs present a barrier to scalable production and widespread adoption.[207]

Natural Source Nanomaterials - Guardians of Male Reproductive Health

Natural source nanomaterials serve as formidable guardians of male reproductive health, embodying a fascinating intersection of nature and cutting-edge science. In this realm where nature meets nanotechnology, the exploration of natural source nanomaterials emerges as a captivating journey towards enhancing male reproductive health. As research unfolds, these guardians offer the prospect of novel, sustainable, and nature-inspired solutions to nurture and protect the intricate complexities of the male reproductive system.

Nanobodies

Nanobodies offer distinct advantages for diagnosing and treating PCa. Their small size and high binding affinity make them particularly suitable for molecular imaging applications. While conventional ultrasound contrast agents are micron-scale, the neovascularization of tumors requires nanoscale agents for effective targeting.[208] For ultrasound molecular imaging, researchers have developed nanobubbles (NBs) functionalized with PSMA-specific nanobodies.[209] Both in vitro and in vivo experiments demonstrated that these targeted nanobubbles efficiently extravasate through tumor vasculature and specifically bind to PSMA-positive cells, generating significantly stronger imaging signals compared to non-targeted

controls.[210] In radionuclide imaging, ^{111}In-labeled anti-PSMA nanobodies (JVZ-007) enable rapid SPECT/CT imaging with favorable pharmacokinetics. These agents exhibit specific PSMA binding, rapid blood clearance, and reduced renal retention due to engineered cysteine modifications. This profile allows imaging within hours post-injection and improves detection of lesions near renal structures, potentially enhancing prostate cancer staging accuracy.[211] Beyond diagnostics, nanobodies show therapeutic potential. Conventional chemotherapy for prostate cancer often exhibits limited efficacy, significant side effects, and poor patient tolerance.[212] By conjugating PSMA-specific nanobodies with chemotherapeutic agents like doxorubicin, researchers achieved targeted drug delivery in PCa models. This approach maintained therapeutic efficacy at substantially reduced doses, potentially minimizing systemic toxicity and improving treatment tolerability.[213]

Extracellular Vesicles and Cell Membranes

Extracellular vesicles, particularly exosomes, serve as promising therapeutic carriers due to their natural role in intercellular communication.[214] Prostate cancer-derived exosomes loaded with paclitaxel enhance drug delivery through membrane internalization, enabling direct intracellular release and potent antitumor effects.[215] In male reproductive disorders, amniotic fluid-derived extracellular vesicles restored spermatogenesis in busulfan-induced non-obstructive azoospermia (NOA) rat models by increasing OCT-3/4$^+$ testicular cells and upregulating spermatogenesis-related genes (eg, *Dazl, Vasa*).[216] Similarly, exosomes from urine-derived stem cells promoted the recovery of spermatogenesis in NOA mice by elevating the expression of *Dazl, Pou5f1, Prm1, Sycp3*, and Uchl1 protein.[217] Cell membrane-coated nanoparticles (CNPs), comprising a functional nanocore enveloped by natural cell membranes, represent a versatile platform with tunable biological properties depending on the membrane source.[218] In magnetic fluid hyperthermia (MFH) for prostate cancer, tri-magnetic nanoparticles (TMNPs) coated with cell membranes and cell-penetrating peptides exhibited enhanced targeting and induced apoptosis via the Caspase-9 pathway, downregulating cell cycle and division processes.[219] In another approach, personalized tumor cell membranes—harvested from surgical specimens and serving as tumor-associated antigens—were coated onto polymer nanoparticles loaded with imiquimod (SCNPs/R837). These vesicles efficiently migrated to draining lymph nodes, activating plasmacytoid dendritic cells and, in combination with anti-PD-1 antibodies, eliciting a robust antitumor immune response.[220]

Notably, nanobodies, exosomes, and CNPs have all demonstrated the ability to cross the blood–brain barrier,[221,222] suggesting a similar potential to traverse the BTB. Their small size, targeting specificity, biocompatibility, and low immunogenicity support their use either as targeting modifiers or as natural drug carriers. By facilitating BTB penetration, these systems can increase local drug concentrations in the testes, improving efficacy while minimizing systemic side effects (Table 5).

Biosafety and Clinical Translation Challenges of Nanomaterials

Biosafety of Nanomaterials

Despite the significant potential of nanomaterials in the diagnosis and treatment of male reproductive system diseases, their biosafety, particularly the potential toxicity of certain metal nanoparticles, poses a central challenge to clinical translation. The toxic effects of silver nanoparticles have been reported in both prokaryotic and eukaryotic systems. Multiple studies demonstrate that uncoated AgNPs exert significant toxic effects on the male reproductive system across various developmental stages in rats. Exposure to AgNPs leads to reduced sperm output, impaired spermatogenesis, abnormal testicular histoarchitecture, and delayed puberty. Furthermore, AgNPs damage sperm plasma membrane integrity, diminish mitochondrial activity, increase the proportion of abnormal sperm, and induce oxidative stress. Notably, some effects are irreversible even after exposure cessation, and sperm cells appear particularly sensitive to low doses of AgNPs, often without concurrent alterations in serum hormone levels.[223–226] Research shows that uncoated zinc oxide nanoparticles can accumulate in living organisms and exert cytotoxicity, causing adverse effects on the male reproductive system. Experiments in Kunming mouse models revealed that ZnO-NPs exposure causes severe testicular damage, including seminiferous tubule atrophy, degeneration, vacuolization, germ cell necrosis, depletion, and a reduction in round spermatids. These structural injuries are accompanied by disruption of the spermatogenic process. Moreover, ZnONPs significantly depress testosterone levels by modulating endoplasmic reticulum stress-related genes and the StAR gene in Leydig cells, with these toxic effects typically being dose-dependent.[227,228] The toxicity of NPs is governed by multiple factors, including size, shape, surface charge, coating, solubility, concentration/dose, surface functionalization, administration route, mechanism of action, exposure duration, and target cell type.[229,230] Substantial

Table 5 Application of Naturally Sourced Nanomaterials in the Male Reproductive System

NPs	Applications	Properties	Effective	References
Ultrasonic NBS carrying anti-PSMA Nb	Ultrasonographic diagnosis of PCa	Specific targeting, small size, high safety	Peak intensity value, enhancement duration↑	[210]
Anti-PSMA Nb (JVZ-007)	CT/SPECT imaging diagnosis of PCa	Tumor targeting, low off-target nodes, rapid blood clearance	Renal retention ↓, prostate cancer imaging results ↑	[211]
Anti-PSMA Nb coupled with DOX	PCa mice	High PSMA affinity, low dissociation rate, long half-life, no effect of PSMA on enzymatic activity	Dose of DOX ↓	[213]
EXO and MVs carrying PtX	PCa cells	Bionic targeted drug carrier, blood-brain barrier penetration, endocytosis	PtX Cytotoxicity↑	[215]
Amniotic fluid-derived EVs	Busulfan-induced NOA rats	Enriched with growth factors	OCT-3/4 positive cell↑, spermatogenesis, sperm function ↑, *Dazl* and *Vasa* gene expression ↑	[216]
USC-exos	Busulfan-induced NOA mice	Carrying substances into cells and regulating receptor cell functions	*Dazl, Pou5f1, Prm1*, and *Sycp3* ↑, spermatogenic genes and *Uchl1* ↑, spermatogenic protein expression, spermatogenesis ↑	[217]
CM and/or LN1 CPP-modified TMNPs	PCa cells	Good cytocompatibility, high PCa cell binding affinity and selectivity, enhanced targeting, good stability	PCa apoptosis ↑, cancer cell invasiveness ↓	[219]
SCNPs/ R837	Prostate cancer in mice	Tumor-targeted, efficient, slow-release action, safe	Mouse survival ↑, tumor volume ↓	[220]

Notes: ↑ indicates an increase; ↓ indicates a decrease.

evidence indicates that exposure to inorganic NPs during spermatogenesis can compromise the integrity of the blood-testis barrier and impair sperm morphology and production, primarily through the induction of ROS generation and/or inflammatory responses.[231–233]

To address the reproductive toxicity associated with NPs, researchers have proposed several mitigation strategies. These include using polyvinylpyrrolidone (PVP) coating to reduce direct NP-induced reproductive toxicity,[234] employing alloy composite NPs as substitutes for the more toxic silver nanoparticles,[235] and administering drugs like quercetin, β-carotene, curcumin, and zingerone to alleviate testicular and sperm damage caused by NPs.[236–239] Overcoming the reproductive toxicity of nanomaterials is crucial for advancing their clinical application. However, it is important to recognize that these modification strategies might concurrently affect their targeting efficiency and therapeutic efficacy. Therefore, conducting systematic, long-term reproductive toxicity assessments and gaining a deep understanding of the structure-activity relationships of nanomaterials are indispensable prerequisites for promoting their clinical translation.

Challenges in Clinical Translation of Nanomaterials

Nanomaterials hold considerable promise for clinical applications in biomedicine, including vaccine development, disease diagnosis, and therapy. For instance, in current clinical practice, PLGA has been approved by the US FDA and the European Medicines Agency (EMA) for parenteral drug delivery systems, owing to its favorable properties such as low systemic toxicity, biodegradability, and sustained-release characteristics. PLGA-based nanoparticles have diverse clinical applications, serving as vaccine delivery systems, therapeutics for cancer, neurological disorders, cardiovascular diseases, various inflammatory conditions, and also showing potential in regenerative medicine.[240,241] Furthermore, lipid nanoparticle (LNP)-based COVID-19 mRNA vaccines and a small interfering RNA (siRNA) therapeutic (ONPATTRO®) have received approval from the US FDA.[242,243]

However, for the majority of nanoformulations, successfully transitioning from highly efficient laboratory prototypes to clinical use requires overcoming a series of systemic barriers. The primary challenge lies in the feasibility of scalable manufacturing and robust quality control. Scaling up NP synthesis from milligram-scale laboratory preparations to gram or even kilogram levels often faces significant batch-to-batch variability. Minor fluctuations in critical parameters like particle size, Zeta potential, and drug loading efficiency can profoundly affect their in vivo pharmacokinetics and

therapeutic outcome.[244] Secondly, regulatory pathways (eg, FDA, EMA) impose stringent requirements on nanomedicines, mandating comprehensive safety evaluations encompassing long-term toxicity, reproductive toxicity, immunogenicity, and in vivo fate (eg, biodistribution, metabolism, clearance). These studies are often time-consuming and costly.[245,246] Finally, the high costs of research, development, and production necessitate that nanomedicines demonstrate a clear and compelling cost-effectiveness advantage, balancing the improved therapeutic outcomes (eg, increased cure rates, reduced side effects) against the additional healthcare expenditures, to gain acceptance by healthcare payment systems. Future research needs concerted efforts in areas such as innovative biomaterial design, standardization of production processes, and early, proactive engagement with regulatory agencies to ultimately bridge the gap from concept to product for nanomedicine in the field of male reproductive health.

Future and Outlook

The comprehensive exploration of nanoreagents in the treatment of male reproductive system diseases marks a significant stride towards innovative therapeutic strategies. The unique advantages conferred by nanoreagents, notably their precision, targeted delivery, and potential for personalized medicine, hold immense promise for reshaping the landscape of male reproductive healthcare.

Despite their remarkable potential, the clinical application of nanoreagents is not without challenges. Issues such as optimal dosage determination, potential side effects, and regulatory considerations need meticulous attention. Future research endeavors should prioritize the refinement of these aspects to ensure the seamless integration of nanoreagents into mainstream clinical practices. Overcoming these challenges will pave the way for more effective and safer treatments for male reproductive system diseases.

In conclusion, this review provides a roadmap for the future of male reproductive healthcare. The synergy of nanoreagents and the exploration of unconventional therapeutic pathways, such as the gut-testis axis, beckon towards a future where male reproductive system diseases can be addressed with unprecedented precision and efficacy. As researchers, clinicians, and policymakers collaborate, the prospect of improved diagnostics and tailored treatments for these complex conditions becomes increasingly tangible. The journey ahead holds immense promise for advancements that will benefit the well-being of individuals facing reproductive health challenges.

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Disclosure

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