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Advances of nanoworms in diagnosis, treatment, and theranostics

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Engineered nanoparticles offer potential applications in the biomedical field, such as drug delivery and magnetic resonance imaging; however, they exhibit poor hemocompatibility. Thus, elongated nanoparticles known as nanoworms with a length of 30 nm have received considerable attention in various applications such as tissue engineering, microfluidics, biosensors, and drug delivery. Synthesizing with different metals, polymers, and biological molecules, nanoworms are used as templates for inorganic nanoparticles, superstructure building blocks, synthetic dendritic cells for immunotherapy, temperature-responsive gels for medical purposes, and traditional nanocarriers for drug delivery. Nanoworms demonstrate significant characteristic benefits over spherical counterparts, such as higher surface area, resembling the extracellular matrix of human cells, availability of numerous attachment points, increased likelihood of effective delivery to biological targets, prolonged circulatory half-life, and clear imaging. Considering nanoworms as an isolated research area, this review article focuses on providing an overview, as well as discussing the advantages, disadvantages, and applications of nanoworms, specifically in the diagnosis, treatment, and theranostics of detrimental diseases such as COVID-19, autoimmune disorders, cancer, bacterial infections, and atherosclerosis. Since the risks, benefits, and wide range of uses of nanoworms remain to be explored, substantial research is beneficial to investigate the development and applicability of their use in the future in a variety of fields, including medicine, electronics, and materials science.

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1. Introduction

Nanomedicine uses tiny materials such as biocompatible nanoparticles (NPs) and nanorobots for a wide range of practices, like diagnosis, evaluation, surveillance, mitigation, and

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intervention of different diseases like cancer, Alzheimer's disease, cardiovascular disorders, *etc.*[1,2]

Among the variety of nanomaterials like liposomes, niosomes, ethosomes, transfersomes, nanorods, and nanotubes, newly discovered nanoworms (NWs) are attracting a lot of attention in applications such as tissue engineering, microfluidics, biosensors, and drug delivery.[3,4] Fig. 1 shows the different types of nanocarriers for targeting drugs in the body. NWs are a type of nanomaterial characterized by elongated cylindrical structures measuring 30 nm in diameter and are composed of a variety of different materials, including metals,[5,6] polymers,[7,8] and biological molecules.[9,10] NWs are used as templates for inorganic NPs, superstructure building blocks, synthetic dendritic cells for immunotherapy, temperature-responsive gels for medical use, and traditional nanocarriers for drug delivery. The small dimension of NWs allows them to easily navigate through the body and reach remote sites unlike traditional medical treatments, making them ideal for targeted drug delivery and medical procedures. Thus, NWs have the potential to improve the diagnosis, treatment, and theranostics (combination of therapy and diagnostics) of various diseases like cancer, neurological conditions, COVID-19, *etc.*

NWs can transport imaging agents such as NPs or fluorescent dyes to visualize specific cells or tissues, greatly improving the accuracy of diagnostic imaging and enabling earlier detection of diseases like cancer.[11–13] NWs are used in treatment to distribute drugs directly to diseased cells, avoiding healthy cells, thereby increasing the effectiveness and decreasing the side effects of chemotherapy such as hair loss, and decreased immunity.[14] Additionally, medical procedures, such as the delivery of gene therapy or removal of plaque from blood vessels, are also carried out using NWs.[15] Engineered NWs are used for theranostics, to improve the efficiency and effectiveness of medical care. NWs can recognize cancer cells and deliver chemotherapy drugs to target cells in the same process. Hence, NWs are a great isolated area of research as they overcome the drawbacks and offer significant advantages over the currently available nanomaterials like nanobulges,[16] nanospheres,[17] nanoflowers,[18] *etc.* as shown in Fig. 2. Although NWs are employed in diagnostic imaging, targeted drug delivery, medical procedures, and theranostics, their further study and development are still in their infancy, and therefore it is essential to carefully consider the potential risks and benefits before utilizing NWs extensively in therapeutic settings.

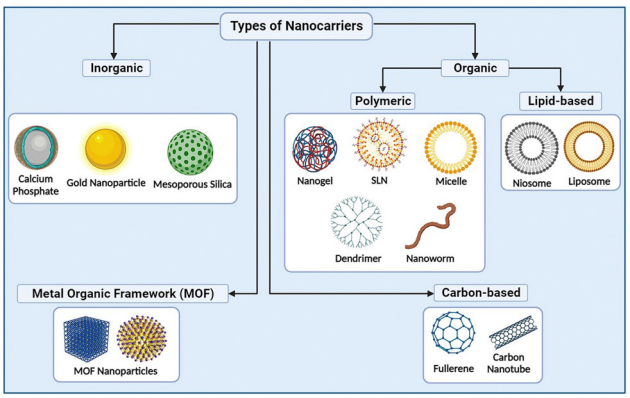

Fig. 1 Several types of nanocarriers proposed for delivery of drugs.

Advantages:

1. The geometric alignment of cores and the elongated shape of NWs provide not only a well-defined morphology but also a variety of desirable physical properties, including high surface area and large aspect ratio (in the range of 75 to 100), thus offering two main advantages over spherical equivalents (liposomes, niosomes, transferosomes, *etc.*).[10]

2. NWs travel through the bloodstream without being significantly hindered by the immune system and target tumors like small anti-cancer missiles because of the shape and the polymer coating on their surfaces. As a result, the worms are able to circulate for up to 24 h in the system.[19]

3. To enable the delivery of drugs to specific malignancies, organs, and other locations in the body, researchers are currently devising approaches to coat NW exteriors with different chemical "zip codes". The zip codes enhance the capacity of NWs to deliver drugs directly to tumors, thereby increasing drug efficacy.[20]

4. NWs reduce the adverse effects of harmful anti-cancer medications and improve the identification of tumor and abnormal lymph by limiting their exposure to healthy tissues.[21]

5. Owing to their iron-oxide composition, NWs are observed clearly in diagnostic equipment, in particular magnetic resonance imagining (MRI), or scanners used to locate tumours. In MRI scans, the NWs' extremely bright appearance is due to the superparamagnetism of the iron oxide used. Hence, it is simpler to detect microscopic tumours, thus aiding medical professionals in diagnosing cancer at an earlier stage of the illness.[22]

6. NWs are more favourable than pre-existing NP systems in terms of kinetics, stability, and half-life, thus demonstrating them as one of the best delivery systems for all kinds of diseases.

Disadvantages:

1. The manufacturing and disposal of NWs result in negative environmental impacts. The materials and chemicals used in the production process are harmful to the environment and potentially to human health. Thus, the disposal of NWs can also be challenging, as they accumulate in soil and water sources and potentially cause harm to wildlife.[23,24]

2. The concern about the potential unintended consequences of using NWs in medical applications is still unclear. Although NWs are useful in targeted drug delivery and disease diagnosis, the long-term effects of introducing these tiny devices into the body are not fully explored. NWs still pose the risk of causing unforeseen side effects, such as triggering an immune response or disrupting natural biological processes.[25]

2. Applications

2.1. Diagnosis

2.1.1. Colon cancer. Colon cancer is a concern as it is the third deadliest and fourth most common cancer worldwide, caused primarily by multiple factors, including an aging population,

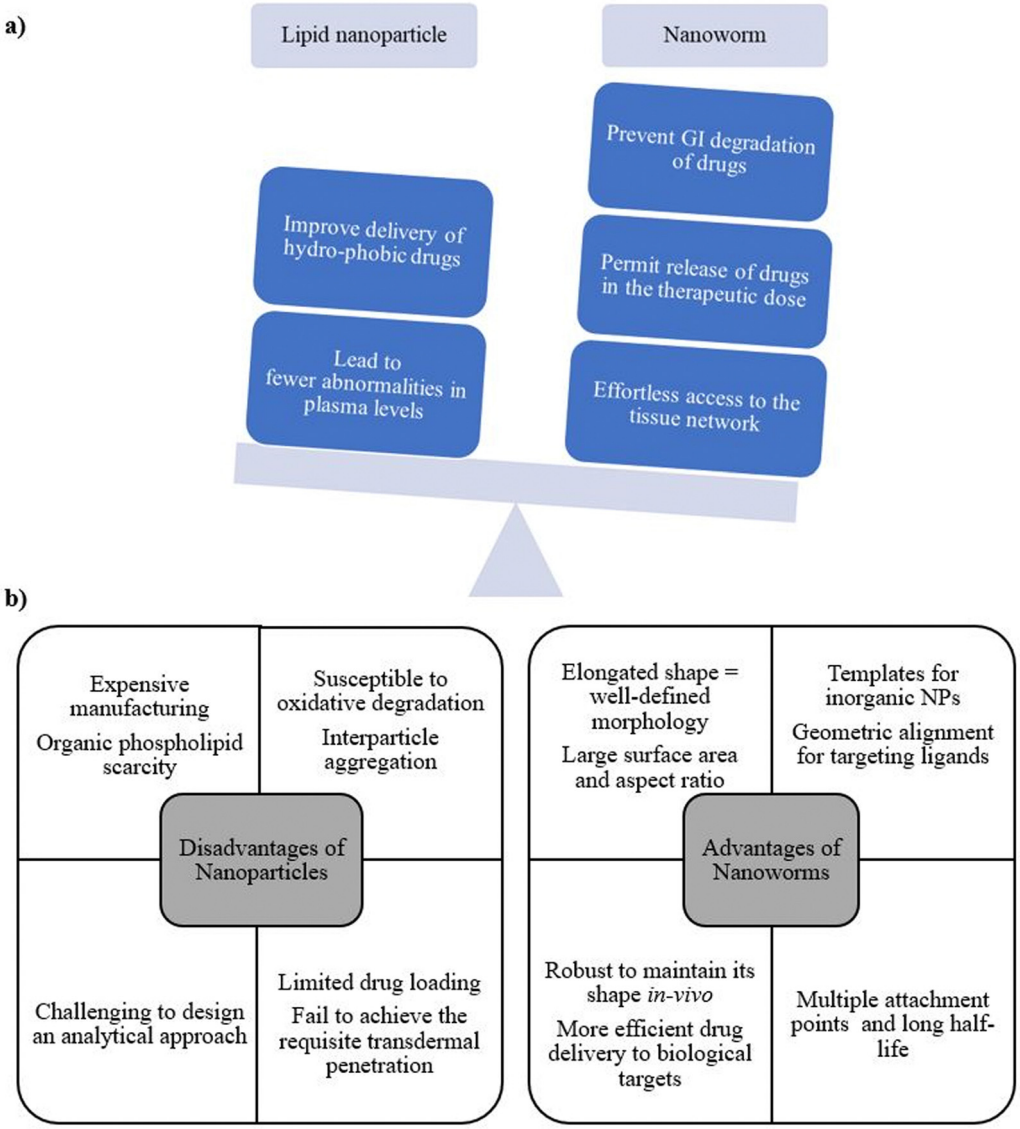

Fig. 2 (a) Similarities between lipid NPs and NWs. (b) Advantages of using NWs over lipid NPs.

sedentary lifestyles, poor diets, and genetic susceptibility. Hence to treat the disease effectively *in vitro*, recent research has mainly focused on developing nanosensors that degrade enzymatically when exposed to a disease-targeting protease, releasing a synthesized bio-indicator in the urine. The probes were built on an artificial biomarker linked to iron oxide nanoworms (IONW) by joining peptides with a cleavage site for a particular protease. The NWs with a diameter of 30 nm and length of 70 nm aggregated in malignant cells either naturally or as a result of specialized targeting ligands like peptide, facilitating detection of cancerous tissue *via* MRI.[26] Enzyme-linked immunosorbent assay (ELISA) was used to detect the artificial bio-indicator excreted in the urine after cleavage from disorder-specific proteases.[27–29] Researchers further improved the biomarker by changing the nanosensors to release a reporter bio-indicator with a unique ligand for lateral flow assay, overcoming the need for a mass spectrometer to detect the urine reporters, preventing the widespread use of the technology for non-invasive identification of fibrosis, thrombosis, sarcoma, and lymphoma. The nano-sensors were developed by combining thrombin or MMP-9 peptide to IONWs. After cleavage of peptides by proteases, the bio-markers were excreted in the urine and detected on a paper test by indicating a colored line due to conjugation with antibodies. The discharge of bio-marker components into the urine following non-specific proteolysis can cause off-target stimulation since remote control of these nanosensors for the detection of proteolytic activity in cancerous cells was not possible. Therefore, a photosensitive spatially and temporally reactive nanosensor shielded by photolabile molecules yet visible in UV light was developed to decrease off-target activation. Hence, researchers were successful in determining non-invasive colon cancer by combining SiMoA and bio-marker at micro-dose level detecting protein biomarkers in blood samples.[30]

2.1.2. Pancreatic tumor. Pancreatic cancer is a malignant disease characterized by a very high degree of malignancy and a

very low survival rate, but early detection of pancreatic sores can aid in effective treatment and improve patient survival.[31] Somatostatin receptor (SSTR), a protein with five different subtypes, is overexpressed in many pancreatic tumours like NETs and islet cell carcinomas. Hence SSTR is a potential biomarker for the disease, as cancer alters its approach during the progression of pancreatic illness by modifying the upregulations of receptor subtypes (SSTR 1–5).[32] A biodegradable magnetic IONW-based dual-mode MRI/optical imaging probe was developed to lower the high death rate of cancer, for instance, pancreatic tumour. Real-time functional and anatomical tomography is possible for tumor lesions during execution due to advancements in medical imaging technology and the availability of high-performance computing. The combination of two or more modalities improves sensitivity, spatial resolution, and signal penetration depth, while positron emission tomography (PET) MRI, a hybrid scan modality, helps in accurate cancer imaging.[33] Superparamagnetic iron oxide nanoparticle (SPIONP) NWs prepared by coprecipitation of iron salts and *in situ* coating with sugars, polymers, or proteins showed promising results as a contrast agent for various biomedical applications due to the high MRI signals and longer bioavailability. A synthetic somatostatin analogue containing a core cyclic backbone peptide with an affinity for SSTR 1–5 was created as a biomarker to target all types as well as subtypes of SSTR. The magnetic IONWs were fabricated by alkaline co-precipitation of iron salts and cross-linking of NaOH with epichlorohydrin for creating a targeted biomarker to interact with SST receptors on PANC1 cells. The targeted IONWs were able to interact with SST receptors on PANC1 cells (50 μg mL^{-1}), and the high surface area of the IONWs allowed for multiple bio-marker binding, as demonstrated by fluorescence photography. Compared to non-targeted NWs, nanoprobes (5–10 nm) targeted SSTR and attached to a core cyclic peptide, demonstrating the enhanced accumulation of target IONWs at the tumor site.[34] *In vivo* studies of the targeted magnetic NW PTR86 demonstrated promising properties for further functionalization with chelating agents such as dodecane tetraacetic acid and radionuclides like Ga68 and Cu64, to be employed in multimodal diagnostics with commercially available PET MRI scanners for cancer targeting and imaging. Overall, the use of targeted magnetic nanoprobes demonstrated potential in enhancing the detection of pancreatic tumours, and further research will lead to more effective treatments for pancreatic cancer.[35]

2.1.3. Breast cancer. The usage of manufactured NPs in nanomedicine offers considerable potential for site-specific medication delivery and medical imaging.[36,37] However, intravenously administered NPs must overcome a number of biological obstacles in order to reach their intended targets within the vascular system. The components of the innate immune system like WBCs and macrophages play a vital role in limiting the blood's ability to transmit infections and NPs.[38,39] Rapid advancements of engineered NPs offer potential applications in the biomedical field, such as drug delivery and magnetic resonance imaging; however, they exhibit poor hemocompatibility. The complement system, making up roughly 5% of the globulins in serum and an important part of innate immunity, is responsible for identifying, getting rid of, and destroying pathogens. The complement gets activated on the surface of foreign agents through the alternative, lectin pathway, or the classical pathway. These pathways converge to form the highly reactive thioester C3b, which covalently binds to reactive groups (such as amines and hydroxyls) on the activator.[40] *In vitro*, using SPIO NWs, mice cells, neutrophils, and monocytes from regular and tumor-induced mice[41] exhibit a competent and dominatingly supplement subordinate take-up. Erythrocytes and thrombocytes are attractively marked after intravenous infusion into wild-type mice, while the labelling is diminished by 95% in supplement C3-lacking mice. Utilizing platelets from normal and breast cancer patient donors, it is reported that SPIO NWs are taken up by neutrophils, monocytes, lymphocytes, and eosinophils and their ingestion is forestalled by EDTA and antiproperdin immunize, acting as a general supplement inhibitor and an inhibitor of the possible substitute pathway of the supplement framework, respectively.

C3 opsonization is similarly reduced by cross-connecting hydrogelation technique of SPIO NW surfaces after treatment with epichlorohydrin, resulting in *in vivo* reduction of utilization by mice leukocytes by 70% in mouse serum. Interestingly, these cross-connected particles are not able to demonstrate a fall in C3 opsonization in the case of human serum, yet they did show a noteworthy decline of about 60% in human leukocyte take-up, as shown in Fig. 3. The take-up of cross-connected NPs is less significantly slowed by the presence of EDTA. Thus, these discoveries reveal the divergence between species in recognition of NPs using the complement system and assimilation by leukocytes, as well as how inhibitors of the supplement elective route and NP surface coating improve human hemocompatibility. These outcomes give significant knowledge of the mechanisms of hemocompatibility of nanomedicines for therapeutic purposes.[41]

2.1.4. Acute hepatic injury. Soft tissues are the main constituent parts of an organism and are supported and shielded by inorganic, non-metallic biomaterials, such as the silicone frustule of a unicellular diatom,[42] the calcareous shell of a snail,[43] and the calcium skeleton of a vertebrate.[44] Hydroxyapatite (HAP) has attracted a lot of interest recently due to its applications in bone and tissue reengineering. HAP-ION NWs were obtained by conjugation of Fe_3O_4 NPs with poly(sodium *p*-styrenesulfonate)

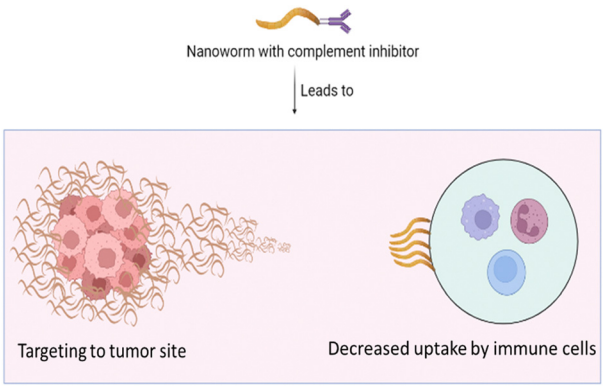

Fig. 3 Blocking nanoworm uptake by immune cells by virtue of addition of complement inhibitors.

coated HAP after reduction in triethylene glycol. To enhance the dissolution and biological compatibility and to lower the toxicity and cell lysis, a layer-by-layer approach using chitosan and sodium alginate was employed. The magnetic characteristics improved the MRI performance of NWs. The HAP-ION NWs were successful in enhancing the contrast to noise ratio (3.71 to 5.39), thus proving beneficial for evaluating liver injury and subsequent therapy.[12]

2.2. NW-based therapies

2.2.1. B-cell non-Hodgkin's lymphoma. Non-Hodgkin's lymphoma (NHL) is a serious health concern affecting a large number of individuals (80, 500) due to exposure to certain pesticides and herbicides, such as glyphosate. The most frequent type of NHL originates from B-cells (85%) due to hypermutation and is characterized by a high incidence rate.[45] Although rituximab is considered as the first-line treatment for NHL, it has limitations due to the finite half-life of B-cells (4 h).[46] In imaging applications, the finite half-life produces an increased signal-to-noise ratio and is therefore unsatisfactory for use as a treatment. Since antibody fragments are simple to express and alter,[47] single-chain variable fragment antibody (scFv) has attracted immense attention in pharmaceutical applications,[48] because of its small size and ability to transport contrast agents and xenobiotics.[49] To investigate the effectiveness of scFv in NHL treatment, researchers produced NWs by bioconjugating recombinant scFv fragments with high molecular weight hydrophilic polymers such as elastin like polypeptide (ELP) with extended biological half-life (20 h).

The resulting NWs were expressed in *E. coli* and cryogenic transmission electron microscopy and light scattering technique were used to examine the efficacy of NWs in NHL. In two B-cell NHL cell lines, the NWs conjugated to CD20 performed apoptosis more effectively than rituximab alone. Rituximab exhibited a concentration-dependent reduction in the feasibility of SUDHL7 cells, resulting in a 4.8 μM IC_{50}. By staining with annexin V/propidium iodide and transferase dutp nick-end label, late-stage apoptosis induction was individually identified at the appropriate time and a similar Fv ratio of 1.5 mg ml^{-1} was used to compare all combinations.[50,51] Using the staining agent annexin V/propidium iodide, NWs significantly increased timely apoptosis (P = 0.0005) and improved programmed cell death in each of the CD20 cell lines in comparison to rituximab alone (P = 0.006). Moreover, in a NHL xenograft model, CD20 NWs effectively reduced the incidence of back cancer compared to rituximab.[52] Thus, according to the findings, CD20 NWs are a convincing persuader of programmed cell death for the treatment of NHL and can potentially overcome the limitations of rituximab *in vitro*.[7]

2.2.2. Hepatocellular carcinoma. Asymmetric microparticle production has led to the development of numerous techniques, including PRINT, as it makes use of block copolymers (BCPs) engaged in controlled self-assembly (depending on physicochemical characteristics related to chain packing and intermolecular interactions).[53] The flexible method enabled bottom-up engineering of non-symmetric nanosystems with flexible functioning for applications such as drug delivery and nanoelectronics.[54] Other examples of techniques leading to non-symmetric particles include induction by polymerization[55] and crystallisation-derived self-assembly.[56] However, very few polymeric constructs are available on the market because of issues associated with replication, carcinogenicity, and producibility as a result of using synthetic compounds and manufacturing techniques using noxious solvents to produce inhomogeneous commodities.

To overcome these drawbacks, researchers developed biodegradable self-assembling NWs by the direct hydration (DH) technique using PEG–PCL*g*TMC and PTMC-Q.[57] The DH method is a significant advance in achieving regulated self-assembly under more biocompatible conditions and avoids the use of hazardous organic solvents. Hydrophobic self-association served as the driving force leading to amphiphilic copolymer self-assembly of drug-loaded NVs produced by DH. BCPs like PEGPTMC served as the fundamental building block and yielded highly pure units able to eliminate the need for refinement prior to use in both *in vitro* and *in vivo* settings.[58,59] Chemical signals like thermally responsive, pH-responsive, or ionic subunits were incorporated in a systematic manner to control BCP assembly, resulting in smart nanostructures, owing to their sensitivity towards changes in the surroundings.[60] Controlling BCP self-assembly by coordinating amphipathic and controlled interactions with ions in solution was a successful technique for controlling particle morphology.[61] The alteration in ionic strength of NaCl (0 to 400 × 10^{-3} M) used to hydrate TerP22-Q BCPs helped the globular elongated micelles switch to NWs. Compared to globular micelles, NWs displayed a 2-fold enhancement in affinity to cancer biological membrane due to the high aspect ratio and interaction between the NWs and the cell membrane as demonstrated by the low IC_{50} data of HepG2 cells (micelles = 207 μg mL^{-1}, NWs = 27.9 μg mL^{-1}). A significant number of anionic phospholipids in the cell membrane revealed pronounced toxicity for cancer cells, while cationic polymer aggregates were selective for cancer cells, supporting their therapeutic promise. Also, enhanced infiltration into 3D multicellular spheroids including melanoma and fit fibroblasts (HeLa : 3T3 = 1 : 5) was achieved due to the unusual elongated form. Thus, the study revealed the potential of NWs for high drug loading capacity of cargo drugs, selective delivery to cancerous tissues and promoting penetration of drugs into cells in anticancer drug delivery.[62]

2.2.3. Suppression of breast tumour. Anti-angiogenic and vascular disrupting substances exhibit potential in cancer therapy, but their effectiveness tends to be limited due to the emergence of treatment resistance, the heterogeneity of tumors, and the potential for adverse effects on normal tissues. A highly effective theranostic nanosystem was previously reported to impede tumor growth and provide cures in both glioblastoma and breast cancer mouse models.[63] The nanosystem comprised IONWs, coated with a composite peptide with tumor-homing and pro-apoptotic domains for enhanced cancer cell targeting and induction of apoptosis in tumor cells. The homing element targeted tumor vasculature by binding to p32/gC1qR present on the surface of tumor endothelial cells. To enhance the effectiveness of the nanosystem, researchers developed an optimally

effective homing peptide with a tumor-penetrating function. A group of candidate p32 binding peptides containing a sequence motif conveying tumor-penetrating activity were evaluated, and among the tested peptides, a peptide called linear TT1 (LinTT1) was identified as a highly effective peptide in promoting tumor localization and nanosystem infiltration. The low affinity was the result of multivalent interactions and the NPs avoid unhinging by the binding site barrier thus preventing molecules with an elevated affinity (130 nM) from penetrating inside the tissue.[64] Furthermore, fluorescence anisotropy experiments demonstrated a distinctly quantifiable affinity for the LinTT1-p32 association with a K_d of 8.7 M, while the K_d of CycTT1 was 0.13 M. Phage library peptides were accurately chosen for fabrication of LinTT1 because it selectively binds to p32 and also is a recombinant protein.[65] According to the data of LinTT1, it is a targeting agonist possessing greater affinity, fewer negative effects, durability, selectivity, and effectiveness, important in monovalent targeting.[66] Because unbound peptides showed a low affinity, NPs are overly expressed on the cell surface exhibiting p32, resulting in optimum tissue penetration. The findings demonstrated that a vasculature disrupting agent's ability to spread outside of the vasculature significantly increases its anti-cancer effectiveness.[63] These results contribute to prospective therapeutics and highlight the role of tumor penetration in cancer therapy effectiveness.[67]

2.2.4. Treatment of COVID-19. The global surge in COVID-19 cases caused by new variants of the virus has raised concerns regarding vaccine efficacy and the need for effective measures to prevent transmission. To combat airborne and surface transmission of SARS-CoV-2 and other viruses, researchers developed a novel spray-based formulation capable of inactivating viral particles and degrading their RNA. The NWs used in the coating efficiently bound to the viral membrane and caused conformational changes that led to membrane rupture, subsequently degrading the RNA. The NW coating was found to be effective in completely inactivating the COVID-19 virus, an advanced variant [B.1.1.7 (alpha)], pseudovirus, and influenza A. The polygalactose functionality on the NWs targeted the S2 subunit on the virion glycoprotein, and further attachment of guanidine groups catalysed the breakdown of the RNA genome. Furthermore, coating surgical masks with the NWs rendered both SARS-CoV-2 types completely inactive, providing a powerful control measure. The NW system was also effective in inactivating influenza A as well as an AAV-HA capsid pseudovirus. The NW coating is environmentally friendly, compatible with large-scale manufacturing processes and has the potential to be modified to target other viruses in future pandemics.[68]

2.3. Theranostics

2.3.1. AntiCD99 scFvELP NWs for management of AML. Recent advancements in the treatment of acute myeloid leukaemia (AML) have been unable to prevent the majority of individuals from dying due to the critical condition as a result of AML's complex genetic and molecular makeup, leading to treatment resistance and disease relapse even after initial remission.[69] In contrast to typical hematopoietic cells, CD99 is highly expressed in AML cells and has emerged as a potential target for therapy using neutralizing agents.[70] Multiple researchers produced mABs specifically directed towards CD99; for example, antimutagenic tendencies using mABs against CD99 were established in several preclinical models of malignant development. However, the development procedure was expensive for introducing mAbs into clinical trials. Recombinant protein engineering allowed easy handling of scFvs and imparted specificity similar to mAbs.[71] The usefulness of scFvs for establishment of therapies is a result of shorter half-life (due to the quick glomerular filtration in the kidneys), purity and low durability attributes.[72,73]

To eliminate the drawbacks, researchers developed A192, an ELP linked to an anti-CD99 scFv for the targeted distribution of cytotoxic agents to AML cells, offering a potentially safer and more effective treatment option for patients. A192 is a human-origin product from tropoelastin designed and tested for survival while CD99 neutralizes cell motility and is the initiator of cellular apoptosis. The combination of A192 and CD99scFv significantly produced stable NWs after 72 h at 37 °C. αCD99A192 demonstrated positive limits for $CD99^+$ cells but not for CD99293T cells across a multitude of AML cell lines. CD99A192 also reduced viability and improved PCD in AML cell lines, thus demonstrating excellent anti-leukemic effects *in vitro* as well as *in vivo*.

One of the advantages of associating A192 with CD99-scFv is the significant recycling of the coupled protein (34 mg L^{-1}) in sample extract followed by bacterial lysis.[74,75] ELP and CD99-scFv worked together to remove scFv and detoxify proteins, balancing dynamic NWs and enhancing the CD99-scFv PK profile. As a prospective treatment for AML, the stated investigation revealed a powerful anti-leukemic potency with the additional benefits of ideal colloidal stability as well as a longer PK half-life.[14]

2.3.2. Magnetically guided NWs to battle localized contagious infections. Bacterial infection has been one of the biggest dangers to human wellbeing during the last two decades, causing the greatest number of deaths due to infectious diseases worldwide.[76] The main course of treatment for bacterial illnesses currently continues to be rigorous antibiotic administration, but the development of antibiotic-resistant bacteria poses a significant challenge.[77] A physical barrier formed in the biofilms of bacteria helps resist antibiotics 1000 times better than planktonic bacteria.[78–80] To address this challenge, researchers developed innovative strategies such as the use of magnetic NWs for targeted delivery of antibacterial agents.

Magnetic NWs of Fe_2O_3 encapsulated in a shell of arginine-modified polydopamine (PDA) with a core of Au–Ag NPs (CitAug NP) capped with citrate were developed to exhibit photothermal repair effects and were remotely controlled by a magnetic field to transport them to the target site. Nitric oxide (NO) is an indigenous volatile component that harms healthy tissues, potentially destroying bacteria by damaging DNA and blocking its repair.[81] NO released *in situ* worked synergistically with Ag particles and reactive oxygen species to eliminate bacterial contamination *in vivo*, enhancing hyperthermia and bactericidal tendencies of Ag particles, as shown in Fig. 4. With a biocompatible nature and magnetic properties, the production of NIR-triggered NO *in situ* is thus a smart and promising NP delivery system to address bacterial infections in the body.[82]

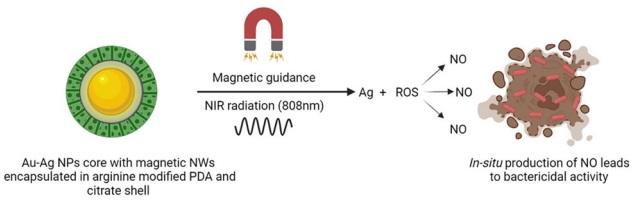

Fig. 4 Magnetically guided release of NO for treatment of bacterial infection.

To support the benefits of AFe/AuAg@PDA NWs, the antibacterial efficacy with and without NIR laser light was researched using *Staphylococcus aureus* and *Escherichia coli.* The turbidity method and optical thickness measurements at 600 nm revealed the effectiveness of NWs in reducing the development of malignancy in both the strains independently of the NIR irradiation. However, the blend of high temperature and Ag particles was not able to kill bacterial cells. Also, without NIR laser light, the restraint productivity of NWs (150 g mL^{-1}) was only 60% and 63.6% for *Escherichia coli*. On the other hand, NWs displayed a definite bactericidal effect (less than 10% of the microorganisms were precipitated in *Kori* and *Staphylococcus aureus*) with NIR laser light.[83] From the results it is evident that magnetic field can precisely control the operation and mobility of magnetostrictive nanosystems to accomplish aggregation and deep tissue infiltration due to the superior biological compatibility,[22,84] demonstrating the effectiveness of magnetically controlled NPs for next-generation personalized medicine.[85,86] Hence, the stated study revealed the first magnetically guided distribution of NWs for the treatment of antibiotic-resistant bacteria without the use of antibiotics utilizing *in situ* synthesized NO gas, demonstrating promising importance for use in commercial gas therapy.[87]

2.3.3. Plasmon NWs for intracellular use. Plasma nanochains display numerous plasmon driven applications such as optical detection,[88] catalysis,[89] and energy harvesting,[90] using one-dimensional plasmonic nanochains (in solution) because of their unique optical and electronic properties. However, due to the constraints of several present methods of 1D assembly, only selected studies explored the application of plasmonic nanochains for intracellular surroundings. For example, researchers previously proposed using aniline to create Au nanochains coated in polyaniline (PANI), but still a simple and effective approach for forming biocompatible nanochains was needed because of significant toxicity from the peripheral PANI shell in mammalian cells.[91] By sonicating citrate-coated gold (CitAu) NPs in dopamine solution of high concentration in alkaline media, PDA-coated plasmon NWs were produced for the treatment of cancer. The PDA shell stabilized the Au-NW structure in solution, increasing the likelihood of Au@PDA-NWs invading HeLa cancer cells.[92] Photothermal degradation of cancer cells was effective using agents responsive to NIR, while the contrast agents were useful in label-free DF cell imaging. The NPs entered HeLa cancer cells efficiently, and retained the core–shell and wormlike conformation for 24 h.[93] To examine the interaction, HeLa cells were treated with NWs having a core Au potency of 0.5 nM for a period of 24 h. It was observed that the cell junctions of NWs were 7 times more than those of NPs. Moreover, NWs penetrated the cell membrane as a complete worm and accumulated in the cytoplasm and perinuclear regions after 24 h of incubation. Plasmonic NWs with Au@PDA shells demonstrated superior properties for intracellular applications; for example, NWs exhibited durability in serum-containing culture media and infiltrated malignant tumours more efficiently than unassembled NPs, while maintaining low cytotoxicity. Under irradiation with an 809 nm laser at 4 W cm^{-2}, the NWs displayed scattering spectra similar to those of unassembled NPs and were subjected to photothermal response and stability tests. In one study, HeLa cells treated for 24 h with varying concentrations of NWs (0.1 nM to 0.5 nM) and followed by irradiation for 5 min with an 809 nm laser showed improved viability.[94] Hence the plasmonic NWs with Au@PDA shells exhibit promise for applications in the treatment of cancer due to the potential for label-free DF cell imaging, cargo delivery, and photothermal death of cancer cells, without noticeable accumulation in acidic compartments.[94] These findings provide a basis for the development of new and effective strategies for personalized medicine in cancer treatment.

2.3.4. Platinum NWs as combined therapy of cancer. Malignancy remains one of the most challenging diseases to treat due to its ability to spread rapidly and invade other tissues in the body. The recent therapeutic approach of laser photothermal therapy involves using laser light to generate heat to destroy cancer cells, showing promising results, and is extensively studied as a potential option for treatment of cancer.[95,96] Nanomaterials with excellent optical properties and biocompatibility are extensively studied for their use in photothermal therapy.[97,98] Radiation therapy is a standard tumor treatment, but its efficiency is severely limited as a consequence of low absorption of X-rays and radioresistance by hypoxia; thus, a variety of radio-sensitizers have been developed to enhance the cancer-killing effects.[99] Under laser light, metformin overcomes radiation resistance, and modest hyperthermia relieves hypoxia inside a tumor by boosting blood flow. Platinum NPs were effectively employed in multimodal imaging-guided cancer therapy due to the ability to assimilate laser light in the second biological window.[100]

In physiological fluids, the NWs displayed a restricted size distribution and were easily observed using photoacoustic and CT dual-mode imaging.[101] To evaluate the ability of Pt-PEG NWs to sensitize cancer cells to radiation, a colonization experiment was conducted *in vitro*. X-Ray-induced DNA damage was assessed using a phosphohistone-H2AX mouse monoclonal antibody and a [4′,6-diamidino-2-phenlyindole] (DAPI) label.[102] Balb/c mice were inoculated with 4T1 cells and treated with NWs for 4 h, then irradiated with X-rays. After injecting cancer-carrying mice with NWs (16 mg kg^{-1}), the major tissues and organs were harvested and liquefied in a blend containing HCl, HNO_3 and $HClO_4$ at a high temperature (2 °C) and scanned with a laser system. The 1064 nm laser has a higher residual power density than the 808 nm laser and can penetrate up to 0.9 mm of pork slice, and thus is beneficial for imaging and treatment of deep cancers like basal-cell carcinoma, gastric cancer, oropharyngeal cancer, *etc.*

The combination of platinum NWs (with excellent biocompatibility and photothermal killing effect) and laser irradiation

is proven to cause thermal necrotic cell death in 4T1 breast cancer cells. NWs in PBS were used as CT contrast agents and showed strong CT signals in cross-sections and reconstructed 3D images. The group receiving laser, X-ray irradiation and NWs showed the strongest antitumor activity and completely suppressed tumor growth. Additionally, studies showed that after injection with NWs into healthy mice, blood levels returned to normal 7 days later and the daily stress response of NWs displayed no long-term damage. Photothermal effects *in vivo* were studied using polyethylene glycol (PEG) NWs with laser irradiation, and the tumor sample was stained with a hypoxic probe consisting of an anti-CD31 antibody and DAPI. The co-administration of Pt-PEG NWs with a combination of a 1064 nm laser and X-rays resulted in a significant reduction in tumor size in mice within 14 days of treatment. The Pt-PEG NWs were prepared using a simple and reproducible process, making them an ideal photothermal agent in the second NIR optical window, as well as a radiosensitizer with remarkable stability in physiological solutions. Hence, the findings suggest the use of platinum NWs in combination with laser irradiation for cancer treatment and imaging applications.[101]

2.3.5. Functional transport of siRNAs. siRNAs are short RNA molecules (composed of <23 nucleotides), used to control gene expression by breaking down specific mRNA sequences due to their complementary base pairing mechanism with the target mRNA strands, and they find practical applications in the treatment of tumors.[103] However, due to the negative charge on the surface, siRNAs face difficulty in penetrating the intended cells. The robust and effective siRNA distribution into the cytosol of recipient cells *in vivo* is a significant barrier for fully realizing the capability of siRNA-based protein regulation. Various delivery methods have been explored, including protamine-antibody fusions[104] and lipid-derived nanoparticles,[105] but they exhibit constraints and lack traceability. Thus, dendrimer-bound magnetically fluorescent NWs, called dendriworms, were introduced for the targeted delivery of siRNA. The NWs were well accepted in mouse brain and maximized the proton sponge effect to robustly achieve protein targeted suppression *in vivo*.[106] The dendriworms were rapidly absorbed by cells and allowed for efficient endosome escape and concentrated loading dose, leading to significant suppression of EGFR expression in a transgenic model of glioblastoma.[107] These results demonstrate dendrites as a multimodal platform for fluorescence-based detection of *in vivo* siRNA delivery, cell invasion, endosome escape, and suppression of target protein. Additionally, numerous amine groups present on the surface render NWs as an ideal platform for combining with other chemicals responsible for tumor absorption, biodistribution, and tissue homing characteristics.[15,108] Thus, the dendriworms offer a potent and versatile treatment option for malignant glioma, with the unique properties of distribution, detection, and targeting.[15]

3. Conclusion

As tiny, biologically inspired robots, NWs possess the potential to revolutionize medicine by navigating through the human body and delivering drugs or performing surgeries with unprecedented precision and efficiency. NWs are a promising choice for improving drug delivery systems for malignant and inflammatory diseases, due to the small size, high surface area, ability to evade physiological elimination, capability to recognize tumours through superparamagnetism, and improved kinetics, stability and shelf-life attributes. NWs find immense applications in diagnostic methods such as MRI and ELISA for more accurate diagnosis of disease, in therapy for efficient delivery systems for a given target with minimum systemic adverse effects and in theranostics for the delivery of siRNA using dendriworms, combating focal bacterial infection, and treating atherosclerosis and deadly diseases like AML. Recent advancements in NWs include surface-coated IONWs for early complement opsonization, hybrid protein–polymer NWs for apoptosis of diseased cells, IONWs for tumor suppression in breast cancer and platinum NWs for multimodal imaging-guided cancer therapy. NWs are still in an early stage of development and are not fully explored, and much research is required to completely realize the applicability of NWs in the future. Future developments in this area will lead to a new generation of revolutionary nano-biomaterials designed to enhance patient quality of life.

Author contributions

All the authors contributed equally. Dr Pravin Shende: conceptualization and supervision; Ms Kadambari Borse: data curation, writing – original draft preparation, reviewing and editing.

Conflicts of interest

There are no conflicts to declare.

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