Received: 8 June 2023 | Accepted: 8 September 2023

DOI: 10.1002/bmm2.12049

REVIEW

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Analgesic nanomedicines for the treatment of chronic pain

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Funding information
National Natural Science Youth Fund, Grant/Award Number: 82202326; Natural Science Foundation of Shanghai Municipality, Grant/Award Number: 21ZR1405300; National Natural Science Foundation of China Youth Fund, Grant/Award Number: 52322213; Shanghai Rising-Star Program, Grant/Award Number: 21QA1400900; National Funds for General Projects, Grant/Award Number: 52272269; Innovation Program of Shanghai Municipal Education Commission, Grant/Award Number: 2023ZKZD01; Key Program of National Natural Science Foundation of China, Grant/Award Number: 22235004

Abstract

Chronic pain is a major cause of suffering that often accompanies diseases and therapies, affecting approximately 20% of individuals at some point in their lives. However, current treatment modalities, such as anesthetic and antipyretic analgesics, have limitations in terms of efficacy and side effects. Nanomedical technology offers a promising avenue to overcome these challenges and introduce new therapeutic mechanisms. This article reviews the recent research on nanomedicine analgesics, integrating analyses of neuroplasticity changes in neurons and pathways related to the transition from acute to chronic pain. Furthermore, it explores potential future strategies using nanomaterials, aiming to provide a roadmap for new analgesic development and improved clinical pain management. By leveraging nanotechnology, these approaches hold the potential to revolutionize pain treatment by delivering targeted and effective relief while minimizing side effects.

KEYWORDS
analgesics, chronic pain, local anesthetics, nanomedicine, neuroplasticity

Hao Liu and Hongjun Zhuang are co-first authors.

1 | INTRODUCTION

Pain, defined as "an unpleasant sensory and emotional experience associated with or resembling actual or potential tissue damage" can be categorized into two types: acute (physiological) and chronic (pathological).[1] Acute pain serves a vital protective role by facilitating a stress response to prevent harm, encouraging avoidance of painful stimuli. However, through maladaptive processes initiated by pathophysiological factors such as neuronal injury, trauma, autoimmune diseases, or tumor metastasis, pain can transition into a chronic state.[2] Chronic pain, despite sharing some characteristics with its acute counterpart, is not merely its temporal extension. It involves unique and complex mechanisms. Maladaptive plasticity alterations occur in sensory conduction pathways, extending from the peripheral to the central nervous system, at various interconnected levels. These alterations are considered responsible for chronic pain development, affecting sensory, emotional, and cognitive components. Although alleviating pain and its associated emotional distress is rewarding, existing analgesics often fall short in their efficacy. This inadequacy stems from the heterogeneous and complex nature of pain conditions and the limitations of analgesics, such as their singular functionality, short duration of action, and the potential for tolerance and addiction. Therefore, research into effective, specific, and safe drugs, characterized by superior efficacy, minimal adverse effects, and reduced abuse potential compared to current options, is of paramount significance.

Nanomedicine encompasses an increasing range of modalities and applications, effectively opening new therapeutic avenues due to its size and the receptivity of its conferred properties. This plays a pivotal role in advancing nanomedicine from the laboratory to clinical care. Nanomedicines typically consist of biomedical nanocarriers and essential active agents, such as functional molecules and bioactive ions. Biomedical nanocarriers function as vehicles for these active agents, facilitating their transport through mechanisms like physical adsorption, encapsulation, molecular self-assembly, or chemical bonding for targeted delivery and responsive release.[3] The active agents loaded within these nanocarriers encompass therapeutic or detection molecules (such as chemical drugs,[4] proteins or peptide molecules,[5] nucleic acids,[6] radionuclides,[7] photosensitive molecules,[8] fluorescent molecules,[9] etc.) and bioactive ions (e.g., Mn^{2+}, Fe^{2+}, Ca^{2+}, Mg^{2+}, etc.). Given the complexity and dynamic variability of pain, nanomedicines enable the design of multifunctional products with diverse characteristics. These innovations have the potential to overcome the limitations of conventional analgesic drugs and can even be internalized into target cells to induce novel therapeutic mechanisms for effective treatment of chronic pain.

In this article, we review recent advancements in analgesic nanomedicine, integrating analyses of neuroplasticity changes in neurons and pathways related to the transition from acute to chronic pain (Figure 1). We particularly discuss the ability of nanomedicine products to target diseased tissues and their role in modulating

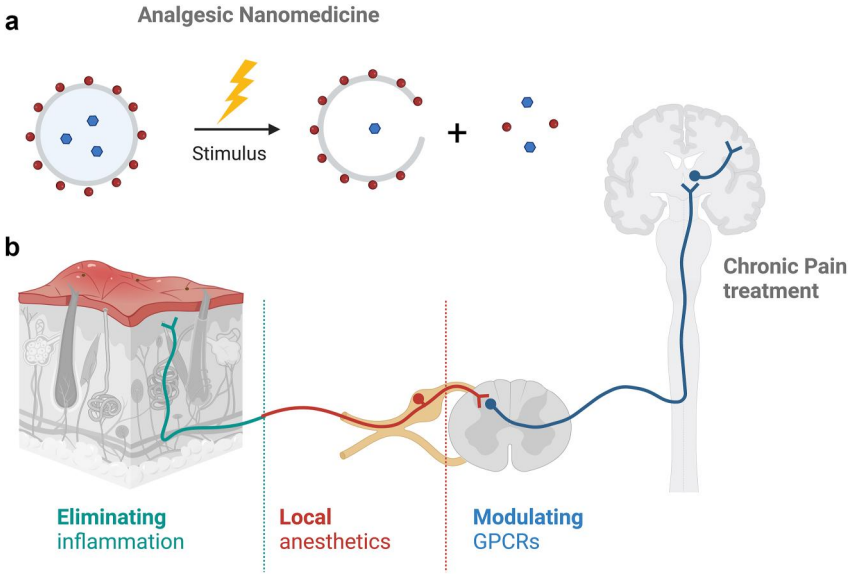

FIGURE 1 (a) Nanomedicine can release functional agents such as bioactive molecules or ions, in response to the external stimuli for the treatment of chronic pain. (b) Each of the three classes of analgesic nanomedicine acts on one or multiple sites in the pain pathway to block or mitigate the signal transduction necessary for pain.

pain-related membrane receptors or eliminating factors causing chronic pain. Additionally, we also delve into the role of nanomedicine in local anesthetics and its application in pain relief. Finally, considering the versatility of nanomedicines, we speculate on the prospects for developing novel analgesic drugs.

2 | MODULATION OF PAIN-RELATED MEMBRANE RECEPTORS

G protein-coupled receptors (GPCRs) play a pivotal role in mediating many of the hypnotic and analgesic effects of drugs used in anesthesia. These receptors, located on the plasma membrane, detect extracellular ligands. Following agonist-induced activation, many GPCRs internalize into endosomes, which are crucial sites for continued GPCR signaling, further regulating essential pathophysiological processes. In the context of chronic pain, various GPCRs, including the opioid receptor, the substance P (SP) neurokinin 1 receptor (NK1R),[10] calcitonin receptor-like receptor,[11] and protease-activated receptor-2,[12] all mediate neuronal excitation and pain transmission. Consequently, targeting these receptors has long been a focus in the development of analgesic drugs.

Opioids are the oldest and most potent drugs used for severe pain management, with indisputable utility in treating acute pain, such as postoperative pain. However, their long-term use for chronic pain has faced increasing scrutiny. Among opioid receptors, δ-, μ- and κ-opioid receptors (DOPr, MOPr, and KOPr) have demonstrated their capacity to inhibit the excitation of primary sensory, spinal, and supraspinal neurons for pain relief. The MOPr agonist, morphine, is renowned for its potent analgesic effect but is also associated with undesirable side effects such as tolerance, physical dependence, respiratory suppression, and constipation.[13,14] The DOPr also exhibits pain inhibition when activated, with fewer side effects. However, its utility for effective pain relief has yet to be established, particularly for chronic pain treatment.[15] Enkephalin, an endogenous neuropeptide, can activate both MOPr and DOPr, with an affinity for the latter that is 10 times greater than for the former. This makes it a potential candidate for a novel analgesic. Nevertheless, the historical use of enkephalins has been limited due to pharmacokinetic concerns and rapid plasma metabolism. To address these issues, Feng et al.[16] engineered bioconjugates of leucine enkephalin (LENK) and squalene (SQ), forming nano-analgesics (LENK-SQ NPs) to prevent the swift plasma degradation of enkephalin. In a rat model of inflammation, LENK-SQ granted the released neuropeptide a significant antihyperalgesic effect, which persisted longer than the effect achieved with morphine treatment (Figure 2a,b). In a thermal hyperalgesia model, this nano-analgesic enabled precise delivery and accumulation in inflamed tissues, providing long-term pain relief without inducing addiction.

To ascertain whether opioid receptors at the plasma membrane or within endosomes mediate the endogenous analgesic pathway, nanomaterials capable of entering the cell through clathrin- and dynamin-dependent endocytosis are ideal for targeting endosomal therapeutics. In 2020, Jimenez-Vargas et al.[17] pioneered a nanoparticle delivery strategy designed to selectively activate DOPr in the endosomes of nociceptors, successfully inducing a long-lasting inhibition of neuronal excitability for the treatment of inflammatory pain. The DOPr agonist DADLE was linked to a liposome shell designed to target DOPr-positive nociceptors and integrated into a mesoporous silica core for the responsive release of DADLE within endosomes (Figure 2c). In colitis-afflicted mice, the nanomedicine activated DOPr on the plasma membrane and was subsequently internalized into endosomes by DOPr-expressing dorsal root ganglion (DRG) cells. Within these endosomes, the acidic and reductive microenvironment initiated the release of DADLE for further activation of DOPr. This continual-release of DADLE inhibited the excitability of mechanically sensitive colonic nociceptors and activated protein kinase C and extracellular regulated protein kinase pathways, thereby alleviating inflammatory pain (Figure 2d).

During the progression of chronic pain, SP-NK1R redistributes from the plasma membrane to acidified endosomes, where it continues to signal, maintaining pain sensitization. Therefore, targeting NK1R in endosomes may serve as a crucial strategy for pain relief.[18,19] Building on this insight, Ramírez-García et al.[20] developed pH-responsive nanoparticles composed of a hydrophobic the monomers 2-[N,N-(diisopropylamino)ethyl] methacrylate (DIPMA) core and a hydrophilic the monomers poly(ethylene glyco monomethyl ether methacrylate) shell. These nanoparticles contained aprepitant (AP), an NK1R antagonist, creating a DIPMA-AP nanomedicine. The pH-responsive DIPMA, featuring a tertiary amine structure, can become protonated and positively charged in acidic condition (Figure 3a). Consequently, when DIPMA-AP is internalized into cells, it disintegrates within endosomes due to the pH-induced charge alteration, thereby releasing AP (Figure 3b,c). A central sensitization model was created by injecting capsaicin into the plantar region of mice to stimulate spinal cord neurons, leading to the release of neuropeptide SP and activating NK1R-containing endosomes, thus inducing pain. Following intrathecal injection into rodents, DIPMA-AP inhibited the SP-induced activation of spinal neurons, thereby preventing pain transmission

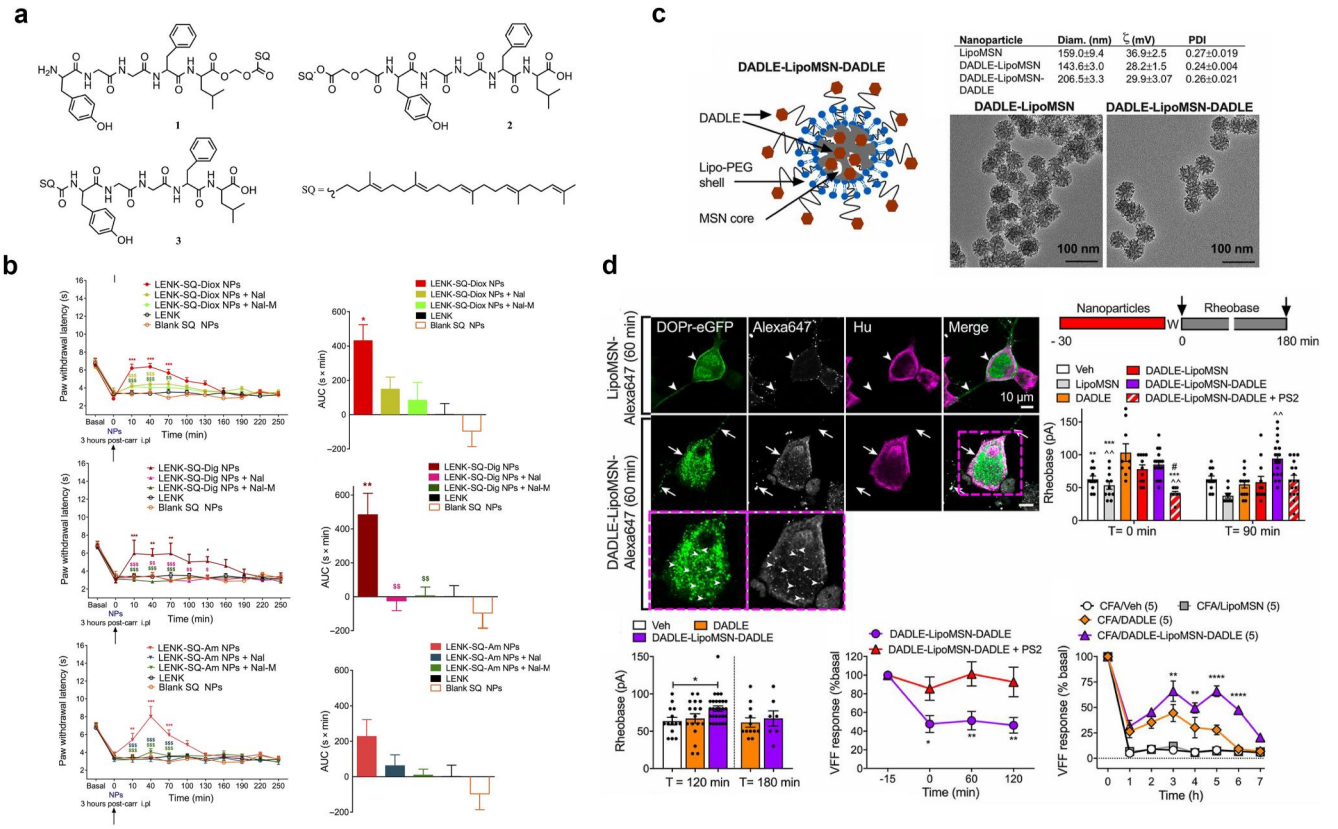

FIGURE 2 (a) Chemical structures of LENK-SQ NPs. (b) Antihyperalgesic effect of LENK-SQ NPs. (c) Characterization of DADLE-LipoMSN-DADLE. Reproduced with permission.[16] Copyright 2019 American Association for the Advancement of Science. (d) Effects of nanoparticle-encapsulated DOPr ligands on nociceptors. Reproduced with permission.[17] Copyright 2020 National Academy of Science.

(Figure 3d). In addition, two peripheral sensitization models were established: arthritis pain triggered by the plantar injection of complete Freund's adjuvant and a nerve injury model brought about by sparing the sural nerve. In both cases, treatment with DIPMA-AP resulted in nearly complete and persistent relief from inflammatory and neuropathic nociception.

In conclusion, the GPCR family holds significant potential as targets for analgesia. Advancement of nanomedicine may provide solutions to many unresolved issues associated with current pharmaceuticals. One such advantage is that nanocarriers can protect these receptor agonists from degradation in the body, while ensuring their delivery to specific diseased regions. Importantly, the nanoscale dimensions of these medicines enable their internalization into cellular endosomes, facilitating therapeutic targeting of GPCRs within these endosomes. This opens up a novel analgesic mechanism that could potentially enhance the performance of conventional drugs, promoting more effective pain relief and even the treatment of chronic pain, with improved efficacy and reduced adverse effects.

3 | ELIMINATION OF NOXIOUS STIMULI

Pain, one of the four cardinal signs of inflammation identified by Celsus in the first-century AD, is a characteristic feature of many chronic inflammatory diseases. The immune system plays a pivotal role in pain sensitization by releasing molecular mediators such as cytokines, lipids, proteases, and growth factors. In response to pain, neurons release neuropeptides and neurotransmitters from their peripheral terminals, which can significantly impact the vascular system and the functions of both innate and adaptive immune cells, thereby exacerbating inflammation. Bidirectional communication between nociceptor sensory neurons and immune cells actively modulates pain and inflammation. Hence, disrupting these signal communications represents a promising strategy for treating chronic pain and inflammatory diseases.

At present, non-steroidal anti-inflammatory drugs (NSAIDs) serve as a prime example of the most commonly used pharmacological inhibitors of chronic pain. Their primary mode of action is the inhibition of

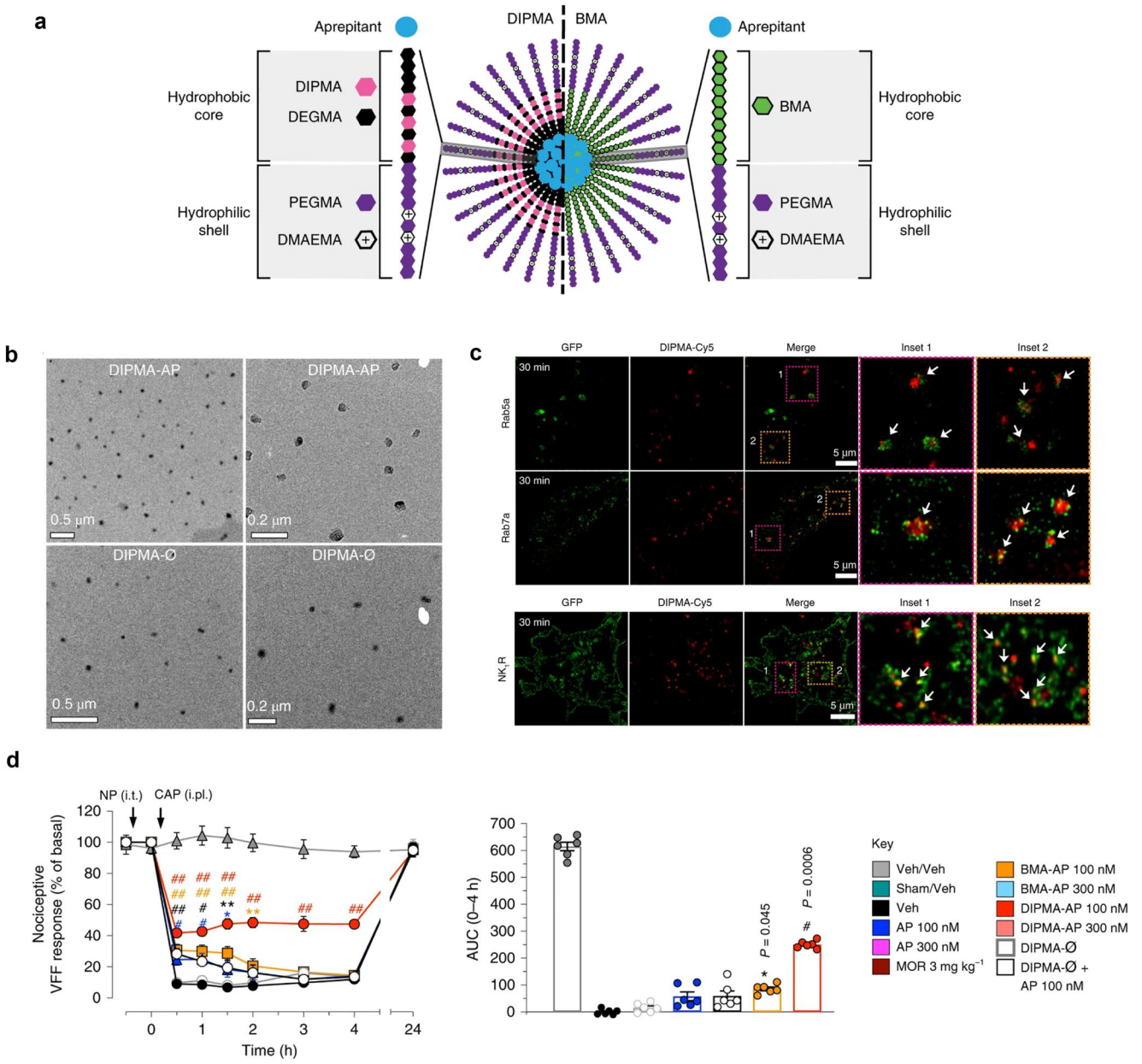

FIGURE 3 (a) Characterization of the monomers 2-[N,N-(diisopropylamino)ethyl] methacrylate (DIPMA) and butyl methacrylate (BMA) nanoparticles. (b) Transmission electron microscopy images of DIPMA-AP (100 nM aprepitant) and DIPMA-Ø nanoparticles. (c) Uptake of DIPMA and BMA nanoparticles in HEK-293 cells. (d) Capsaicin-induced mechanical allodynia in mice: kinetic von Frey filaments (VFF) response and integrated response as area under the curve (AUC). Reproduced with permission.[20] Copyright 2019 Springer Nature.

cyclooxygenase,[21] resulting in a reduction of inflammatory mediator prostaglandin production.[22,23] However, when considering the molecular mechanisms of pain sensitization, a growing body of evidence suggests that the production of chemical noxious factors (e.g., reactive oxygen species [ROS], H^+, ATP, and glutamate) is amplified in the nociceptive system during chronic inflammatory and neuropathic pain. These factors can function as specific signaling molecules for pain processing and the development of chronic pain. Although reducing or eliminating these noxious stimuli can reshape neuroplasticity to manage pain, this approach is not currently achievable with existing drugs in the context of comprehensive pain management.

Oxidative stress, the result of an imbalance between ROS and antioxidants in the body, plays a crucial role in the pathogenesis of chronic pain. ROS, known to damage DNA, lipids, and proteins, are a major risk factor for pain processing. Antioxidant enzymes can catalyze the degradation of ROS, maintaining the body's redox

homeostasis. However, the high production cost, low stability, and propensity for inactivation of natural antioxidant enzymes pose challenges for their practical use as drugs. Artificial nanozymes with enzyme-like catalytic activity are gradually becoming an alternative due to their long-term stability, high tolerance, and catalytic versatility. For instance, Ling et al.,[24] developed an antioxidant cascade nanozyme, SOD&Fe_3O_4@ZIF-8 (SFZ), by encapsulating superoxide dismutase (SOD) and Fe_3O_4 in Zeolitic Imidazolate Framework-8 (ZIF-8) for the treatment of inflammatory pain (Figure 4a,b). SOD is a primary antioxidant enzyme in the body that can catalyze the conversion of superoxide anion radicals into hydrogen peroxide and oxygen, thus reducing oxidative stress. Fe_3O_4 nanoparticles, with SOD-like and catalase-like activities, have also been shown to alleviate inflammatory pain in mice by scavenging ROS.[25] ZIF-8, a representative metal-organic framework material with regular mesoporous structure, is used for loading and delivery of SOD and Fe_3O_4.[26] The researchers created an inflammatory pain model by inducing an inflammatory response in the spinal cord. When injected intrathecally, SFZ degraded in the acidic inflammatory environment, releasing the antioxidant enzymes (Figure 4c). Due to the combined effects of SOD and Fe_3O_4, intracellular ROS were effectively scavenged, leading to a reduction in TNF-α, IL-6, and IL-1β levels. This, in turn, effectively inhibited the infiltration of inflammatory cells and the transmission of inflammatory signals.

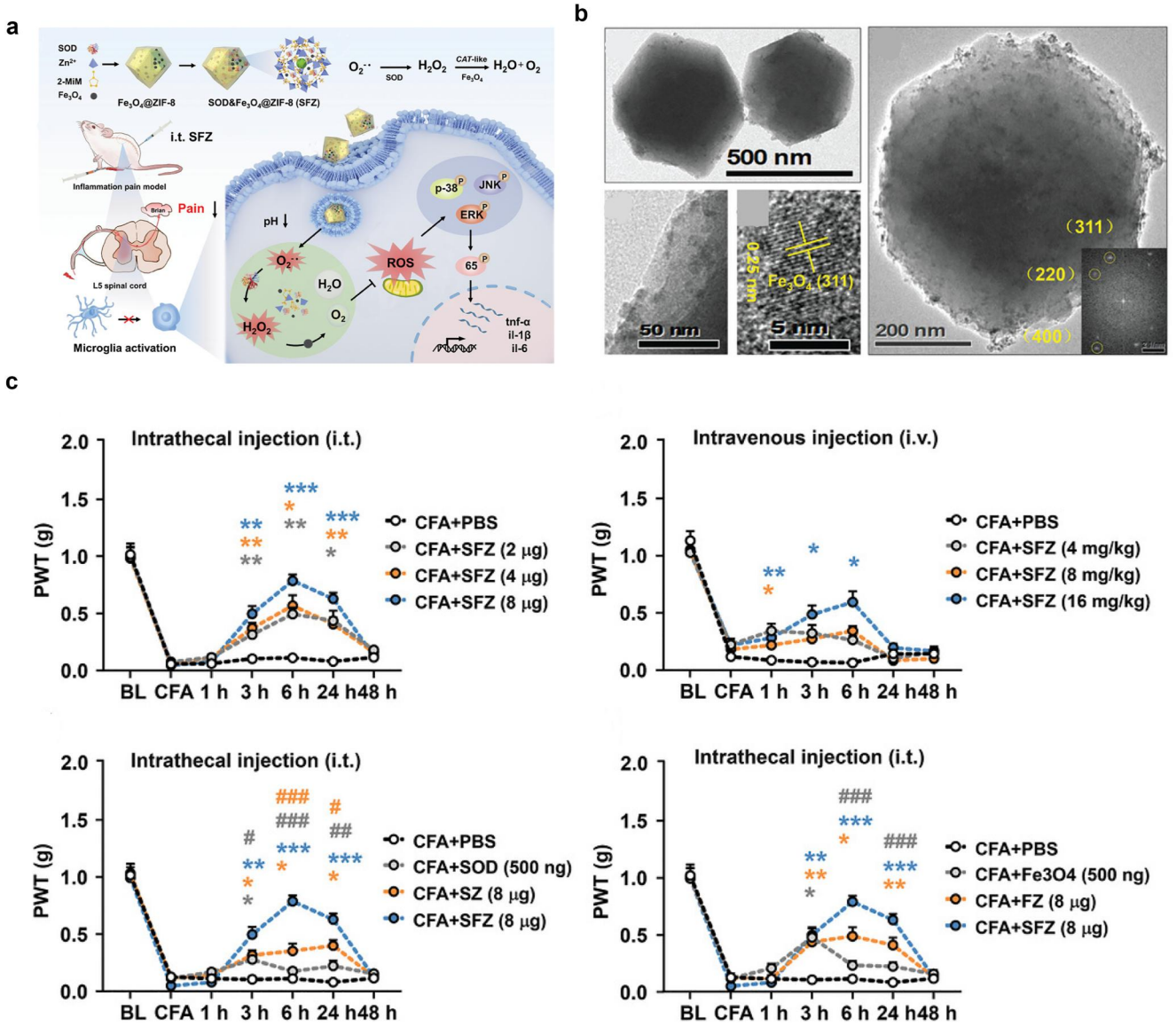

FIGURE 4 (a) Schematic illustration of the synthetic route of SOD&Fe_3O_4@ZIF-8 NPs with multi-enzyme mimicking activities and its analgesic mechanism of anti-oxidative and anti-inflammatory effects on inflammatory pain. (b) Characterization of SFZ NPs. (c) Mechanical allodynia of CFA-induced mice treated with different concentration gradients of SFZ NPs. Reproduced with permission.[24] Copyright 2023 Wiley-VCH. CFA, complete Freund's adjuvant; SFZ, SOD&Fe_3O_4@ZIF-8.

The excessive accumulation of ROS in the spinal cord is known to play a critical role in the development of neuropathic pain, primarily due to the activation of N-methyl-D-aspartate (NMDA) receptors in neurons.[27] To address this issue, Kartha et al.[28] designed an efficient antioxidant system by encapsulating the antioxidant enzyme SOD within the aqueous phase of a porous polymer. This formulation aimed to protect the spinal cord from ROS-induced damage, potentially reversing central sensitization. The porous polymersomes used in this strategy provided a permeable membrane that could permit free superoxide radicals to pass into the interior aqueous environment and interact with the encapsulated SOD. In a pain sensitization model constructed in rats with C7 dorsal nerve root compression injury, it was found that this nanomedicine could effectively deliver SOD to the central nerves, offering a promising strategy for pain management. These results highlight the potential of nanomedicine strategies in the development of effective treatments for conditions related to chronic and neuropathic pain.

You et al.[29] innovatively employed hydrogen (H_2) gas, which is emerging as a therapeutic gas due to its excellent biosafety, high tissue permeability, and free radical capture ability. They constructed ultrathin 2D silicon nanosheets that can generate hydrogen on-demand for antioxidant disease therapy. During the synthesis process, calcium (Ca^{2+}) in the $CaSi_2$ crystal structure was removed by hydrochloric acid, resulting in a large number of hydrogenated dangling bonds forming on the surface. These bonds enable the material to react intensively with water releasing H_2. The efficacy of this material was assessed in two acute inflammation models: ear swelling and paw edema. The results demonstrated that the material effectively removed ROS at the inflammation site, thereby alleviating the oxidative stress. This was evidenced by a reduction in various inflammation indicators, highlighting the potential of this material as an antioxidant therapy. This innovative use of nanotechnology for on-demand hydrogen release provides a promising direction for antioxidant therapies and potentially the management of chronic pain related to inflammation.

The innovative approach taken by our group addresses the inadequacy of anti-inflammatory drugs in managing severe pains such as those associated with cancer. This is especially crucial as inflammation-based pain relief is largely ineffective for cancer-related pain. By developing a multi-functional nanocomposite that interrupts the bidirectional signal communication between bone tumors and peripheral nerves, our group[30] has introduced a potential method to inhibit tumor growth and treat metastatic bone cancer pain simultaneously. The nanocomposite is based on a magnesium-aluminum layered double hydroxide (LDH) supramolecular nanomaterial. This material was synthesized to accommodate an inner loading of AZ-23 (a nerve growth inhibitor) and an external modification with alendronate, resulting in the formation of the LDH/AZ-ALD (alendronate) therapeutic nanoagent (Figure 5a,b). Once this agent targets and enters the bone tumor, LDH reacts swiftly with excessive hydrogen ions (H^+), which are implicated in causing pain, effectively reducing the damaging stimulation to the tumor peripheral nerves and

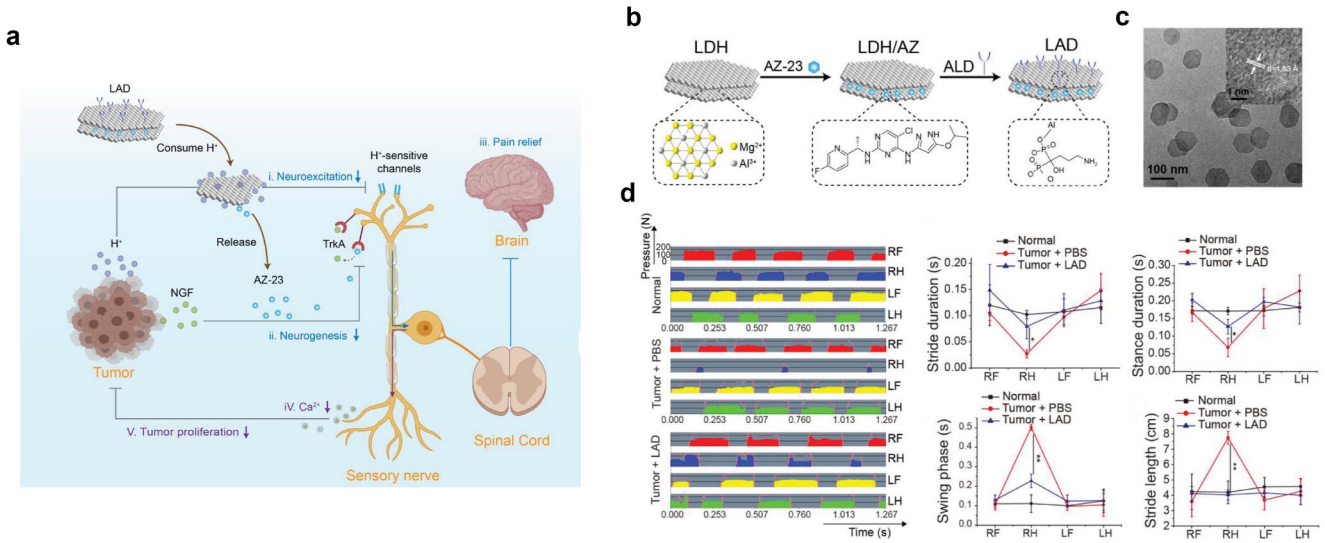

FIGURE 5 (a) Schematic diagram of nerve–cancer crosstalk blocking strategy induced by LAD (LDH/AZ-ALD) for metastatic bone cancer pain treatment. (b) Characterization of LAD. (c) Transmission electron microscope (TEM) image of LAD. (d) The treatment effects of LAD on bone metastasis tumor-induced pain. Reproduced with permission.[30] Copyright 2022 Wiley-VCH.

thus leading to a rapid analgesic effect. Concurrently, the released magnesium ions (Mg^{2+}) and AZ-23 following LDH decomposition would exert reparative actions on bone and peripheral nerve tissues, respectively (Figure 5c). This would mitigate bone damage caused by bone metastases and inhibit nerve growth factor/TrKA-mediated abnormal nerve proliferation. This approach, therefore, not only provides effective relief to cancer pain but also contributes to the repair of bone damage. The results show a nearly 30% increase in the cancer pain threshold compared to the control group over a 21-day observation period, demonstrating the promising potential of this innovative nanomedicine approach for cancer pain management (Figure 5d).

The diminished efficacy of NSAIDs has relegated them from their once dominant position in clinical pain management, especially considering the superior analgesic effects of opioids and local anesthetics. However, the advent of nanomedicine has breathed new life into the application of NSAIDs, ameliorating their previously poor efficacy. Numerous reports attest to the remarkable resilience of nanomedicines against inflammatory and oxidative damage. The fundamental approach involves encapsulating therapeutic agents within nanocarriers, enabling precise targeting of specific receptors or lesions. This targeted delivery facilitates the efficient removal of oxidative stress and inflammatory substances, thus alleviating nociceptive stimuli. Consequently, nociceptors are protected, fulfilling the objective of pain alleviation.

4 | LOCAL ANESTHESIA

Local anesthetics are extensively employed to preempt or alleviate acute pain and manage chronic pain symptoms. They induce a loss of sensation in specific parts of the body without causing loss of consciousness, facilitating surgical procedures and postoperative pain control. Their mechanism involves blocking action potentials within neurons by inhibiting voltage-gated sodium channels. This inhibition occurs when the drug binds to a site located in the channel's inner pore, accessible from the cytoplasmic opening.[31] However, their duration of effectiveness is typically brief, lasting only a few hours. Furthermore, local anesthetics can cause direct toxicity to the corneal epithelium, stroma, and endothelium, potentially leading to respiratory and cardiovascular disorders. Consequently, a pressing challenge in the field is the development of nanomedicine-based local anesthetics that offer an extended duration of action and diminished toxicity.

Selective site-1 sodium channel blockers (S1SCBs) such as tetrodotoxin (TTX) and saxitoxin represent a class of naturally potent neurotoxins employed for local analgesia. However, they are associated with severe systemic toxicity. While delivery systems could be employed to diminish this toxicity, the hydrophilicity of S1SCBs complicates their encapsulation. In a noteworthy study, Ji et al.[32] introduced a self-assembled delivery system for S1SCBs. The design was inspired by the specific interactions between S1SCBs and two peptide sequences on the sodium channel. They first synthesized the hydrophobic sequences, which were then combined with S1SCBs, facilitating their assembly into nanostructures via supra-molecular interactions (Figure 6a–c). This nanomedicine allowed for binding and sustained release of S1SCBs, facilitating a local anesthetic effect that lasted up to 16 h - a duration seven times longer than that provided by carrier-free TTX (Figure 6d,e). Owing to the viscosity of this assembly system, the sciatic nerve's retention time post-local injection extended beyond 3 days in vivo, enabling a significantly prolonged nerve blockade with S1SCBs. Importantly, due to the commendable biocompatibility of the polypeptide, this nanocarrier did not induce muscle or neurotoxicity. Wang et al.[33] specifically bound the phosphorothioate-modified aptamer to the TTX to form a non-covalent aptamer/drug complex, thereby creating a sustained release system. This greatly prolonged the duration of local anesthesia and reduced systemic toxicity. Zhang et al.[34] designed and synthesized a macromolecular prodrug in which the local anesthetic tetracaine is attached to the polymer poloxamer 407 via a photocleavable coumarin linkage. The solution is an injectable liquid at room temperature and gels near body temperature. It has no anesthetic effect unless irradiated with a low-power blue light emitting diode, resulting in local anesthesia.

In the context of postoperative analgesia, Zhang et al.[35] devised an injectable hydrogel/microsphere (GEL/MS) composite co-encapsulating bupivacaine (BUP) and dexmedetomidine (DEX). The design allowed for the initial release of DEX from the GEL matrix to induce a sustained vasoconstriction effect, enhancing the local concentration of BUP by restricting its diffusion into the bloodstream. Consequently, BUP could effectively block the Na^+ channels on neurons, facilitating long-term analgesia. In vivo analyses confirmed that DEX significantly extended the analgesic effect of BUP within the GEL/MS composite. Furthermore, the GEL/MS composite demonstrated commendable biodegradability and biocompatibility, as indicated by histological analyses. Subsequently, Chen et al.[36] engineered an injectable composite comprising ropivacaine-loaded poly (ε-caprolactone) electrospun fiber and clonidine-loaded F127 hydrogel, referred to as the Fiber-Rop/Gel-Clo

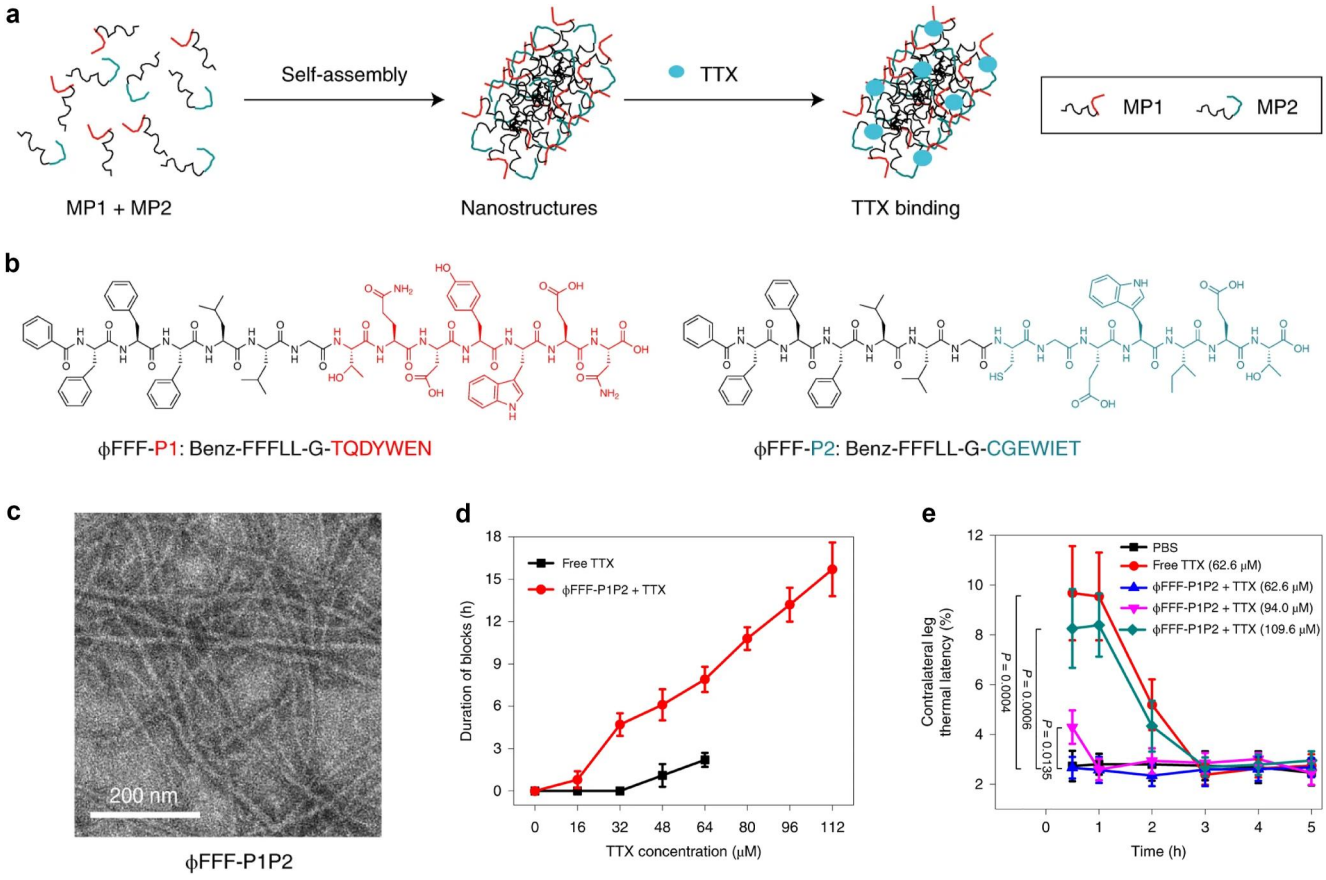

FIGURE 6 (a) Schematic of TTX binding to modified peptides (MPs) approximated by self-assembly into nanostructures. (b) Nanostructures of the self-assembled MP pairs. (c) Transmission electron microscope (TEM) images of ϕFFF-P1P2. (d) Duration of sensory nerve blocks. (e) Thermal latency in the uninjected (contralateral) extremity. Reproduced with permission.[32] Copyright 2021 Springer Nature. TTX, tetrodotoxin.

composite. This nanomaterial was employed for analgesia, with Clonidine and Ropivacaine functioning similarly to DEX and BUP, respectively (Figure 7a). In a more recent development, Yin et al.[37] introduced a near-infrared triggered analgesic system. They formulated core/shell-structured two-dimensional (2D) silicene nanosheets coated by a mesoporous silica layer, known as Silicene@MSNs. Given the distinct photothermal properties of the 2D silicene core, the local anesthetic system could be activated by a near-infrared laser to trigger the release of the encapsulated Ropivacaine, facilitating on-demand and enduring regional anesthesia. In a mouse plantar incision pain model, the nanomedicine demonstrated an analgesic effect nearly five times longer than that of free Ropivacaine, achieved by inhibiting the activation of DRG and spinal substantia gelatinosa neurons (Figure 7b).

Drug delivery endeavors to optimize bioavailability at the site of disease while simultaneously minimizing the side effects of drugs. Biomimetic nanomedicine can offer innovative strategies to enhance the analgesic effect, extend the duration of anesthesia, and improve the biosafety of local anesthetics. The potential of nanotechnology extends beyond nanomaterials and nanopharmaceuticals. The application of nanoelectronics can also provide insightful guidance for clinical anesthesia or postoperative analgesia. A case in point is the innovative work of Reeder et al.,[38] who developed a soft, bioabsorbable microfluidic cooling device designed for peripheral nerve block analgesia, achieving on-demand analgesia and damage protection through localized cooling.

5 | CONCLUSIONS AND PROSPECTS

Once chronic pain is established, the lack of intervention and treatment can lead to pathological remodeling of the nervous system, resulting in pain sensitization. This condition leads to severe pain arising from minor stimuli or injuries, severely impacting patients' quality of life,[39] altering their emotional state, and potentially leading to mental disorders such as depression[40] and anxiety.[41] The management of chronic pain relies predominantly on

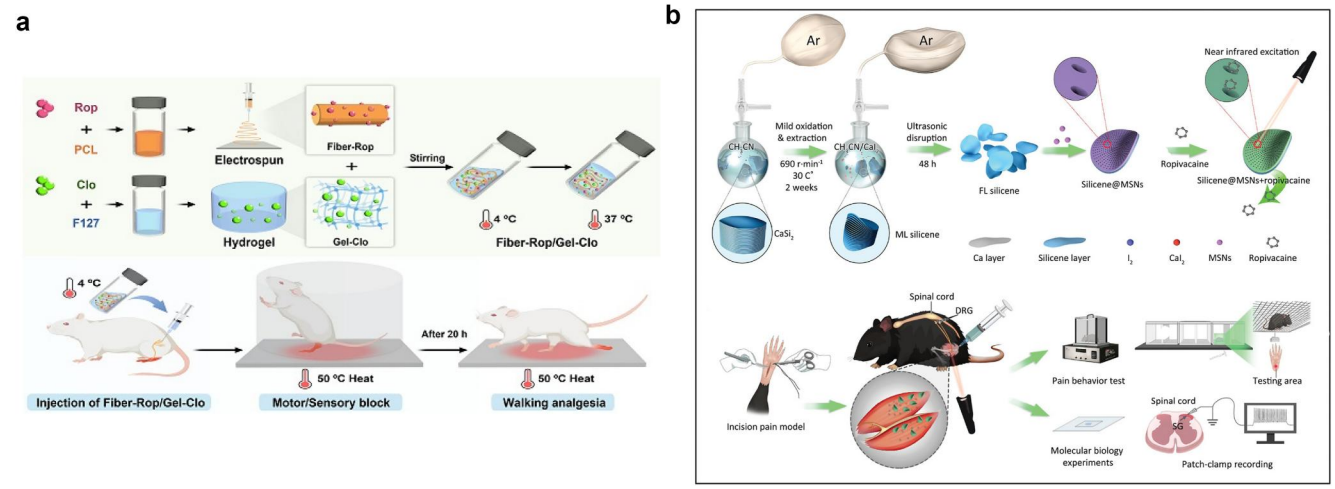

FIGURE 7 (a) Schematic illustration of the fabrication and sciatic nerve blockade effect of the Fiber-Rop/Gel-Clo composite. Reproduced with permission,[35] Copyright 2022 Ivyspring International Publisher. (b) Schematic illustration of the preparation process of Silicene@MSNs loading with Ropivacaine (RP) and their application as a local anesthesia system. Reproduced with permission.[36] Copyright 2022 Wiley-VCH.

opioids, local anesthetics, and NSAIDs. However, their irreversible toxicity and side effects, particularly in the case of opioids and local anesthetics, coupled with low efficacy, pose significant challenges. The ligands and molecular targets involved in pain signal transduction within the nervous system often lack specificity in their pharmacological activity and biological distribution. As a result, advancements in novel drug research have been stagnant for decades, and developing safe and effective drugs remains a substantial challenge in clinical analgesia.

The emergence of nanomedicine has indeed opened up new possibilities for analgesic applications. By manipulating the structure, size, and surface properties of nanomaterials, researchers can enhance the pharmacokinetics and biodistribution of medications, leading to improved drug delivery and therapeutic outcomes. In the field of analgesics, nanomedicine offers the potential for precise targeting and controlled release of drugs, which can improve pain management. Various innovative approaches are being explored to harness the potential of nanomedicine for analgesic applications. One such approach involves using nanomaterials to deliver nucleic acid substances, such as DNA or RNA, to mediate endogenous receptor activation. This technique aims to activate specific cellular analgesic pathways or silence pain expression channels, providing pain relief.

Additionally, nanomaterials can be utilized to interact with the body's active substances, such as proteases, lipids, sugars, and water, through chemical reactions. This interaction can promote the self-assembly of nanomaterials, catalyze the synthesis and processing of nanomaterials, or even utilize the reaction products directly to alleviate pain. For example, nanozymes, which are nanoparticles with enzyme-like properties, can participate in biochemical reactions to facilitate the transformation and metabolism of pain-causing chemicals. They can also up-regulate the synthesis and secretion of natural analgesic substances, such as endorphins and enkephalins, providing pain relief. In addition, compared with traditional small molecule drugs, nanomedicines have certain advantages in pharmacokinetic behavior, passive or active targeting, and reduction of toxic and side effects. However, the diversity of nanomedicines and the particularity of their physical and chemical properties make their therapeutic principles and in vivo metabolic characteristics significantly different from traditional small molecule or biomacromolecular drugs, and the potential safety risks are quite different. Therefore, in order to achieve the clinical translation of nanomedicines, it is necessary to focus on safety evaluation and safety issues involved in the design and use of nanomedicines. Overall, the field of nanomedicine holds great promise to advance analgesic applications and has the potential to revolutionize pain treatment.

ACKNOWLEDGMENTS

This work has been financially supported by the Key Program of National Natural Science Foundation of China (No. 22235004), the National Natural Science Foundation of China Youth Fund (No. 52322213), the National Natural Science Youth Fund (82202326), Innovation Program of Shanghai Municipal Education Commission (No. 2023ZKZD01), the National Funds for General Projects (No. 52272269), Shanghai Rising-Star

Program (No. 21QA1400900), Natural Science Foundation of Shanghai (No. 21ZR1405300).

CONFLICT OF INTEREST STATEMENT

Wenbo Bu is on the editorial board of this journal and was not involved in the editorial review or the decision to publish this article. All authors declare no competing financial interest.

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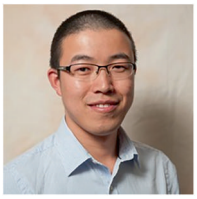

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How to cite this article: H. Liu, H. Zhuang, Y. Wang, Y. Y. Cheng, F. Chen, J. Chen, X. Song, R. Zhang, Y. Liu, W. Bu, *BMEMat* **2024**, *2*(1), e12049. https://doi.org/10.1002/bmm2.12049