Nano Today 42 (2022) 101335

Contents lists available at ScienceDirect

Nano Today

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

Review

Theranostic nanoparticles with disease-specific administration strategies

Peisen Zhang[a], Yingying Li[a], Wen Tang[b], Jie Zhao[a], Lihong Jing[a,*], Kevin J. McHugh[c,*]

[a] Key Laboratory of Colloid, Interface and Chemical Thermodynamics, Institute of Chemistry, Chinese Academy of Sciences, Bei Yi Jie 2, Zhong Guan Cun, Beijing 100190, China
[b] South China Advanced Institute for Soft Matter Science and Technology, State Key Laboratory of Luminescent Materials and Devices, South China University of Technology, Guangzhou 510640
[c] Department of Bioengineering, Rice University, 6100 Main Street, MS-142, Houston, TX 77005, USA

ARTICLE INFO

Article history:
Received 22 August 2021
Received in revised form 19 October 2021
Accepted 31 October 2021
Available online 10 November 2021

Keywords:
Theranostic nanoparticles
Administration routes
Drug delivery
Diseases
Precision medicine

ABSTRACT

Recent advances in the synthesis of nanomaterials with diagnostic and therapeutic capabilities have been rapidly reshaping the landscape of precision medicine. Impressive progress has been made toward the design and production of innovative theranostic nanomaterials to treat a variety of diseases, yet their potential is currently limited by low bioavailability, biocompatibility, or undesirable pharmacokinetics, hindering their widespread clinical implementation. Here, we summarize the state of the art for theranostic nanoparticles and discuss the diverse administration routes being used in the diagnosis and treatment of different diseases. In addition to the most commonly used intravenous (IV) administration, newly emerging nanomaterial administration routes are described in depth to explore the potential benefits of these routes that can bypass biological barriers and thereby facilitate the delivery of nanoparticles to boost imaging sensitivity and therapeutic efficacy in specific use cases. Some of the biggest challenges facing nanoparticle delivery systems are site-specific targeting, controlled nanoparticle accumulation, and safe metabolic processing. By providing examples of their in vivo applications for various diseases, we highlight the benefits, challenges, and opportunities of theranostic nanoprobes and routes of administration to inform future nanoparticle design.

Contents

* Corresponding authors.
E-mail addresses: jinglh@iccas.ac.cn (L. Jing), kjmchugh@rice.edu (K.J. McHugh).

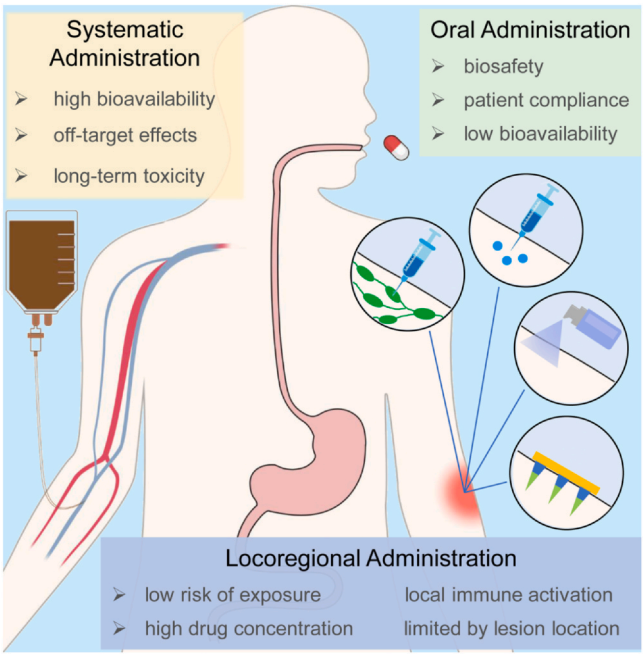
https://doi.org/10.1016/j.nantod.2021.101335
1748-0132/

Introduction

Nanomaterials, especially those exhibiting diagnostic and therapeutic functions, have proven to be powerful tools for biomedical applications with utility across a broad array of diseases [1–11]. With respect to in vivo applications, nanomaterials can be engineered to maximize the benefits of their unique properties. These efforts have improved nanoparticle contrast to enable ultra-sensitive imaging, increased circulation time relative to small molecules, employed multiple surface binding sites to confer multiple functionalities, achieved higher accumulation in diseased tissues, reduced toxicity, and provided a number of other application-specific benefits. Their high surface-to-volume ratio facilitates the incorporation of multiple moieties such as targeting or antifouling molecules, while their small size is favorable for diverse administration routes that can achieve favorable biodistribution in target tissues of interest. Their administration routes can strongly affect drug pharmacokinetics, absorption, distribution, metabolism, the duration of the therapeutic effect, excretion, and toxicity. As new theranostic nanoformulations are rapidly emerging, there is an increasing need for improving their delivery to ensure satisfactory safety and efficacy.

Although the need to design functional nanoparticles that are safe and effective within the context of their disease application is obvious, the effect of administration routes on these factors has been underappreciated, as shown in Scheme 1. For instance, intravenous administration of nanoparticles is still considered as the potentially curative therapeutic approach for some cancers and vascular diseases. Nanoparticles modified with targeting moieties can readily target the tissue of interest and be modified with anti-biofouling polymers to create reticuloendothelial system (RES)-evading particles with long circulation half-lives. However, nanoparticles directly entering the systemic circulation via intravenous injection may accumulate undesirably in the liver and spleen, causing chronic inflammation and long-term toxicity, particularly when they are not biodegradable. Similarly, oral administration is often the preferred route for clinical administration due to its safety, convenience, and patient compliance, but it suffers from low bioavailability due to the biochemical barriers in the complex gastrointestinal (GI) environment and physiological barriers such as the mucus layer and robust intestinal epithelial cell tight junctions. Moreover, early degradation in the oral cavity can lead to nanoparticle activity in non-target tissues that can reduce their efficacy and cause adverse side effects. Alternatively, locoregional administration enables nanomaterials to bypass key biological barriers to achieve a high local concentration in the desired area, enabling their use for long-term drug release while reducing the risk of systemic toxicity [6,12–14]. In some cases, the unique immunogenicity of nanomaterials can activate the local immune response [15]. However, this route may be difficult to use for deep tissue targets due to poor accessibility. Therefore, administration route is a key factor that should be considered when engineering advanced theranostic nanotools.

In this review, we focus on the recent advances in functional nanomaterials and their administration pathways suitable for disease theranostic applications. Using examples that include in vivo studies for different diseases, we highlight both the opportunities and benefits of the theranostic nanoprobes are highlighted. Finally, we then present the current challenges and future perspectives for both fundamental studies and potential clinical translation.



Scheme 1. Nanomaterial administration routes with their advantages and disadvantages.

Intravenously administered nanoparticles as theranostics

Intravenous injection is currently one of the most commonly used administration route in the clinic [16,17]. It has several significant advantages including the rapid onset of effects, easy dose control, and high bioavailability because it bypasses first-pass metabolism and is compatible with large dosage volumes.

Theranostic nanoparticles are most commonly administered via this route in preclinical research and demonstrated exciting potential for the diagnosis and treatment of cancer and vascular diseases [18–21]. Through the use of intravenous nanoformulations, the rapid, nonspecific clearance and poor biodistribution that plague conventional low molecular weight drugs can be overcome by packaging the agents within sterically stabilized, long-circulating nanosystems. The surface of these nanosystems can be further modified with ligands to actively target cellular/molecular targets in the diseased tissue [22,23]. Based on these advantages, several nano-based formulations medicated by this route have been approved by FDA [24,25], such as the PEGylated liposomal encapsulation of doxorubicin for ovarian cancer treatment (Doxil, 1995), the ultrasmall superparamagnetic iron oxide for metastatic disease detection in lymph nodes (Combidex, 2005), and the nanoparticle albumin-bound paclitaxel for the treatment of breast cancer (Abraxane, 2005) that is followed by metastatic non-small cell lung cancer (2012) and metastatic pancreatic cancer (2013).

Nevertheless, the intravenous route still poses several problems, including the harmful side effects associated with systemic distribution [26–28]. A large proportion of intravenously administered nanoparticles will be recognized by the immune system and captured by the RES (e.g., liver and spleen), which could accumulate

and cause chronic damage to these tissues if they are difficult to break down and clear [29,30], largely preventing their clinical application.

Recent studies have investigated the interactions between nanoparticles and various proteins in bodily fluids (e.g. the protein corona) [31–34], developed new approaches for targeting nanoagents to tumors [35], engineered particles to be compatible with standard in vivo clearance pathways [36,37], designed particles that avoid potential systemic toxicity after intravenous injection [38,39]. These studies help to provide insight into best practices for the clinical implementation of injectable nano-preparations to accelerate translation.

The design of tumor-targeting nanomaterials administered intravenously was motivated primarily by the enhanced permeability and retention (EPR) effect, sometimes termed the "royal gate" for drug delivery since nanomaterials could pass through the compromised integrity of tumor vasculature and accumulate inside tumors, thereby reducing side effects compared to conventional treatments [40,41]. However, some researchers have challenged the value and even existence of the EPR effect in humans, suggesting that it may only function in rodents [42,43]. However, regardless of the advantages provided by the EPR, nanomedicines can still present key advantages for cancer therapy including their compatibility with active targeting strategies to improve delivery to the tumor microenvironment.

Due to a wide variety of sizes, compositions, and surface functionalization strategies, it is difficult to directly compare nanomaterials produced by different labs, resulting in the unpredictability of in vivo pharmacokinetics and pharmacodynamics. Ideally, the field would implement a standardized set of analytical methods to enable the formation of broad conclusions regarding the effects of basic properties (size, surface charge and modification) and important downstream properties (diagnosis, therapeutics, biological distribution, biocompatibility, and clearance) on formulation quality and safety. This cohesive effort could enable researchers developing intravenously injected nanoparticles to understand the principles of nanomaterial safety and thereby rationally design their formulations to overcome current safety concerns and progress towards clinical translation.

Cancer theranostics

Nanotherapeutics have been considered promising cancer treatments for several decades because of their potential to overcome the lack of specificity of conventional chemotherapeutic drugs and provide clinicians with a better option for cancer treatment [5]. In order to ensure their distribution to tumors throughout the body, nano-based anti-cancer therapies have been most widely administered via intravenous injection.

The aforementioned EPR effect is the most basic passive mechanism by which intravenous nanomaterials can passively target tumors. This mechanism was originally applied to macromolecular drugs [44], but has elicited more interest in the field of nanodrugs. In contrast to macromolecular drugs, the permeability of particles through the vasculature decreases as particle size increases. Therefore, nanomedicines with sizes ranging from 20 to 200 nm have the advantage of remaining in circulation for an extended period of time because, unlike smaller molecules and particles which can easily pass through most vascular epithelium, these materials do not readily pass through vasculature [19]. This special pharmacokinetic behavior provides nanomedicines with better tumor targeting efficiency because nanoparticle extravasation through tumor vasculature into the tumor is a cumulative process. As such, the route of intravenous administration represents a unique advantage in tumor selectivity for nano anti-cancer drugs.

Based on the theoretical advantages of intravenous nano-formulations, there has been an explosion in the investigation of nanomaterials for cancer diagnosis and treatment over the past several decades. In the 1970 s, researchers found that liposomes can serve as a convenient and controllable drug carrier, which provided a new therapeutic feature in the treatment of cancer [45–48]. In the subsequent studies, other nanomaterials with distinctive chemical compositions and physical properties were identified and applied to cancer diagnosis and treatment [49–51]. These nanomaterials have been combined with constantly improving imaging modalities, sometimes enabling microscopic localization. In 1999, Weissleder proposed the concept of "molecular imaging", which shifted the focus of imaging from nonspecific physiologic or anatomical properties to specific molecular sources [52]. The construction of targeted molecular probes that can actively identify biomarker molecules of disease after intravenous injection has become one critical and growing area of research. By modifying nanoprobes with targeted moieties, they can both passively accumulate in tumor sites through the EPR effect and actively detect cancer biomarkers, which will have a synergistic effect on tumor contrast [53]. The Gao group proposed a concise "one-pot" route to prepare surface-reactive, biocompatible Fe_3O_4 nanocrystals as magnetic resonance (MR) contrast agents featuring an anti-carcinoembryonic antigen monoclonal antibody which improved tumor accumulation and cancer diagnosis of nanoparticles [54,55]. Similarly, $NaGdF_4$ nanoparticles covalently functionalized with an anti-EGFR monoclonal antibody (mAb) achieved promising tumor-specific targeting and strong magnetic resonance (MR) contrast enhancement in an intraperitoneal xenograft tumor model in mice [56]. In order to further improve the targeting efficiency of nanoprobes, Liu et al. subsequently replaced larger antibodies with a smaller target molecule, folic acid, to increase the loading capacity, which can specifically assist the nanoparticles to identify the folate receptor highly expressed on the surface of the tumor cell membrane. The primary tumors in more complicated physiological environments can be successfully detected by such targeted nanoprobes [57]. Similarly, Li et al. designed tumor-specific rare earth nanoprobes consisting of core-shell-shell structures and folic acid to detect subcutaneous tumors through up-conversion (UCL) and down-conversion emissions, respectively, which allowed to image the heterogeneous expression of folate receptor within the tumors [58]. This work clearly showed the spatial distribution of pathological-related molecules within small tumors, but also demonstrated the superior potential of optical imaging (OI) techniques in extracting additional information with high imaging sensitivity. Further, this was achieved with imaging equipment that costs far less than modalities currently used in the clinic, such as magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET). Another notable advantage of OI techniques is that multiple targeted probes with different spectral characteristics can be used for multichannel imaging simultaneously, enabling co-localization analyses of different pathological molecules [59]. The Dai group combined ErNPs and PbS QDs with different spectral properties to image the heterogeneous bio-distributions of PD-L1 and $CD8^+$ cytotoxic T lymphocytes (CTLs), respectively. This multichannel OI technology based on multi-target nanomaterials approach can be used to detect CTLs in the tumor microenvironment in response to immunotherapy as well as altered CD8 signals in tumor and spleen due to immune activation, which can serve as a tool for evaluating the efficacy of cancer immunotherapies [60].

Due to the different vascular distribution between tissues and inherent resolution limitations of a single imaging modality, the accurate imaging of smaller tumors without known biomarkers that can be targeted or in complex pathological environments is a key challenge for intravenous nanoformulations. Improving the targeting capability of nanoprobes has proven insufficient to date, so new

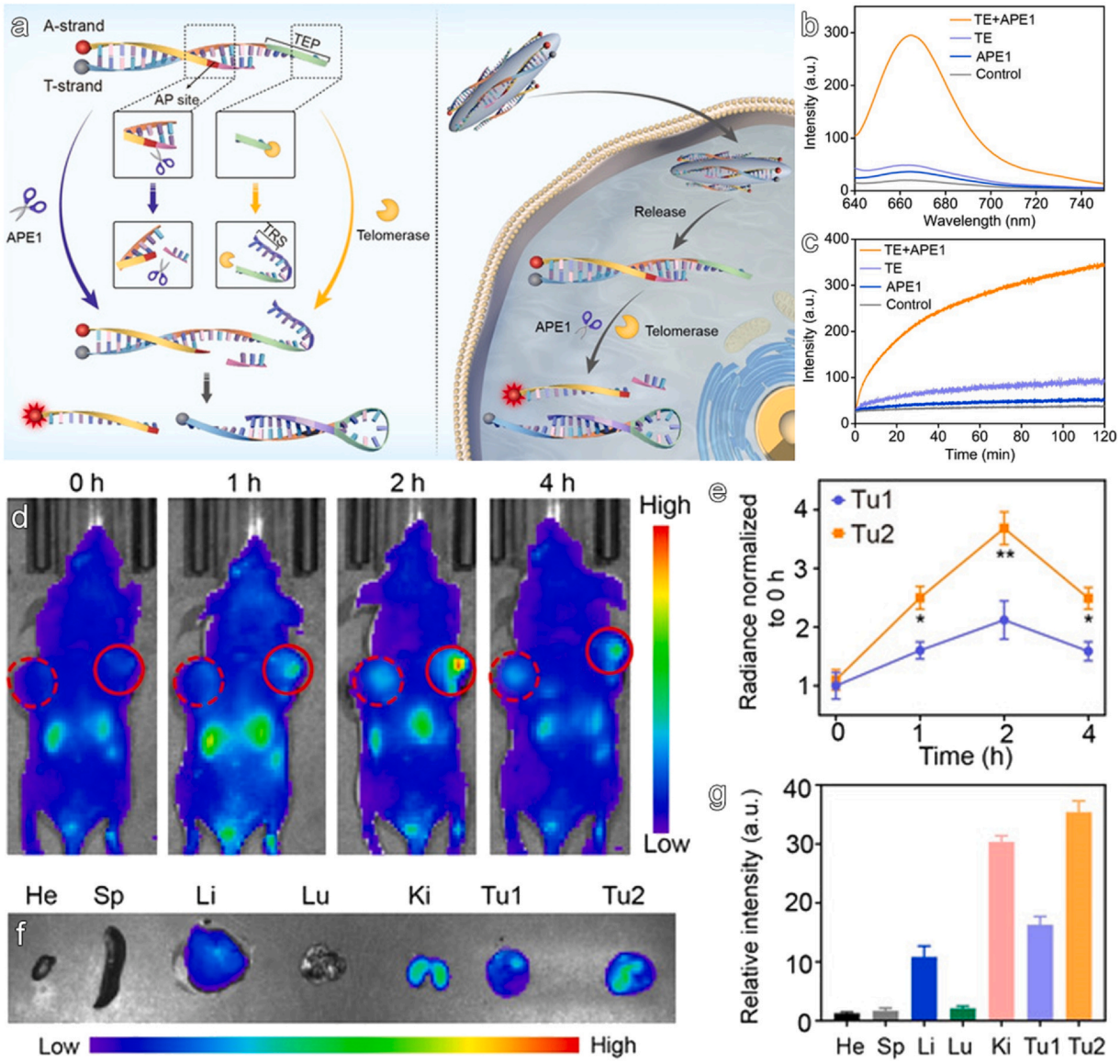


Fig. 1. (a) The working mechanism of the DNA-based fluorescent reporter, which must be simultaneously processed by TE and APE1 to produce a specific fluorescent signal, enabling the imaging of the correlated activity of the two enzymes both in vitro and in vivo. (b) Fluorescence spectra and (c) reaction kinetics of TP–AP (50 nM) responding to TE (10 U L^{-1}) and/or APE1 (1 U mL^{-1}). (d) Fluorescence images of mice with a bilateral tumor model at different time points after i.v. injection of TP–AP. (e) Quantification of the fluorescence intensity at the two tumor sites in (d). (f) *Ex vivo* imaging and (g) fluorescence intensities of the tumors and major organs at 4 h post-injection of the probe. Reproduced with permission [74]. Copyright 2021 Wiley-VCH Verlag GmbH & Co. KgaA.

trials focused on enhancing the performance of imaging techniques are currently being explored. One of the approaches recently being studied is the use of multiple modalities to overcome the weakness of a single imaging modality with the strengths of other imaging modalities [61–63]. For example, the versatility of magnetic nanoparticles has allowed them to become an important platform for multi-modal imaging applications, such as MRI-PET/SPECT or MRI-OI, which combines the advantages of each imaging modality to achieve highly accurate and informative images [64]. Gao and coworkers labeled radionuclide ^{125}I on the previously synthesized MR contrast agent Fe_3O_4-mAb to develop a novel dual-modality molecular probe, which successfully obtained tumor information from both MR and single-photon emission computed tomography (SPECT) [65]. They designed ultrasensitive magnetic/upconversion fluorescent dual-modal molecular probes through a bioconjugation reaction with tumor-specific antibodies with $NaGdF_4$ particles, which successfully detected both subcutaneous and intraperitoneal tumors with MRI and OI [66]. Similarly, Ding et al. employed Mn-doped quantum dots with high luminescence efficiency to realize tumor OI/MRI dual-modal imaging [67,68]. Very recently, Lan and Hou designed a novel probe using MDA-MB-231 cancer cell membrane-mimic Gd^{3+}-doped upconversion nanoparticles (CCm-UCNPs) to detect triple-negative breast cancer (TNBC), a subtype of breast cancer that is particularly difficult to target because it does not overexpress estrogen receptor, progesterone receptor, or human epidermal growth factor receptor 2. To prepare this probe, natural cell membranes were isolated from cancer cells and coated onto the UCNPs, which exhibited homologous targeting and immune escaping abilities. Featuring the upconversion luminescence of UCNPs, the paramagnetism of Gd^{3+}, and surface labelling with ^{18}F, CCm-UCNPs were used for ultra-sensitive in vivo UCL/MRI/PET multimodality precise imaging of TNBC, and differentiating MDA-MB-231 from MCF-7 tumors in mouse models, showing the potential for multiple clinical applications [69]. The intravenous nanoprobes mentioned above were designed to induce an adequate signal in multiple imaging modalities, which, in combination, achieved both

high spatial resolution (via MRI) and high sensitivity (via OI, PET, or SPECT), thereby detecting the biological targets with higher accuracy. This multimodality imaging approach enhances the potential clinical value of intravenously administered nanoformulations for cancer.

Because intravenously injected nanomaterials are inevitably distributed in normal tissues while entering the disease lesions, another strategy to improve imaging accuracy is to reduce the background of normal tissue, thereby highlighting the signal of the lesion. Nano-systems incorporating stimuli-responsive materials have been designed to sensitively produce signals only in the target region(s), which greatly increases the signal-to-background ratio, thereby providing high resolution and real-time quantitative detection of certain biomarkers [70]. These important hallmarks, including hypoxia, low extracellular pH, enzymes, and reducing conditions are closely associated with the proliferation, angiogenesis, invasion, and metastasis of cancer, presenting the potential of "smart" stimuli-responsive nanoprobes [71]. Gao and coworkers proposed a protease-activated pH-sensitive ratiometric optical imaging nanoprobe. In this system, a matrix metalloproteinase-9 (MMP-9)-cleavable peptide served as the linker to conjugate the ratiometric fluorescent dye (ANNA) to Fe_3O_4 nanocrystals, an ideal quencher for this ratiometric dye. After the cleavage of the peptide in the MMP-rich tumor microenvironment, the fluorescence of the dye is no longer quenched. In this strategy, the responsibility of MMP-9 is to reduce the nonspecific background, while ratiometric fluorescence can mitigate the negative effects of fluorophore concentration and tissue depth on fluorescence intensity, and allow quantitative measurement of pH [72]. On this basis, Ma et al. extended the concept by adding the NIR fluorescent dye Cy5.5 as the internal reference. The constant emission of this internal reference and the fluorescence of MMP-activated pH-sensitive ratiometric dye (ANNA) can form another ratiometric fluorescent system to quantitatively map the activity of MMP-9 in the tumor microenvironment. The correlation between pH and MMP-9 during tumor growth and invasion can be deeply understood by using this probe [73]. Single stimulus–responsive probes provide selective and sensitive strategies for visualizing the tumor microenvironment with a high signal-to-background ratio. Comparing with the single stimuli-responsive probes, multi-stimuli ones enable more exact and specific imaging of tumor, avoiding the possibility of a "false positive" result. Very recently, Li and coworkers developed a cooperatively activatable, DNA-based fluorescent reporter named TP-AP that can precisely visualize the correlated activity of two key enzymes related to tumor development and prognosis, including telomerase (TE) and apurinic/apyrimidinic endonuclease 1 (APE1). Through the TE-triggered DNA elongation and the APE1- induced cleavage, the conformation of TP-AP will be altered inside the tumor region, thereby activating the fluorescent signal by breaking the fluorescence resonance energy transfer (FRET) to further visualize the activity of two enzymes (Fig. 1**a-c**). More importantly, TP-AP can be used to perform real-time pharmacodynamic assessments through monitoring the activities of two enzymes in tumors. The fluorescent intensity in the cisplatin-treated tumor was 2.1-fold higher than that of untreated tumors, which is a very promising finding, potentially improving the accuracy of clinical cancer prognosis (Fig. 1**d-g**) [74]. Intravenous administration of nanoformulations with multi-parameter imaging capabilities can serve as a non-invasive tool to replace many of the functions of invasive multi-index biopsies, which could greatly reduce the pain of patients and avoid the potential risk of invasive detection to promote cancer metastasis. In addition, this approach is also promising because it could be used to customize specific treatment strategies for individual patients and enable the establishment of patient-specific "personalized medicine" in the near future. Apart from the optical imaging, Zhang et al. further realized the non-invasive and quantitative detection of tumor-specific biomarkers in vivo through clinically compatible imaging modality, i.e., MRI. They reported an Fe_3O_4 nanoparticle-based glutathione (GSH) responsive nanoprobe, which can form agglomerates within tumors to give rise to strong GSH concentration-dependent interlocked relaxivities. Through the theoretical analysis, a quantitative correlation between the interlocked MRI signals and local GSH concentration was established, which was further applied for mapping the heterogeneous distribution of GSH within an intracranial tumor (2.4 mm × 1.6 mm) in vivo. This methodology will offer a practical route for quantitatively mapping tumor-specific biomarkers in vivo with unlimited detection depth [75].

Intravenous nanotherapeutics have not only been used as tumor imaging agents, but also as carriers that prolong drug circulation time and control drug release [76,77]. Nanomaterials with integrated single/multi-modal diagnostic and therapeutic functional agents have attracted considerable attention in recent years due to their promising potential in precision medicine [78–80]. For example, Li and coworkers developed a bovine serum albumin (BSA)-mediated aqueous synthesis approach for ultrasmall Bi_2S_3 nanoparticles. Owing to their small size and colloidal stability, BSA-capped Bi_2S_3 nanoparticles display outstanding residence time in circulation with a half-life of up to 14.85 h, which is favorable for the accumulation of nanoparticles in the tumor to achieve specific PA/CT imaging. Owing to the synergy between their excellent photothermal conversion efficiency up to 51% and large X-ray attenuation coefficient, the photothermal and radiosensitization effects of these nanoparticles enable effective eradication of tumors in mice with the ability to increase survival up to 100% 40 d after treatment [81]. This type of noninvasive imaging-guided treatment strategy combines diagnostic and therapeutic capabilities, which provide information about the size and location of tumor as well as a clear target for exogenous stimulation that can minimize damage to normal tissue surrounding the tumor.

Surgical resection is currently one of the most important means for the treatment of early-stage cancers; however, the precise and complete removal of the tumor remains challenging due to a myriad of issues including loss-of-function from excessive healthy tissue excision, which is especially problematic when tumors are in critical tissues, such as brain. To address this problem, intravenous nanomaterials can be combined with image-guided surgery (IGS) [82]. The highly specific, robust detection of tumors using high contrast images has the propensity to not only ensure complete tumor removal at the margin but also reduce excessive resection of surrounding normal tissues. Tumor-specific nano-imaging agents can precisely delineate the carcinoma boundary to provide more reliable operation guidance [8,83]. For instance, under the guidance of Ag_2S QD-based NIR-II fluorescence, the deep sentinel lymph nodes and lymphatic vessels of tumor-bearing nude mice can be clearly identified with high spatial and temporal resolution for accurate dissection, thereby reducing the probability of tumor recurrence [84]. Similarly, these Ag_2S QDs have also been used for the highly sensitive preoperative tumor imaging and intraoperative excision of brain tumors using NIR-II fluorescence imaging. This study showed that fewer residual tumor cells (4.5%) at the surgical site were detected compared with that of the naked eye-guided surgery (14.2%) [85].

Unfortunately, nanoparticle distribution is not confined to tumors. Even when using targeted nanoparticles, a subset of the intravenous injection is invariably delivered to normal tissues nonspecifically, especially the liver and spleen, which may lead to potential side effects. The stimuli-responsive nanomaterials mentioned above may be able to overcome this challenge because they only become activated in the tumor while remaining "silent" in

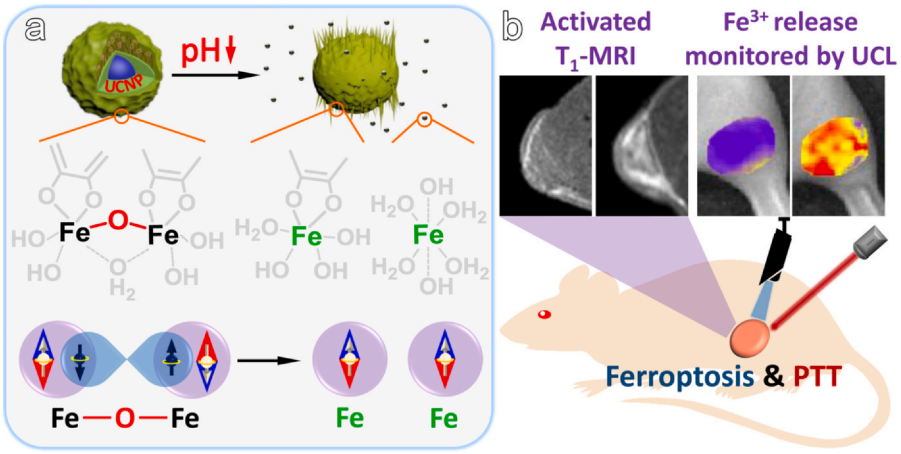


Fig. 2. (a) Illustration of the activation of upconversion nanoparticle (UCNP) based UCNP@GA-Fe(III) probe in the acidic tumor microenvironment. (b) The activated T_1-weighted MR images of tumor acquired before and after the injection of UCNP@GA-Fe(III) probes and Fe^{3+} release mapping within the tumor based on I475/I800 ratio of upconversion luminescence together with the probe's therapeutic mechanisms, including PTT treatment and the ferroptosis pathway. Reproduced with permission [87]. Copyright 2019 Wiley-VCH Verlag GmbH & Co. KgaA.

normal tissues [22,23,86]. Zhang et al. designed an activable nanoprobe by coating upconversion nanoparticles with coordinatively unsaturated gallic acid(GA)-Fe(III) complexes. After intravenous injection, the nanoprobe binds to transferrin to enhance tumor targeting, passes the impaired blood vessel, and consequently accumulates in the tumor. Once internalized by cancer cells through transferrin receptor-mediated endocytosis, the coordinatively unsaturated shell of the probes is activated by the low lysosomal pH by breaking the superexchange coupling to release Fe(III), T_1 effect for MRI is boosted. Apart from this activatable MR imaging property, the released Fe^{3+} ions in the tumor are capable of directly catalyzing damaging free radical formation via Fenton-like reaction, known as Ferroptosis, while the remaining GA-Fe(III) serve as heating centers upon laser irradiation to realize MRI-guided PTT (Fig. 2) [87]. These kinds of nanoagents can greatly reduce the systemic toxicity caused by intravenous administration, and therefore have great potential for clinical translation.

In recent years, cancer immunotherapy has achieved substantial success in the clinic, which mainly includes chimeric antigen receptor (CAR) T-cell therapies and checkpoint blockade treatment with antibodies that block the inhibitory receptors cytotoxic T lymphocyte antigen-4 (CTLA-4) or programmed death-1 (PD-1) [3,13,88–100]. A variety of injectable nano-immunoregulators have been developed to provoke host immunity and result in anticancer effects of immune systems. Tan and Liu designed a kind of aptamer–multivalent–drug conjugate (ApMDC) nanomicelles. After optimizing the pharmacokinetics by adjusting the feed ratio in co–selfassembly, the best complementation was reached to ensure both blood circulation and tumor-targeting ability, which led to strong ICD of tumor cells and further boosted the antitumor immune responses of the checkpoint blockade [93]. In another work, Liu and co-workers reported a chemotherapy and photodynamic combined treatment to provoke the antitumor immune response against PD-1 (α-PD1) through core-shell metal ion-drug nanoparticles formed by self-assembly of Mn^{2+} with chemotherapeutic doxorubicin and photosensitizer chlorin e6. After intraveneous injection, nanoparticles promoted the antitumor immune response of the checkpoint blockade to fight against both the primary and distant tumors. Moreover, Mn^{2+} endowed the nanoparticles with T1 MRI performance for tumor diagnosis as well [89]. Compared with traditional molecular-based contrast agents or therapeutic drugs, intravenous nanoformulations have exciting capabilities that can combine multiple beneficial functions, such as cell targeting, ultra-sensitive imaging, and stimuli-responsive therapy in a single entity.

Theranostics for cardiovascular diseases

The advantages of nanotherapeutics administered intravenously, such as long circulation time and excellent active targeting performance for special biomarkers, can be leveraged for applications beyond oncology and are especially well-suited for characterizing and treating cardiovascular diseases [19,101,102].

Angiography, a vascular imaging technology through intravenous injection of relevant contrast agents, has been used to detect carotid stenosis, cerebral aneurysm, peripheral vascular disease, and other vascular diseases [103,104]. MRI and CT are the most commonly used imaging modalities in clinical angiography. Intravenous injection of a contrast agent significantly enhances the contrast between blood vessels and surrounding tissues, subsequently improving the image quality [105,106]. However, the short half-life of blood and rapid extravasation into the extravascular space limit the usefulness of low-molecular-weight contrast agents [107–111]. Alternatively, nanomaterials, which feature a slightly larger size less prone to extravasation and offer a prolonged circulation lifetime, can be employed as enhanced angiography agents [112,113].

Superparamagnetic iron oxide nanoparticles are among the most common nanosized MRI contrast agents administered via intravenous injection. The MR relaxivity of magnetic iron oxide can be tuned by altering nanoparticle size [114,115]. Large iron oxide nanoparticles can be used as a good T_2 contrast agent because of the high r_2 derived from their innately high magnetic moment [116,117]. The magnetic moment of iron oxide nanoparticles declines rapidly with a decrease in particle size due to a reduction in the volume magnetic anisotropy and spin disorders on their surfaces. Small iron oxide nanoparticles featuring five unpaired electrons and a large surface area are potential candidates for T_1 contrast agents [118,119]. The Hyeon group prepared uniform, extremely small-sized iron oxide nanoparticles (ESIONs) at various sizes down to 1.5 nm with high r_1 relaxivities greater than 4.7 mM^{-1} s^{-1}, 3 T and low r_2/r_1 ratios of less than 6.2, which can escape from the RES and resist clearance by the kidney. ESIONs with high r_1 relaxivity and long circulation time enabled high-resolution T_1-weighted MR imaging of blood vessels as small as 0.2 mm in diameter [120]. Subsequently, they used polyethylene glycol-stabilized iron oxide nanoclusters as T_1 MRI contrast agents and shown the ability to enhance the contrast of magnetic resonance angiography (MRA) in several large animal models, including rabbits, dogs, and macaques. Moreover, dynamic MRI also enables the detection of cerebral ischemia in macaques and beagles and shows higher sensitivity than clinical gadolinium-based

contrast agents [121]. Very recently, Cheon and coworkers designed a nanoparticle with a polysaccharide supramolecular core and a shell of amorphous-like hydrous ferric oxide, which exhibited great T_1 MRI performance. This particle allowed for depicting the cerebral, coronary, and peripheral microvessels in rodents and lower-extremity vessels in rabbits through MRI at resolutions of the order of a few hundred micrometers, largely expanding the range of preclinical and clinical applications of MR angiography [119].

Recently, in addition to conventional MR and CT angiography, OI in the second near-infrared window (NIR-II, 1000–1700 nm) under ~800–1000 nm excitation has afforded high-resolution imaging at sub-centimeter tissue depths, benefiting from suppressed photon scattering and diminished tissue autofluorescence in this spectral range [122,123]. Dai and coworkers used this type of optical angiography by employing single-walled carbon nanotubes as fluorophores to perform real-time in vivo fluorescence imaging of mouse hind limb vasculature in the NIR II region. Both high spatial (~30 μm) and temporal (< 200 ms per frame) resolution for small-vessel imaging were achieved at depths of 1–3 mm in the hind limbs. Additionally, arterial and venous vessels can be clearly distinguished by using a dynamic contrast-enhanced NIR-II imaging technique [124]. They also engineered rare-earth Er-based nanoparticles for rapid imaging of mouse cerebral vasculature in the NIR-IIb window, which was achieved with a short, 20 ms exposure time per frame to yield high spatiotemporal resolution [125]. Due to their advantages, which include a high signal-to-noise ratio and high time-resolution, NIR-IIb emissive nanoparticles have promise for potential clinical use.

Although there are many forms of cardiovascular diseases, acute cardiovascular events, which are often caused by atherosclerosis [126,127], remain one of the leading causes of mortality and morbidity worldwide. Traditionally, imaging of atherosclerosis has focused on anatomical or physiological features at advanced stages of the disease, either by directly revealing luminal stenosis or by indirectly evaluating the functional consequences of the stenosis. These techniques are based on contrast analysis, but do not provide information on the active cellular and molecular processes that drive the evolution of atherosclerotic plaques [128,129]. This is a key limitation because many plaques that cause acute coronary syndrome originate from non-flow-limiting lesions, which can also lead to the formation of thrombosis and are likely to cause fatal acute myocardial infarctions or sudden coronary deaths [130,131]. Currently, clinical risk factors and available biomarkers are unable to accurately predict acute events caused by plaques. Therefore, more advanced technologies are needed to detect “vulnerable atherosclerotic plaques,” which are more likely to cause an acute vascular event. To overcome this limitation, one group has investigated a method for determining the biological composition of the plaque, which is the direct evidence of clinical acute complications of atherosclerotic vascular disease [132,133]. Nanomaterials with the ability to identify specific biomarkers have been employed as novel tools to distinguish the biological characteristics of atherosclerotic plaques and thereby determine their potential to produce acute complications. Gao and Cao synthesized Fe_3O_4 nanoparticles as MRI/optical dual-modality probes to detect vulnerable plaques in vivo based on osteopontin (OPN) content, which is highly expressed in foamy macrophages in vulnerable atherosclerotic plaque [134]. After that, they constructed another OPN-specific nanoprobe (UCNP-anti-OPN) based on upconversion luminescent nanoparticles. Because of their binding specificity, these nano-probes are able to differentiate vulnerable and stable atherosclerotic plaques optical and MR in vivo (Fig. 3**a-e**) [135]. More recently, these researchers constructed $NaGdF_4$:Yb,Er@$NaGdF_4$ upconversion nanoparticles targeting macrophage receptor with collagenous structure (MARCO) by conjugating polyclonal antibodies to the surface of $NaGdF_4$:Yb,Er@$NaGdF_4$ via a condensation reaction. This nanoprobe with favorable biocompatibility and affinity for binding M1 macrophages could be used for non-invasive dual MRI and OI to identify macrophages exhibiting an M1 phenotype in vulnerable atherosclerotic plaque in vivo (Fig. 3**f-g**) [136].

In addition to the specific detection of vulnerable plaques, nanomaterials can also influence biological processes in a targeted manner, providing a new means for therapeutic plaque disruption [137]. For example, activation of peroxisome proliferator-activated receptor gamma (PPARγ) pathways in vulnerable plaques can effectively reduce plaque burden and associated inflammation. Using this strategy, Choi developed a macrophage mannose receptor (MMR)-targeted biocompatible nanocarrier loaded with lobeglitazone (MMR-Lobe), which is able to specifically activate PPARγ pathways within inflamed vulnerable plaques and effectively reduce both plaque burden and inflammation. This nanotherapeutics with targetable PPARγ activation capabilities could be a promising therapeutic strategy for treating vulnerable plaques [138].

Taken together, it is clear that theranostic nanoparticles administered intravenously have the potential to provide additional information about atherosclerotic plaques that can assist in risk segmentation and treatment selection. Once an inflamed plaque at risk of rupture is identified, the optimal systemic or local intervention can be employed to reduce the risk of a severe acute event. Further, this combined diagnostic and therapeutic approach can not only improve plaque detection but also directly act on plaques to improve outcomes in preclinical studies and potentially in patients as well.

Orally administered nanoparticles as theranostics

Oral administration remains the preferred route for clinical treatment of many diseases mainly due to its safety, convenience, and high patient compliance [139–149]. When drugs are administered via this route, their therapeutic efficacy largely depends on consistent systemic exposure following adequate absorption. These orally administered drugs must be absorbed through the gastrointestinal tract into the systemic circulation or site of action to exhibit their pharmacological effect. However, many drugs display low oral bioavailability mainly due to poor transport across the intestinal epithelium and first-pass metabolism, a pre-systemic phenomenon in which a drug is routed to the liver where it is vulnerable to clearance before entering the systemic circulation [150,151].

Fortunately, recent advances in oral nanoparticle delivery has indicated the potential to overcome these challenges. Several studies have demonstrated that nanoparticle-mediated delivery can dramatically improve bioavailability, drug circulation time, and biodistribution, which are important factors for the diagnosis and treatment of many diseases [152–154]. Specifically, the physicochemical and pharmacokinetic parameters of encapsulated drugs can be finely tuned by adjusting the physicochemical properties, and surface modification of nanocarriers to ensure that the drugs can reach their target after passing through the long digestive tract [155]. In addition, nanocarriers also have the ability to protect the drugs from the harsh environment of the GI tract, which prevents premature drug degradation and thereby functionally increases systemic bioavailability [156]. Ferumoxsil, a formulation of superparamagnetic silanized iron oxide nanocrystals, was approved by the FDA in 1996 as an oral MRI contrast agent that is well-tolerated and effective in marking the bowel and in delineating the normal organs as well as the pathologic targets [157]. At present, more and more orally administered nano-formulations are being developed to deal with various diseases [158–160].

Colon disease theranostics

Oral drug administration is an obvious choice for targeting colonic diseases, such as colorectal cancer (CRC), irritable bowel

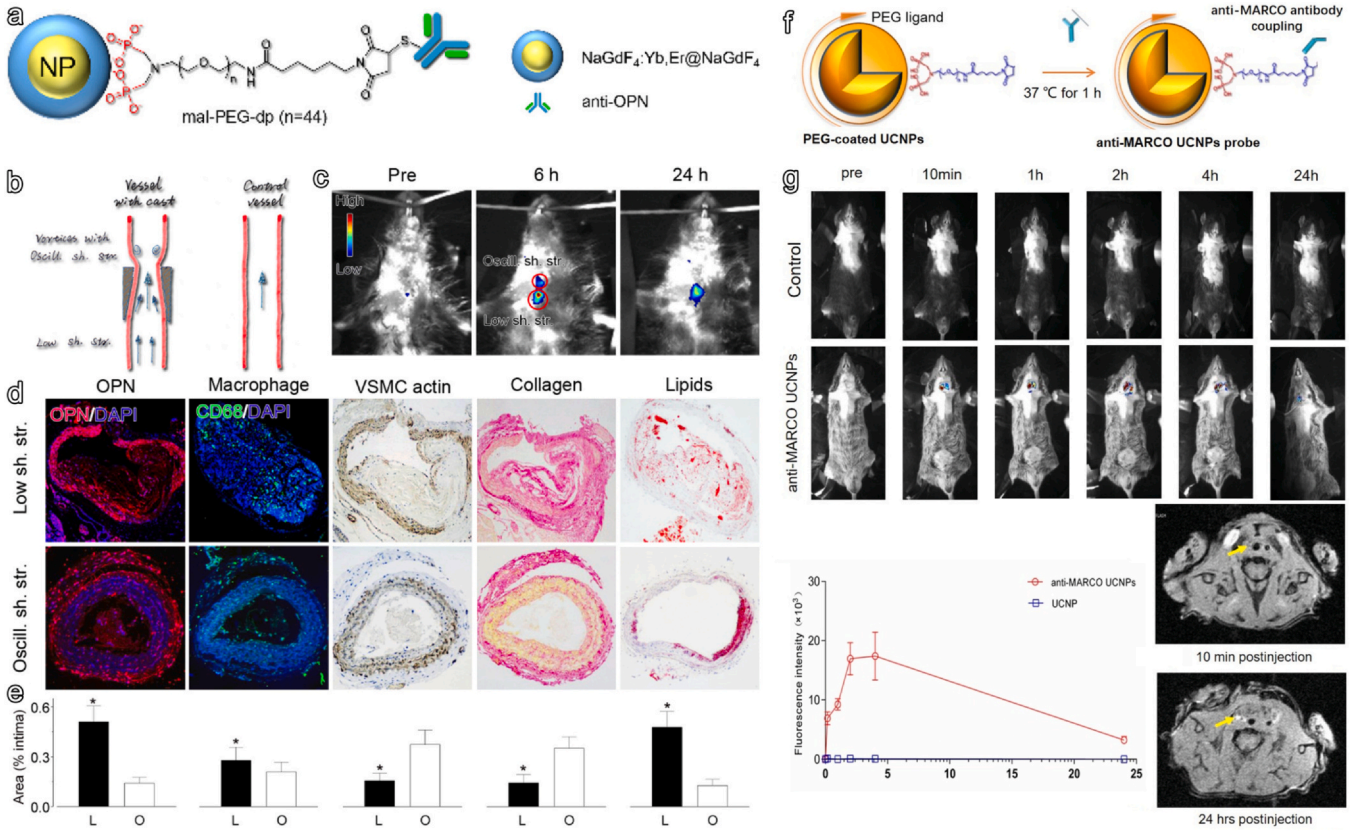


Fig. 3. (a) A depiction of the UCNP-anti-OPN probe, and (b) the varied stress-induced plagues in ApoE$^{-/-}$ mouse, (c) in vivo upconversion luminescent images after intravenous injection of the UCNP-anti-OPN probe (the region of interest is encircled with red circles for showing the oscillatory shear stress (top) and lowered shear stress region (bottom) of the constrained vessel), (d) histological analyses, and (e) quantified data of the different plaque regions upon various staining. Reproduced with permission [135]. Copyright 2017, American Chemical Society. (f) Illustration of anti-MARCO UCNP probe, in vivo upconversion luminescent images of carotid artery before and at different time points after intravenous injection of the anti-MARCO UCNPs probe, the quantitative analysis of signal intensity, (g) together with an MRI of the carotid arteries of apoE$^{-/-}$ mice after intravenous injection of antiMARCO UCNP probe. Reproduced with permission [136]. Copyright 2019, Elsevier.

syndrome (IBS), and inflammatory bowel disease (IBD). It is crucial to precisely identify and target diseased areas in the distal colon to avoid harm to surrounding healthy tissue [161,162].

CRC is one of the most serious malignant diseases, stemming from the epithelial cells lining the colon of the GI tract, which is the second most common cause of cancer death in the United States. It is estimated that in 2020, approximately 147,950 individuals would be diagnosed with CRC and 53,200 would die from this disease [163]. CRC usually originates from polyps in the inner wall of the colorectal epithelium, which is able to invade muscles and tumor-draining lymph nodes and finally spreads to other organs, mainly the liver. On the other hand, IBD is a collective term for a group of chronic recurrent gastrointestinal diseases, which can share some general clinical features, such as cycles of relapsing and remitting mucosal inflammation. The exact cause of IBD has not been fully understood, and there is no cure for IBD at present. The current treatment strategy is mainly to seek the relief of inflammation.

Although the site-specific accumulation of oral drugs has become increasingly important in the local treatment of colon diseases, it also poses some limitations in this administration route. The complexity of the GI environment, variable pH, and the presence of digestive enzymes may promote the early degradation of drugs, which leads to the pre-systemic metabolism of drugs in the stomach and small intestine, thereby causing the reduction in reaching the target site(s) and increases the potential of adverse side effects [164]. Therefore, it is necessary to design systems that protect against these factors to achieve consistent controlled drug release. Currently, several systems (such as pellets, tablets, and capsules) have been used clinically to control the release of drug in the GI tract, but they are largely unable to combat the drawbacks of these conventional colon-targeted drugs. Therefore, nanotechnology has been employed to develop the new oral formulations, which are expected to safely escort drugs to colonic disease targets [165]. These nanomaterials, which possess a large specific surface area and targeting moieties, are able to increase interactions between drugs and the GI tract and specifically bind to tumor cells to promote drug internalization as well. Based on these advantages, oral nanomaterials have been widely studied in preclinical animal models to demonstrate proof of concept [166,167].

As mentioned above, loading targeting molecules onto the surface of nanodrug delivery systems is a viable approach that can enable them to target a site of interest. During the pathogenesis of many colon diseases, some ligands or receptors are commonly overexpressed by colon epithelial cells and immune cells, which can be used as targets for nano-drug delivery systems [161]. For example, Shen and coworkers designed a doxorubicin and superparamagnetic iron oxide nanoparticle-loaded solid lipid nanoparticle (SLN) delivery system that accumulates in colon tumors and provides chemo/magnetothermal combination therapy at tumors through the hierarchical targeting of folate (FA) and dextran-coated on the particle surface. Both in vitro and in vivo characterization showed that the dextran shells on SLN surfaces not only retarded the cellular transport of the FA-coated SLNs by the proton-coupled FA transporter on brush border membranes in the small intestine, but also enhanced particle residence time in the colon through specific associations with dextranase. The enzymatic degradation of the dextran shell in the colon can expose FA residues, thereby enhancing cell uptake of SLN. After oral administration, this

SLN treatment system can effectively inhibit primary colon cancer and prevent peritoneal metastasis in mice without obvious systemic side effects [168]. In addition to the artificial modification of target molecules, natural polysaccharides have been frequently investigated as colon-specific oral delivery systems. Because of their immunogenicity, they can be selectively phagocytized by immune cells such as DCs and macrophages, leading to preferential accumulation in inflamed tissues. Xu and coworkers reported a targeted oral delivery system that loaded the clinically used anti-inflammatory drug methotrexate (MTX) into yeast glucan particles (YGPs) for IBD therapy. YGPs/MTX were internalized by RAW264.7 macrophage cells through dectin-1 and CR3 receptors and demonstrated enhanced accumulation in inflamed tissue using a mouse model of colitis, which significantly improved the efficacy of MTX while reducing side effects. This study provides new insight into incorporating naturally occurring polysaccharides as targeting agents for the treatment of inflammatory diseases [169].

Nanomaterials can also be designed to specifically protect GI from physical and chemical damage. For example, after radiation therapy of CRC, the healthy part of GI may also be destroyed, which will lead to a series of gastrointestinal diseases including anorexia, abdominal pain, diarrhea, and hematochezia, badly reducing the life quality of patients. Zhao and coworkers developed nanoparticles based on BSA-modified graphdiyne (GDY), known as GDY-BSA nanoparticles. These nanoparticles possessed satisfied chemical stability and can retain in GI after oral administration, which consequently prevented ROS-induced apoptosis of gastrointestinal cells, and successfully decreased radiation-induced diarrhea of mice [170]. In another study, Gu and coworkers carried out a series of studies on GI radioprotection by using carbon nanoparticles suspension injection (CNSI), the first clinically approved carbon nanoparticles in China. CNSI is stable enough to maintain a long residence time in GI and can effectively scavenge the free radicals to inhibit the ROS-induced mitochondrial membrane and DNA damages [171].

Stimuli-responsive nanomaterials used in intravenous administration (mentioned in Section 2.1) can also serve as delivery systems for oral drugs to further control drug release. The complicated gastrointestinal environment provides a rich source of stimuli that can trigger drug release from environmentally responsive nanomaterials, such as pH-dependent [172], ROS-sensitive [173,174], microbial-targeting [175,176], or enzyme-sensitive [177] particles. For example, Li and coworkers developed a nanotube-in-microsphere drug delivery platform by encapsulating halloysite nanotubes (HNTs) in a pH-responsive hydroxypropyl methylcellulose acetate succinate polymer using microfluidics. This nanotube/pH-responsive polymer composite prevented the premature release of loaded drugs after exposure to the harsh conditions of the gastrointestinal tract (pH < 6.5), but quickly released drug and enhanced the drug permeability to inhibit colon cancer cell proliferation in response to the neutral colon pH [178]. In another study, Nagasaki and coworkers designed redox nanoparticles (RNPO) for oral chemotherapy with ROS responsiveness and scavenging abilities. The results indicated that RNPO showed higher accumulation in colonic mucosa and selective internalization in tumor cells using a mouse model. No significant toxicity was observed in off-target organs after long-term oral administration, which can be attributed to the avoidance of systemic absorption and lower uptake by healthy intestinal cells. Moreover, benefiting from the ability of ROS scavenging, RNPO significantly suppressed tumor growth after accumulation at tumor sites [179]. In addition, a smart ROS-responsive nanoparticles (AON) containing a pro-resolving annexin A1-mimetic peptide Ac2–26 was developed by Zhang and coworkers, which released packaged Ac2–26 peptide only at disease sites with highly expressed ROS. After oral administration, AON effectively protected Ac2–26 from degradation in the complex environment of the GI tract. Once the nanoparticles reached the inflamed colons of mice with IBD, site-specific release and accumulation of Ac2–26 was be triggered by high levels of ROS. Therapeutically, AON reduced symptoms of inflammation, accelerated intestinal mucosal healing, reshaped the gut microbiota composition, and increased short-chain fatty acid production (Fig. 4). Additionally, oral delivery of this nanomedicine displayed an excellent safety profile in a mouse model, enhancing confidence about its clinical potential as a targeted precision therapy for IBD and other inflammatory diseases [175]. Zheng and coworkers found that the microbiota in the human gut is strongly correlated with the progression of CRC. They showed that oral administration of irinotecan-loaded dextran nanoparticles covalently linked to azide-modified phages that inhibit the growth of *F. nucleatum* can significantly improve the efficiency of first-line chemotherapy treatments of CRC using mice bearing orthotopic colorectal tumors or with spontaneously formed colorectal tumors. They also showed that the oral administration of the phage-guided, irinotecan-loaded nanoparticles in piglets does not cause adverse reactions such as allergy, which indicated the potential safety of this approach [180].

However, in some circumstances, smart oral drug release controlled by a single stimulus is still limited by the response mechanism and may not be intelligent enough to effectively deliver drugs to colon diseases [165]. For instance, time-dependent drug delivery systems may release drug prematurely in the stomach or small intestine, leading to drug absorption into the bloodstream, which reduces the amount of drug that reaches colonic lesions and can contribute to side effects. In addition, gastrointestinal disorders and microbial changes associated with the disease may affect physiological parameters, such as pH, enzyme expression, etc., which may lead to unanticipated drug release behavior. To improve the accuracy of drug delivery, smarter nanodrug delivery systems employing multiple stimuli-responsive drug release strategies may be a feasible approach to further improve efficacy. For example, in one study, nanoparticles composed of enzyme-sensitive polymers and pH-sensitive polymers were formulated and employed to jointly control the drug release [181,182]. In another study, particles with pH- and temperature-responsiveness were prepared, which could potentially be applied for small intestine (and colon)-specific oral drug delivery [183]. Compared with single-sensitive nano-systems, the dual-sensitive nanoparticles displayed better drug delivery and release capabilities.

Overall, these studies demonstrate the potential for nanotherapeutics to achieve targeted drug delivery to diseases in the colorectal region via oral administration.

Diabetes mellitus theranostics

Diabetes mellitus is a highly prevalent metabolic disease that results in abnormally high blood sugar levels. While treatments are available, completely curing the disease has proven difficult. Hyperglycemia can cause both acute and chronic issues, such as retinopathy and neuropathy, which seriously compromise patients' quality of life [184]. Owing to their different pathology, diabetes mellitus can be classified into two types. Type 1 diabetes is associated with an autoimmune disorder, in which pancreatic β-cells are attacked, reducing or impairing insulin production. Type 2 diabetes, on the other hand, is characterized by a lack of responsiveness to insulin. The subcutaneous injection of insulin or its analogs can be used in both types of diabetes patients, in order to manage the blood sugar level [185,186]. However, due to the pain, discomfort, and the risk of local infection, the fear of injection is pervasive across patient populations, resulting in sub-optimal compliance.

Oral medication of insulin or its analogs, therefore, has been proposed to realize painless self-administration, which is expected to improve patient experience, compliance, and disease outcomes [187]. However, the physiologically complicated gastrointestinal tract has thus far prevented the clinical translation of the vast

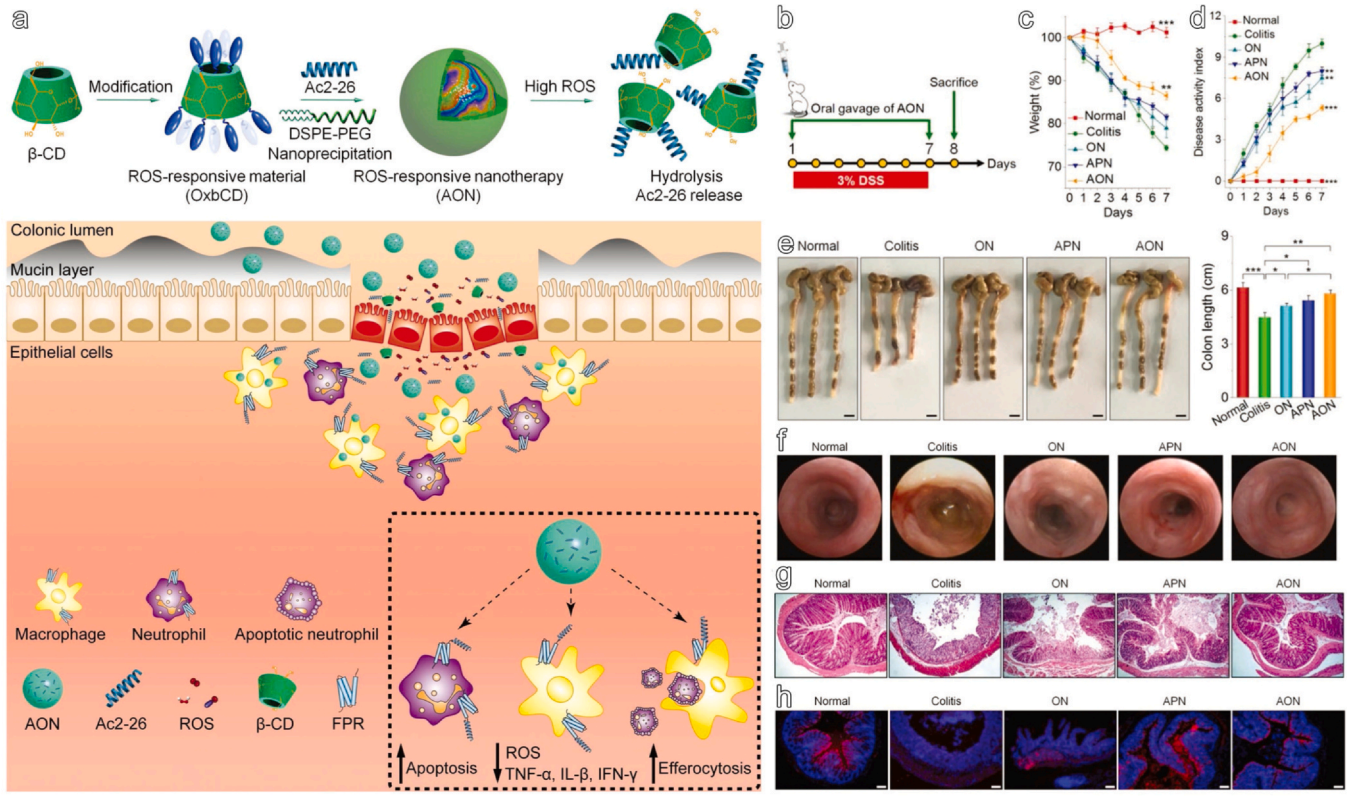


Fig. 4. (a) Schematic illustration of a ROS-responsive peptide nanotherapy and targeted treatment of colitis. (b) Schematic illustration of treatment regimens. (c) The relative bodyweight of mice during a 7-day treatment course. (d) Changes in disease activity index (DAI). (e) Photos (left) and quantified lengths (right) of colonic tissues isolated from mice after 7 days of treatment. (f) Miniendoscopic images of colons from mice at day 7 after different treatments. (g) H&E-stained histological sections of colonic tissues. (h) Immunofluorescence analysis of colonic cryosections. Epithelial cells were stained with a Cy3-labeled anti-cytokeratin 18 antibody, and nuclei were stained with DAPI. Reproduced with permission [175]. Copyright 2019, Wiley-VCH Verlag GmbH & Co. KgaA.

majority of oral protein formulations, including insulin [188,189]. The first biochemical barriers to oral protein delivery include the acidic pH of the stomach and proteolytic enzymes. The former can unfold the proteins, rendering them inactive, while the latter can readily cleave proteins. In this case, nano-systems have been developed to serve as insulin carriers in order to protect insulin from being destroyed [190,191]. For example, inorganic nanoparticles have been used for the oral delivery of peptides and proteins [192]. The main merits of these particles include their favorable biocompatibility, high physical and chemical stability, their ability to respond to specific stimuli, and their good stability in acidic and high-enzyme environments, enabling them to protect their protein cargo. Joshi and coworkers orally administered insulin-loaded gold nanoparticles to diabetic Wistar rats, which effectively controlled the blood glucose level [193]. Deng and coworkers fabricated insulin-loaded SeNPs through an ionic cross-linking/in situ reduction, which exhibited good stability in the digestive fluids and controllable insulin release, thereby causing a comparable decrease in glycemic levels relative to subcutaneous insulin injection in both normal and diabetic rats [194]. Similarly, titanium dioxide [195], mesoporous silica [196], and zirconium phosphate [197] nanoparticles have been used to deliver proteins orally and have shown the ability to effectively prevent the degradation of proteins in the GI tract.

In addition to the aforementioned biochemical barriers to oral protein delivery, insulin must also pass through the mucus layer, a hydrogel-like layer mainly composed of mucins lining the GI tract, and cross another formidable physical barrier formed by intestinal epithelial cells between the intestinal lumen and blood flow before entering the bloodstream [198]. Endothelial cell tight junctiosn lock the cell-cell interface, preventing paracellular transport of most ions and large molecules, including insulin, which may lead to the sharply decreased bioavailability of protein drugs.

To break through these barriers, several nanoscale drug delivery systems have been designed. One reasonable approach is to extend the residence time of drugs in the gut through mucoadhesion, so as to increase the probability of drugs entering the bloodstream [199]. For example, the use of polymer micelles might prevent unwanted drug release in the acidic conditions of the stomach while also promoting mucoadhesion and increasing the gut residence time to enhance the bioavailability [200,201]. Durrer and coworkers found that the mucoadhesion of poly(styrene) latex nanoparticles showed enough adsorption to serve as drug carriers for enhanced oral administration [202,203]. In addition to mucosal adsorption, some engineered nano-formulations can interact with specific receptors on intestinal epithelial cells through the use of targeting molecules [204,205]. Since bioadhesion is receptor-mediated, it is not restricted to mere binding, but may subsequently trigger the active transport of large molecules or nanoscale drug carrier systems by vesicular transport processes (endo-/transcytosis). For instance, Pridgen and coworkers developed drug-encapsulated nanoparticles by modifying the IgG Fc (NP-Fc) on the surface, which is capable of targeting FcRn that is expressed throughout the intestine for and enhanced nanoparticle absorption through the intestinal epithelium after oral administration. Using a mouse model, they demonstrated that FcRn enabled the NP-Fc to cross the intestinal epithelium and reach systemic circulation. This targeted ability of NP-Fc to FcRn improved absorption efficiency at least 11.5-fold compared to non-targeted NPs. More importantly, the targeted nanoparticles loaded with insulin as a model nanoparticle-based therapy for diabetes were orally administered at a clinically relevant insulin dose of 1.1 U kg^{-1} and elicited a prolonged hypoglycemic response in wild-

type mice. This effect was abolished in FcRn knockout mice, indicating that the enhanced nanoparticle transport was specifically due to FcRn [206]. It is also feasible to combine drug delivery systems with permeation enhancers to facilitate transepithelial transport [207]. Whitehead and coworkers found that anionic nanoparticles can induce the relaxation of tight junction, increasing intestinal permeability and enabling the oral delivery of proteins. They loaded insulin and exenatide on negatively charged silica nanoparticles as oral nano-formulations, which possess permeation-enhancing ability attributable to integrin binding on the surface of epithelial cells. As a result of the hypoglycemic effect, in healthy mice, the duration of oral administration of 10 U kg^{-1} insulin to maintain hypoglycemia was several hours longer than that of subcutaneous injection of 1 U kg^{-1} insulin. In addition, the oral delivery of 10 U kg^{-1} insulin led to a dose-adjusted bioactivity of 35%, 29%, and 23% of the subcutaneous injection of 1 U kg^{-1} insulin in healthy, hyperglycemic, and diabetic mice, respectively [208]. Li and coworkers encapsulated insulin inside a nanoemulsion containing the permeation enhancer C10 glyceride, which showed the ability to open tight junctions between intestinal epithelial cells reversibly to increase the trans-epithelial permeability of insulin via paracellular transport [209]. In addition to the aforementioned approaches for approving the absorption of nanomaterials, recently, Cao and coworkers reported a micelle platform featuring a virus-mimetic zwitterionic surface, a betaine side chain, and an ultralow critical micelle concentration, which promotes the drug penetration through the mucus and efficient transporter-mediated epithelial absorption without the need for tight junction opening. This micellar platform was used to fabricate a prototype oral insulin formulation by encapsulating a freeze-dried powder of zwitterionic micelle insulin into an enteric-coated capsule. These biocompatible oral insulin formulations exhibited a high oral bioavailability of more than 40%, which offers a possibility to fine-tune insulin administration profiles and provide long-term safety, enabling the oral delivery of protein drugs (Fig. 5) [210].

Although these nanoscale oral administration strategies have shown promising bioavailability and effective penetration enhancement necessary to address the clinical need, the potential systemic toxicity should be considered more carefully. In addition, more research, especially pharmacokinetic studies, is required in non-human primates to assess interspecies translatability and the potential for clinical use.

Cancer theranostics

As mentioned above, orally administered formulations possess many merits, such as easy acceptance and convenience for patients. With respect to cancer, compared with intravenous injection, oral administration of chemotherapeutic agents offers additional advantages, including the potential elimination of the pain and log duration of intravenous infusions [211,212]. However, due to the properties of clinical chemotherapy drugs and contrast agents (including toxicity and metabolic behavior) as well as the complicated physical and chemical barriers in the gastrointestinal tract, the majority of anti-cancer agents are given by intravenous administration and only a small number of them are currently provided to patients as oral formulations [213].

Orally administered nanotherapeutics have also shown the potential to serve as general diagnostics for cancer. For example, Li and coworkers developed a nano-based oral formulation for breast cancer detection. They prepared highly bright and long afterglow Cr^{3+}-doped $ZnGa_2O_4$ (ZGC) nanoparticles, which can be activated repetitively by 657 nm LED light for deep tissue penetration and long-term bioimaging. The surface c(RGDyK) peptide and the radioisotope ^{99m}Tc endow these nanomaterials with great targeting properties and afterglow luminescence/SPECT/CT dual-modality imaging of orthotopic breast cancer after oral administration. Importantly, the lattice fringes presented by nanoparticles found in feces and urine demonstrated their in vivo stability, thus minimizing their potential side effect [214]. Nanosystems can also be used as drug carriers to realize the oral delivery of chemotherapy drugs [215,216]. For example, Lin and coworkers demonstrated that the nanosuspension of niclosamide (nano-NI) can effectively inhibit the growth of ovarian cancer cells. This suspension induced a metabolic shift to glycolysis at a concentration of less than 3 μM in vitro and suppressed tumor growth without obvious toxicity at an oral dose of 100 mg/kg in vivo. In a pharmacokinetic study, oral administration of nano-NI showed rapid absorption (reaching the maximum plasma concentration within 5 min) and improved bioavailability (the estimated bioavailability for oral nano-NI was 25%) [217]. In another study, Sung and coworkers proposed an oral drug delivery system that spontaneously initiates an effervescent reaction to form gas-bubble carriers, which concurrently deliver lipophilic paclitaxel (PTX) and hydrophilic gemcitabine (GEM) in the small intestine (Fig. 6). The bursting of the bubbles promotes the intestinal absorption of the drugs, in which the lipophilic PTX is initially absorbed through the intestinal lymphatic system and then enters systemic circulation, whereas the hydrophilic GEM is directly taken up into circulation, ultimately accumulating in pancreatic tumors. According to the PET imaging, the ^{18}F-FDG uptake in the group treated with oral drugs was considerably less than that in the other control groups, suggesting a markedly reduced metabolic activity of the tumor cells. This orally delivered formulation minimized toxic side effects and increased the bioavailability of PTX, which can enhance the suppression of tumor growth relative to the intravenous formulation [218].

In addition, immunotherapy through oral administration is also a possible strategy for treating cancer. In this approach, the natural function of the immune system is used to protect the patient and can be highly advantageous because of the immune system's potency, specificity, and memory [219]. Cancer vaccines, a recently developed class of immunotherapies, have also demonstrated promise for preventing tumor progression and stymieing cancer recurrence [92,143,220–226]. Due to the undesirable nature of injections, several needle-free oral nanovaccine delivery systems have been developed to cope with various diseases, including cancers. Compared with injectable nanovaccines, oral vaccines can produce both antigenic-specific systemic antibodies (IgG) in blood and mucosal antigen-specific (IgA) antibodies, resulting in a more comprehensive immune response [219,227]. Currently, nanoparticle formulations are being explored to develop stable oral vaccines. These formulations possess some degree of intrinsic adjuvant or immunostimulatory properties due to their larger sizes, have the ability to co-modify multiple antigenic epitopes, targeting ligands, or external adjuvants on a single carrier, and are expected to effectively deliver antigens to the desired area with the structural integrity, and promote these substances to synergistically induce an immune response. Huang and coworkers designed virus-like particles based on papillomavirus pseudoviruses encoding the truncated carcinoembryonic antigen (CEA) without NH_2-terminal signal peptide as an oral nanovaccine to induce intestinal mucosal and systemic CEA-specific CTL responses, which inhibited the growth of CEA^+ colorectal tumors [228]. Ge and coworkers encapsulated the melanoma-associated antigen (MAGE-1), heat shock protein (HSP70), and staphylococcal enterotoxins A (SEA) complex protein in a nanoemulsion using a magnetic ultrasound method to prepare the nanovaccine NE (MHS), which can fiercely elicit the cellular immune responses against melanoma associated antigen (MAGE-1), thus delaying the growth of B16-MAGE-1 tumors in mice and prevent tumor recurrence as well [229]. Similarly, Tan constructed alginic acid-coated chitosan nanoparticles (A.C.NPs) as oral delivery carriers for a legumain DNA vaccine to protect against breast cancer. This oral DNA

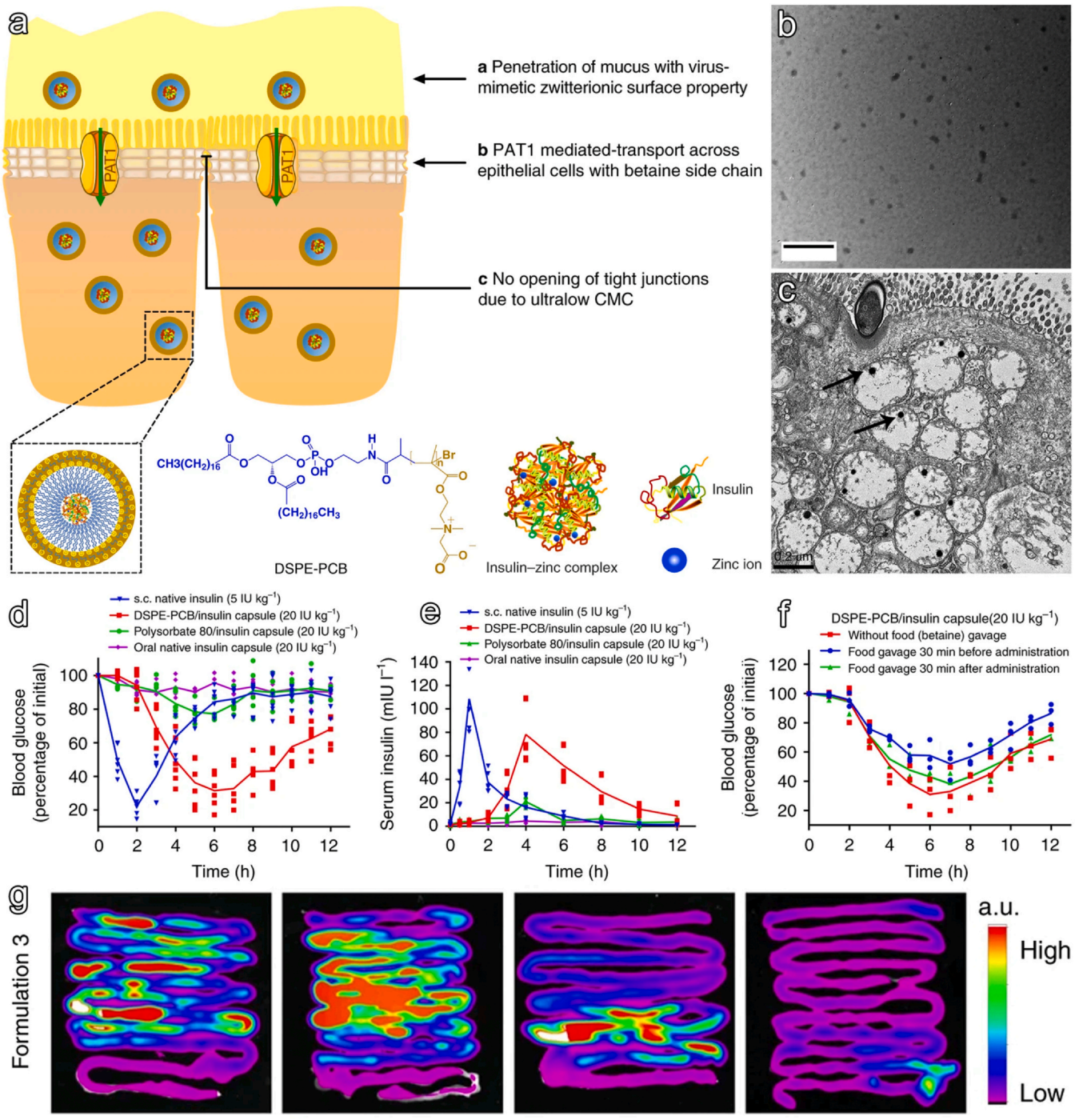


Fig. 5. (a) Schematic representation of DSPE-PCB micelles for oral delivery of insulin. (b) Representative TEM image of DSPE-PCB/insulin formulation. (c) Representative TEM image of epithelial tissues collected 1 h after the ileum injection of DSPE-PCB/gold nanoparticles. Scale bar, 0.2 μm. (d) Blood glucose-lowering (pharmacological) performance of the DSPE-PCB/insulin capsule on diabetic rats through oral gavage. (e) Serum insulin concentration (bioavailability) for the DSPE-PCB/insulin capsule on diabetic rats through oral gavage, compared with that of the Polysorbate 80/insulin capsule and native insulin capsule at the same dose of 20 IU/ kg^{-1}. s.c. injected native insulin at 5 IU kg^{-1} was used as a control. (f) Food effect on the glucose-lowing efficacy of the DSPE-PCB/insulin capsule. (g) Absorption sites and kinetics of orally delivered insulin. Reproduced with permission [210]. Copyright 2020, Nature Publishing Group.

vaccine demonstrated the ability to prevent DNA degradation in acidic environments and suppress tumor growth through activation of CTL to prolong survival time in a mouse model of orthotopic breast cancer [230]. More recently, Miao and coworkers developed nanoscale biomimetically mineralized Al-based MOFs that can be used to preserve a protein antigen as protective armor at ambient temperature, and function both as an antigen delivery vehicle in highly degradative GI environments and an adjuvant to promote immune reactions. Furthermore, to overcome mucosal barriers, a yeast-derived capsule is used to carry the Al-MOF-armored antigen as a "Trojan Horse"-like transport platform to target intestinal M cells and convey them through the main gateway of the mucosal epithelium, inducing potent and long-lasting immunity, suggesting the strong potential of this approach for oral vaccination [189].

These preclinical studies have demonstrated the prospects of oral nanovaccine for tumor immunotherapy. Despite all this, oral nanovaccines still have their shortcomings. In comparison with injected vaccines, oral administration requires more numerous and larger

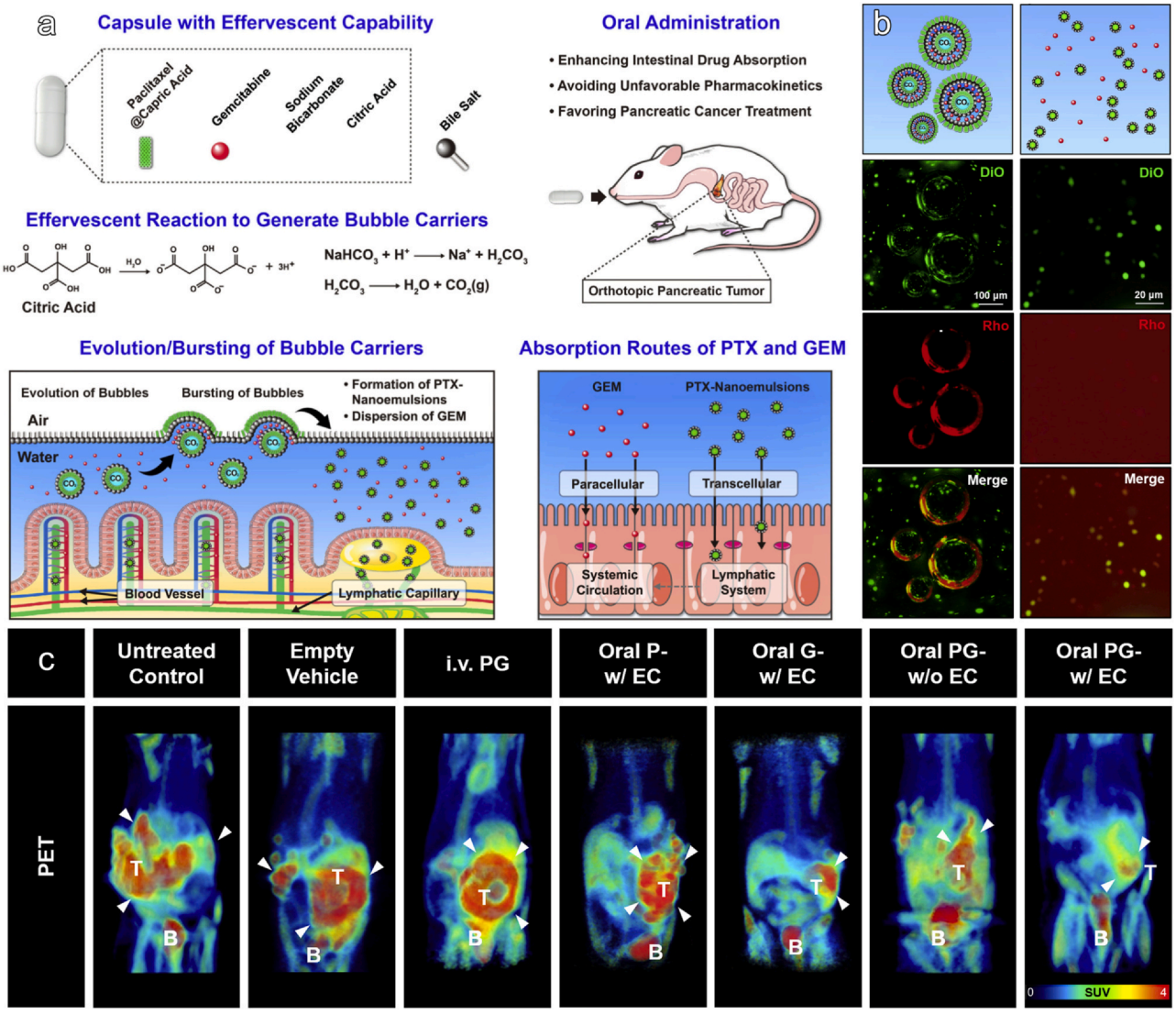


Fig. 6. (a) Compounds in an enteric-coated capsule and mechanisms by which they spontaneously initiate effervescent reaction to generate gas-bubble carriers that enable concurrent delivery of PTX and GEM in the small intestine and their routes of absorption following continuous bursting of bubbles. (b) Schematics and corresponding fluorescence microscopic photomicrographs of the evolution of CO_2 bubble carriers and their transformation to DiO-encapsulated nanoemulsions and dispersion of Rho in SIF. (c) Antitumor efficacy of each treatment modality revealed by PET imaging. Reproduced with permission [218]. Copyright 2020, Elsevier.

doses to achieve a potent and long-lasting immunogenic effect [231], which could cause oral tolerance [232]. Furthermore, due to the complexity of the gastrointestinal environment, it is difficult to quantify the actual degree of the immune response at different mucosal sites following oral administration.

Locoregionally administered nanoparticles as theranostics

One potential limitation of oral and systemic administration is the inadequate therapeutic concentration at the target site. Even with the aforementioned nano-delivery systems containing targeting molecules, the local concentration in the desired area remains limited by the level of receptor expression of the cells within lesions and the specificity of interactions [233,234]. These restrictions can be overcome by locoregional administration, in which the theranostic agents can be directly delivered to target sites after the locations of lesions are identified [6,12,235,236]. In addition, locoregional administration is an attractive approach for reducing potential systemic toxicity caused by non-specific uptake by organs [12,237–239]. Under this route of administration, nano-drug delivery systems show considerable promise not only because they can control the kinetics of drug release to meet the long-term drug demand of chronic diseases, but also because they combine multiple treatment modalities to achieve multi-pathway therapeutics, which could enable them to overcome the inherent biological complexity of a variety of diseases [12,240–244].

Implantation for long-term diseases treatment

Systemic delivery of nanodrugs through intravenous injection is able to transport drugs throughout the body. However, even for nanodrug systems with targeting moieties, this administration route does not avoid some level of nonspecific distribution, which may consequently result in damage to vital organs, such as the liver, kidneys, and spleen, causing long-term complications and systemic toxicity [245,246]. In addition, drugs delivered through the circulation can also be limited in their ability to target sites that are relatively nonvascularized or blocked by additional biological barriers, such as bone and joint diseases or brain diseases isolated by blood-brain barrier [247,248]. For these diseases, the implantation of drug delivery depots locally at the target site offers a promising approach to ensure the concentration of drug in the desired area [12].

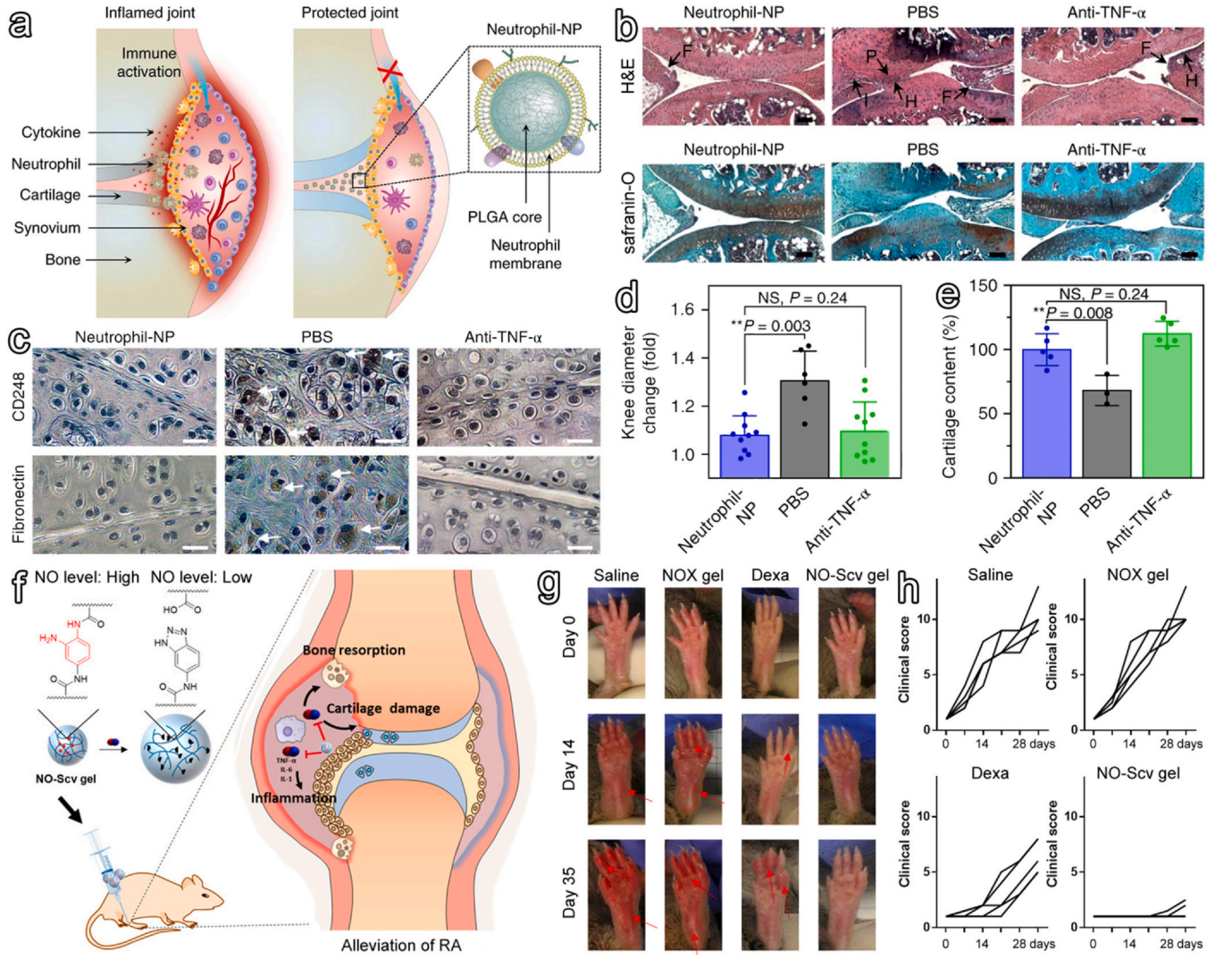


Fig. 7. (a) Schematic illustration of neutrophil-NPs for suppressing synovial inflammation and ameliorating joint destruction in inflammatory arthritis. Neutrophil-NPs are constructed by wrapping polymeric cores in natural human neutrophil membranes, which mimic source cells to bind with immunoregulatory molecules without potentiating the immune cascades for disease progression. (b) Images of H&E staining and safranin-O staining on knee sections from mice treated with neutrophil-NPs, PBS, or anti-TNF-α antibody. (c) Images of immunohistochemical staining for CD248 and fibronectin on knee sections from mice treated in different groups. (d) Change of hind knee diameter on day 70 compared to that on day 0. (e) Cartilage content was quantified from safranin-O-stained sections of mice treated in different groups. Reproduced with permission [264]. Copyright 2018, Nature Publishing Group. (f) Mechanism of NO-induced inflammatory effect in RA and alleviation of RA by NO-Scv gel. NO directly damages cartilage, upregulates osteoclasts inducing deformation of bone, and further aggravates the inflammation along with proinflammatory cytokines. (g) Images of paws and (h) clinical score of RA model mice treated with different samples until day 35. Reproduced with permission [265]. Copyright 2019, American Chemical Society.

Locoregionally implanted nanosystems may be most beneficial if they remain at the target site for a prolonged period of time and exhibit controlled release over that period, which can improve efficacy while decreasing side effects [12]. For example, surgically implanting biodegradable polyphosphoester microspheres that demonstrate the controlled release of paclitaxel (Paclimer) can safely bypass the blood-brain barrier and locally release paclitaxel for up to 90 days in brain tumors, which extends survival in a rodent model of glioma with minimal morbidity and optimal pharmacokinetics [249]. This Paclimer-based delivery of paclitaxel was subsequently shown to be safe for intraparenchymal delivery at the tested doses in normal dogs [250]. In another study, Nance and coworkers demonstrate that paclitaxel (PTX)-loaded, poly(lactic-co-glycolic acid) (PLGA)-co-PEG block copolymer nanoparticles with an average diameter of 70 nm can effectively penetrate the brain tumor parenchyma and significantly delay tumor growth following local administration to the gliosarcomas bearing Fischer rats, suggesting that the employment of drug-loaded brain penetrating nanoparticles is a promising approach to achieve sustained and more uniform drug delivery to treat aggressive gliomas and potentially other brain disorders [251].

In addition to brain tumors, the accessibility of the prostate due to its anatomical location makes it a potential candidate for locoregional nanodrug delivery with a minimally invasive procedure [252]. For example, in one study, radioactive ^{103}Pd:Pd@^{198}Au:Au-PEG nanoparticles were injected intratumorally in a mice model of prostate cancer. After 4 weeks of treatment, tumor volume was 75% lower compared with the control group [253]. In another study, the pharmacokinetic behavior of drugs administered intravenously and into the prostate was compared using a beagle dog model. This study showed that the drug plasma concentration in the group received intraprostatic infusions of drug was only 4% of the plasma concentration delivered by intravenous injection of the same dose of doxorubicin, suggesting that the systemic exposure by intraprostatic route is comparatively low, which is hopeful to largely avoid the nonspecific delivery of the drugs to the healthy tissue [254]. Due to the reduced toxicity of locoregionally delivered anti-cancer drugs, these nanotherapeutics have attracted more attention and are

currently being studied in preclinical and clinical trials. In a murine model of colon cancer with liver metastases, galactosylated liposomes loaded with doxorubicin administered locoregionally through the spleen showed higher hepatic deposition than when they were administered tail vein injection, displaying a corresponding significant decrease of tumor progression in the liver and mesenteric lymph nodes [255]. In addition to maintaining high local concentrations, nanodrug delivery systems can combine multiple therapeutic effects to overcome the tolerance of cancer cells to monotherapy. For example, Liu's group designed a NIR-triggered in situ hybrid hydrogel system consisting ^{131}I-labeled copper sulfide (CuS/^{131}I) nanoparticles as the photothermal-/radiotherapeutic agents, poly(ethylene glycol) double acrylates (PEGDA) as a polymeric matrix, and the 2, 2′-azobis[2-(2-imidazolin-2-yl)propane] dihydrochloride (AIPH) as the thermal initiator. After locoregional administration of the precursor solution into tumors, photoacoustic imaging was employed to track the intra-tumor diffusion of CuS/^{131}I NPs. Under the monitoring of photoacoustic imaging, the tumor was exposed to 915 nm NIR laser at the most suitable time after administration, which could induce photothermal heating of CuS/^{131}I NPs and a mild increase in tumor temperature to activate the AIPH and initiate the polymerization of PEGDA. With in situ gelation, CuS/^{131}I NPs are then fixed within the tumor for a long time without significant leakage into normal organs. Meanwhile, photothermal heating could also result in effective relief of tumor hypoxia by promoting tumor blood flow, providing an excellent synergistic treatment response to eliminate tumors with photothermal-brachytherapy [256].

Apart from cancer treatments, local administration can also be used for orthopedic diseases [257]. Rheumatoid arthritis (RA) is a common chronic inflammatory disorder, the exact cause of which still remains elusive [258,259]. Thus the current treatment of this disease mainly aims to alleviate inflammation [260]. Intervention with small molecule drugs or biological agents via local administration (intra-articular injection) is one of the main approaches used in conservative treatment, which puts the drugs precisely in the arthritic area to eliminate inflammation to slow disease progression [261,262]. Through this administration route, multifunctional nanosystems can not only optimize the pharmacokinetics such as the longer half-life and higher residence time in the local area, but also boost the pharmacodynamics profile through simultaneously participating in or regulating a variety of biochemical reactions occurred in the inflammatory region such as downregulating the expression of inflammatory cytokines and improving oxidation protection, therefore realizing better efficacy of RA [263]. The Zhang group showed a nanoparticle-based broad-spectrum anti-inflammatory strategy for RA treatment administered via intra-articular administration. By fusing neutrophil membranes onto polymeric cores, the membrane-coated nanoparticles neutralized proinflammatory cytokines, suppressed synovial inflammation, targeted deep into the cartilage matrix, and provided strong chondroprotection against joint damage. In a mouse model of collagen-induced arthritis and a human transgenic mouse model of arthritis, the neutrophil membrane-coated nanoparticles yielded significant therapeutic improvement by ameliorating joint damage and suppressing overall arthritis severity (Fig. 7**a-e**) [264]. Similarly, Kim and coworkers developed an innovative NO-scavenging nanogel (NO-Scv gel) as a therapeutic material for treating RA, which has been shown to effectively consume NO by its NO-cleavable moieties in vitro to reduce the inflammatory effects caused by activated macrophages (Fig. 7**f-h**). Importantly, the most promising therapeutic effect of the NO-Scv gel is in its ability to suppress the onset of RA in vivo in a mouse model when compared to the effects of commercial drug dexamethasone through intra-articular administration [265]. In addition, Yan and coworkers developed a nano-system with the advantages of both efficient lubrication and favorable drug release behavior, which not only protected the chondrocytes from oxidative stress-induced degeneration, but also provided prevented the development of osteoarthritis based on a rat destabilization of the medial meniscus (DMM) model [266]. More recently, Zheng and coworkers proposed a new strategy based on nanofibers made of poly (ε-caprolactone) (PCL) and a PCL-grafted lignin (PCL-g-lignin) copolymer for the treatment of osteoarthritis in which lignin offers intrinsic antioxidant activity and PCL tailors the mechanical properties. After arthroscopic implantation of nanofibrous membranes of PCL-lignin, the membranes effectively inhibited ROS generation and activated antioxidant enzymes through an autophagic mechanism [267].

In addition to arthritis, pneumonia can be treated through a similar localized approach. Tu and coworkers used N-fumaroylated diketopiperazine (FDKP) as a carrier to prepare azithromycin (AZM)-loaded effervescent inhalable microparticles (AZM@FDKP-E-MPs), which achieved deep lung deposition, helped evade pulmonary phagocytosis, and enhanced the antibacterial efficacy of AZM. This antibiotic delivery route significantly reduced the dose and frequency of administration needed to achieve a similar therapeutic effect by providing a higher local therapeutic efficacy rather than through conventional systemic administration, which potentially minimized the possibility of antibiotic resistance development [268].

Overall, locally administered nano-based drug depots is a feasible approach, which can effectively ensure the local concentration of the drug and reduce the risk of systemic exposure as well compared with intravenous administration [12]. Different from the low-molecular-weight drugs with high diffusion rates in tissues, nanosystems can readily realize long-term retention in the local area and controlled drug release for prolonging the duration of favorable local drug concentrations, which is very significant for delaying the progression of chronic diseases. In particular, nanosystems can be designed to integrate multiple functions, such as releasing diversified drugs at the same time or simultaneously participating in a variety of biochemical reactions. The synergy brought by such design can undoubtedly produce a more significant curative effect in local treatment. Despite these merits, this administered route is still limited to situations in which the target location is well-defined in advance and easily accessible.

Immunomodulation for cancer immunotherapy

As mentioned in Section 3.3, cancer immunotherapies have attracted considerable attention and been effective in some patients in the clinic. However, it may be a double-edged sword: drugs that activate the immune system may also cause severe nonspecific systemic inflammation and autoimmune side effects, resulting in significant weight loss, systemic cytokine storms, and even lethality from systemic immunotoxicity [269]. The oral administration of nanovaccines (mentioned in Section 3.3) may be able to reduce toxicity to mitigate immunotoxicity, which reduces the possibility of systemic side effects. Another simple approach is the direct local administration of immunomodulatory drugs [270].

For oral administered immunomodulatory drugs, due to the insufficient interaction between antigens and cells of the adaptive immune system, many orally and intravenously administered vaccine are limited by an inadequate immune response [271]. In contrast, locally administered vaccines that directly deliver the antigens and adjuvants in immune cell-rich areas can overcome these limitations. Different from traditional local implant chemotherapy drugs depots, the local immune response after locoregional administration can provide systemic protection to other sites that did not directly receive any drug, which is a key clinical advantage of local immunotherapy for treating both primary and metastatic disease [96,272,273].

Antigen-presenting cells (APCs) are a class of immune cells that are responsible for ingesting antigens and presenting them to T lymphocytes, which plays a key role in both innate and adaptive immunity [274,275]. Based on this property, *ex vivo* artificially engineered APCs pulsed with tumor-specific neoantigens have been employed as vaccines to specifically present the tumor-associated antigens to T cells in patient's body, and activate their immune system to fight against tumors [276,277]. Despite the success of autologous APC production to date, engineers continue to develop approaches that can improve the yield and function of cultured APCs [275]. In this regard, nanoparticle-antigen complexes with strong immunogenicity can be more efficiently engulfed by APCs and subsequently induce their maturity, in which nanomaterials with large specific areas and high loading capacities have been used as carriers to transport antigen cargos to the desired area [97]. Dendritic cells (DCs) are one of the most powerful antigen-presenting cells, which can not only capture the antigens and present them to T lymphocytes, but also secrete various cytokines to promote the activation of T cells and B cells simultaneously. However, the DCs and T lymphocytes in tumor-draining lymph nodes are often immunosuppressed by cancer cells. Therefore, local administration of nano-based engineering DCs to tumor-draining lymph nodes can significantly increase the anti-tumor immune response of the body. Liu's group loaded ovalbumin (OVA) on UCNPs, which can be efficiently engulfed by DCs to label them and induce DCs maturation and cytokine release to construct a DC-based vaccine. The in vivo homing behavior of this vaccine to draining lymph nodes after intradermal injection at the right footpad was observed through upconversion luminescence (UCL) imaging. Importantly, the strong antigen-specific immune responses including enhanced T cell proliferation, interferon gamma (IFN-γ) production, and cytotoxic T lymphocyte (CTL)-mediated responses induced by nanoparticle-pulsed DC vaccine, suggesting promise for DC-based immunotherapy against cancer [278]. Kim and coworkers introduced immunostimulatory adjuvants to nanoparticle-antigen complexes to construct a nanovaccine for the effective and simultaneous delivery of both antigen and adjuvant to DCs. Their *ex vivo* engineered DCs were then shown to induce a powerful T cell-mediated immune response and enhance antitumor immunity through injecting subcutaneously into the footpad [279].

The results of preclinical researches have shown that it is feasible to activate T cells in the body by employing the artificially modified APCs *ex vivo* [280]. However, the quality and activity of extracted APCs are limited by the patient's physical condition. Moreover, manufacturing APC-based vaccines is an expensive and cumbersome procedure and also elicits robust regulatory scrutiny, which may pose additional obstacles to their development [281]. For example, Sipuleucel-T (Provenge; Dendreon), the first autologous APC-based therapeutic cancer vaccine approved by FDA in 2010, can indeed prolong the survival of patients with advanced prostate cancer [282], however, due to the high price and unsatisfied efficacy, the market performance of Sipuleucel-T fails to meet expectations, which eventually led to the bankruptcy of Dendreon. To overcome the challenges, acellular approaches, in which the chemosynthetic immunomodulators are directly injected into the body to induce the maturity of APCs in vivo, have been developed to complement vaccine-based tumor immunotherapies, and may even be therapeutically superior. This approach can not only avoid the complicated process of APC extraction and *ex vivo* culture, but also make it feasible to do large-scale synthesis. Compared with engineered APC vaccines, the main challenge of acellular vaccines are the decreased efficacy at inducing APC maturation in vivo. Thus, the locoregional administration of acellular vaccines in APC-rich area is often employed. However, even with this improved route, the conventional immunostimulants with small molecular size and amphiphilic characteristics still diffuse quickly with no enough time to activate the DCs, therefore various nano-based formulations have been developed to promote better local retention of immunotherapeutics and block their passive diffusion into the circulation [223,224,283,284]. Nanoscale vaccines are expected to stay in the desired site for a long time period due to their size and surface modification, which not only ensures a high local drug concentration, but also extends interaction time between agents and DCs, subsequently eliciting stronger immune response. Yang and coworkers constructed a nanovaccine formulation by coating adjuvant NPs with mannose-modified tumor cell membranes for cancer immunotherapy. Specifically, PLGA nanoparticles were loaded with R837, an agonist against toll-like receptor 7 (TLR 7), and then encapsulated with membranes from B16-OVA cancer cells, which is further modified with mannose to target DCs. As a result, the nanovaccine showed enhanced DC uptake and achieved a stronger stimulatory effect to trigger DC maturation. Upon intradermal injection, the nanovacccine was shown to migrate to draining lymph nodes and trigger tumor-specific immune responses, acting as an effective prophylactic vaccine to delay tumor development [285]. Li and coworkers have developed a novel class of magnetosomes through coating TLR agonist CpG-ODN and Fe_3O_4 nanoparticles with anti-CD205 mAb-modified cancer cell membranes. The Fe_3O_4 nanoparticles enabled magnetic retention of the magnetosomes in the lymph nodes as detected by MRI, which increased the time window for antigen uptake by DCs. Moreover, the cancer cell membrane provided various cancer-specific neoantigens for a subsequent multi-antigenic response. In addition, the anti-CD205 mAb was shown to promote the uptake of $CD8^+$ DCs, thus facilitating MHC I cross-presentation [286].

In addition, the tumor-specific immune response triggered by localized nanovaccines has the potential to be combined with immune checkpoint blockade (ICB) therapy to not only a significant abscopal effect to attack whole-body spreading metastatic cancer cells, but also result in immune memory to inhibit tumor recurrence [287,288]. Liu group designed an in situ formed alginate (ALG)-based hydrogel to trap radioisotope ^{131}I-labeled catalase (Cat) along with immune adjuvant (CpG) (^{131}I-Cat/CpG/ALG). After intratumoral injection, ^{131}I-Cat/ CpG/ALG not only relieved hypoxia in the tumor by decomposing the tumor endogenous H_2O_2 to promote the radiotherapy of tumor, but also triggered a strong systemic anti-tumor immune response after local radiotherapy. This anti-tumor responses were further amplified after anti-CTLA-4 treatment, significantly inhibiting the tumor metastasis and recurrence [289].

In addition to peri-tumor or peri-tumor draining lymph node administration, another application of nano-based local immunotherapy is for the treatment of lung tumors. Zhao and coworkers reported an inhalable nanoparticle immunotherapy targeting pulmonary APCs to enhance anti-cancer immunity against lung metastases (Fig. 8). Inhalation of phosphatidylserine-coated liposomes loaded with the STimulator of INterferon Genes (STING) agonist cyclic guanosine monophosphate–adenosine monophosphate (NP-cGAMP) can rapidly distribute to both lungs and subsequently be taken up by APCs without causing immunopathology in mouse models of lung metastases. This process can enhance cytosolic release of cGAMP to stimulate STING signaling and type I interferons production by APCs, resulting in the pro-inflammatory tumor microenvironment in multifocal lung metastases [290]. More recently, in another work, Perry and coworkers utilized PRINT (particle replication in nonwetting templates) nanoparticles as a vehicle to deliver CpG into murine lungs through orotracheal inhalation for treating metastatic lung cancer through immunotherapy. In two murine orthotopic metastasis models of non-small-cell lung cancer-344SQ (lung adenocarcinoma) and KAL-LN2E1 (lung squamous carcinoma), local delivery of PRINT-CpG into the lungs promoted substantial tumor regression and mitigated the systemic toxicity that is typically associated with soluble CpG. After

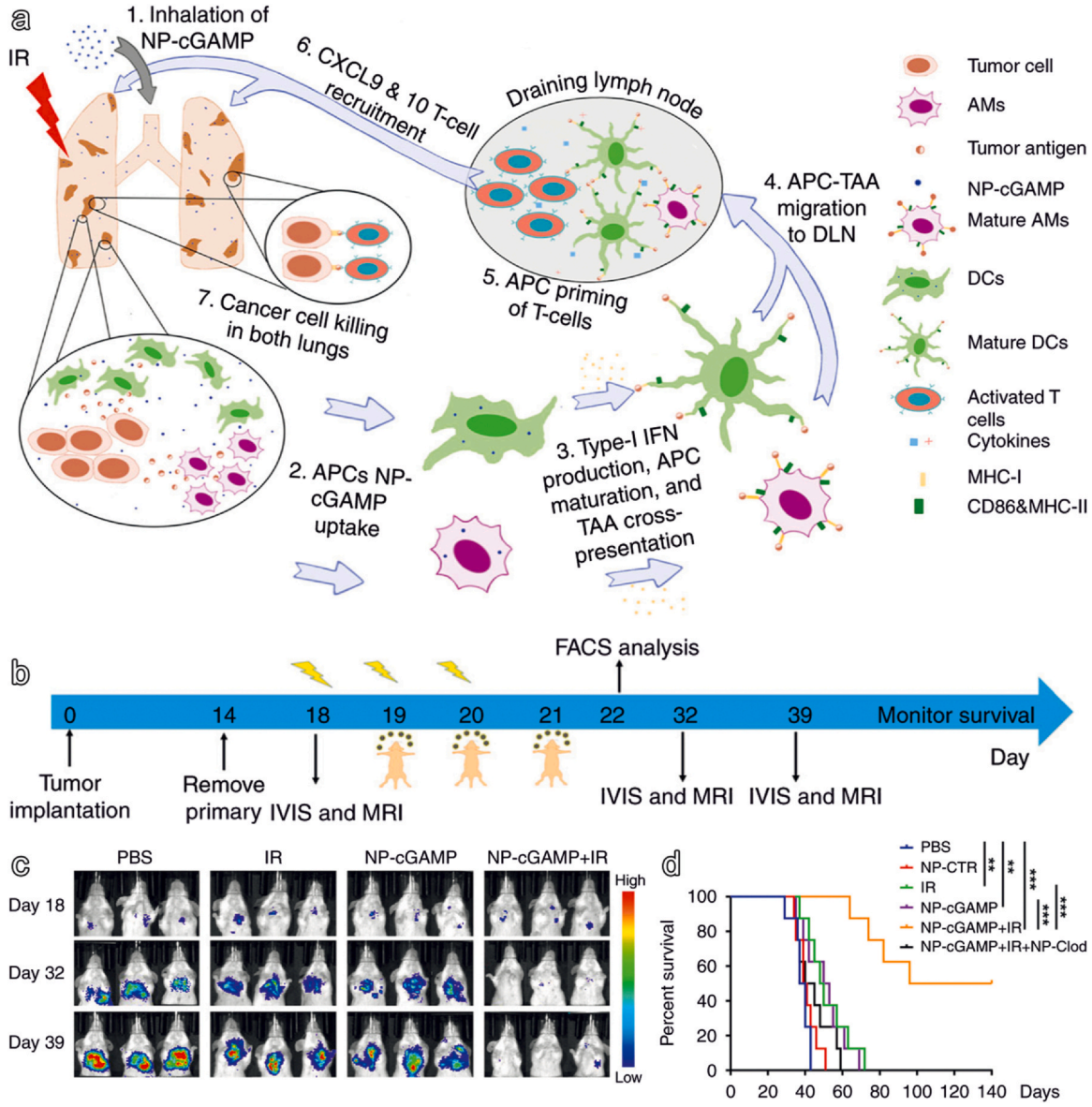


Fig. 8. (a) Schematic of the action of the inhalable NP-cGAMP for enhancing antitumor immunity against lung metastases. (b) Procedures of tumor model establishment, treatment, and imaging process. (c) IVIS images of three representative animals from each treatment group. (d) Kaplan–Meier survival curves of the treatment groups up to 140 days after tumor were plotted and statistically analyzed by log-rank test. Reproduced with permission [290]. Copyright 2019, Nature Publishing Group.

treatment, the cured mice were also resistant to tumor rechallenge. Importantly, these nanoparticles showed extended retention of CpG within the lungs, thereby prolonging the elevation of proinflammatory cytokines within the lungs without a corresponding—and potentially harmful—systemic increase, which highlights the enhanced safety of local immunotherapy [291].

The strong performance of current pre-clinical studies using locally administered nanovaccines provides motivation for further advancing nano-based immunotherapies for human cancer treatment [98]. However, the local administration of nanoimmune agents does not completely limit their systemic exposure and subsequent toxicity [270]. Although lymph node follicles are able to capture and retain antigens to induce germinal centers and long-lived humoral immunity, this control over antigen retention has been limited. The extended release of immunotherapeutics from nanomaterial matrices confers vastly superior safety and efficacy relative to administration of the same small molecular compounds in solution, but these immunomodulatory agents still have the possibility of directly entering the systemic circulation via lymphatic drainage. Chen discovered that antigen conjugated to nanoparticle carriers of different sizes impacts the intralymph node transport and specific cell interaction. As a result, the smaller nanomaterials (5 −15 nm) will be eliminated by follicular dendritic cell (FDC) networks within 48 h whereas a majority of larger particles (50 −100 nm) will be retained for at least 5 weeks [292]. In addition, nanomaterials may also leak into the bloodstream through the incomplete blood vessel in the tumor site after in situ injection [35]. Similarly, studies have shown that during long-term interstitial retention of nanoparticles in the lung, nanoparticles can translocate across the air–blood barrier, leading to persistent retention in secondary organs and tissues in the ranking order liver > soft issue > spleen > kidneys > skeleton > blood > uterus > heart > brain, which may pose potential safety risks [293,294]. Therefore, while local administration is a well-characterized strategy that can alter the pharmacokinetics of drug treatments, this simple approach does not fully isolate immunotherapies from the systemic circulation. Combining this administration route with the advantage in larger and surface-modified nanomaterials may provide a better approach that can

make full use of the abscopal-like effects of immunotherapies while mitigating systemic toxicity.

Microneedle mediated transdermal delivery

Transdermal drug delivery is a useful alternative drug administration route compared to oral administration because it avoids degradation in the GI tract and first-pass metabolism through the hepatic portal vein system, thereby lowering the risk of off-target accumulation and systemic toxicity [295–297].

Piercing the stratum corneum by physical means to reach physiological fluid is one of the main approaches being studied to deliver nanomaterials. However, conventional subcutaneous injection with needles or syringes is associated with pain and transdermal administration often causes more intense pain than intravenous administration due to an abundance of nerve endings in the epidermis, which scares many patients.

To overcome this limitation, microneedle (MN) technologies have been developed by academic laboratories and pharmaceutical companies and are rapidly emerging as a minimally invasive approach for transdermal sensing, sampling, and molecule delivery [295,296,298–305]. The microscale sharp needles with appropriate length can pierce the stratum corneum while avoiding nerves or damaging dermal blood vessels, resulting in painless access to dermal layers. The tiny and shallow wounds resulting from the MNs can heal on the order of minutes to hours. Over the last decade, MNs have been extensively applied to transdermal delivery of therapeutic compounds (e.g., insulin, proteins, DNA, vaccines, and cells) and transdermal diagnostic applications [295,306,307].

MN technology can be perfectly integrated with nanotechnology to apply in medical fields [308]. In combination, nanomaterials can be successfully delivered to the dermis, so as to realize the detection and monitoring of a variety of physiological parameters, as well as the treatment of some specific diseases. Langer, Jaklenec, and coworkers developed dissolvable microneedles that deliver spatial distribution patterns of biocompatible, near-infrared quantum dots (NIR QDs) encapsulated in polymeric microparticles to the skin dermis (Fig. 9). These particle patterns from QDs, with a copper indium selenide core and aluminum-doped zinc sulfide shell, are invisible to the naked eye yet detectable using an inexpensive, modified smartphone. By co-delivering a vaccine, the patterns of particles in the skin could serve as an on-person medical record to encode key information, such as vaccination history. Benefiting from their greatest resistance to photobleaching, discrete microneedle-delivered QD patterns remained bright and could be accurately identified using a machine learning algorithm 9 months after they were administered intradermally to rats, while co-delivery of inactivated poliovirus led to protective antibody production. This invisible, intradermal “on-body” recordkeeping opens up new avenues for decentralized data storage and biosensing applications, which has great potential for clinical translation, and could enhance the distribution of medical care, especially in the developing world [309].

Stimuli-responsive nanomaterials can selectively respond to specific stimuli even in complicated physiological or pathological environments. Based on such properties, these responsive nanomaterials can serve as a drug carrier to fill or embed in microneedles to achieve both painless transdermal drug delivery and precisely controlled drug release [310,311]. The Gu group reported a novel glucose-responsive insulin delivery device to mimic the function of pancreatic cells by using a painless microneedle-array patch containing glucose-responsive nanovesicles GRVs, which were loaded with insulin and glucose oxidase (GOx) enzyme. The GRVs were self-assembled from hypoxia-sensitive hyaluronic acid (HS-HA) conjugated with 2-nitroimidazole (NI). In the hyperglycemic state, the glucose will be oxidized by enzymes, leading to a local hypoxic microenvironment, which will promote the reduction of HS-HA and rapidly trigger the dissociation of vesicles and subsequent insulin release. This smart insulin patch can effectively regulate the blood glucose in a mouse model of chemically induced type 1 diabetes [312]. Since the diffusion of glucose in MNs may limit the release of insulin, they subsequently described innovative MN-based glucose-signal amplifiers for smart insulin delivery. The MNs encapsulated synthetic glucose-responsive nanovesicles, which were used to amplify the glucose signals through sequential enzymatic reactions. The amplified glucose signal within the MN microenvironment was able to trigger insulin secretion from the pancreatic β-cell capsules positioned on the base of the patch [313]. Similarly, this technology can also be used to avoid the frequent and repeated administration of insulin, which can result in poor patient compliance, as previously mentioned. Chen and coworkers designed MN array patches loaded with a mineralized particle formula to deliver exendin-4 (Ex4) while avoiding the leakage of GOx for the long-term treatment of type 2 diabetes. Using diabetic C57BL/6 db/db mice as a model, they demonstrated that a crosslinked alginate patch loaded with 300 μg Ex4 could control the BG of mice for 5–6 days [314].

These results demonstrated the advantages of combining MNs and nanotechnology, which could potentially facilitate desirable nanoparticle deposition or permeation into deeper skin layers. By delivering nanoparticles in microneedles, they can diffuse within the skin, thus expanding their spatial treatment coverage. Benefiting from these properties, the combination of the nanoparticles and MNs drug delivery system has been also employed for superficial disease treatment. For example, Zhu and coworkers successfully fabricated composite-dissolving MN patches for treating superficial tumors with a combination of chemotherapy and PTT. DOX and indocyanine green (ICG) were encapsulated in the MNs, in which the PVP and mesoporous silica nanoparticles were used as stabilizers to ensure the chemotherapy and PTT efficiency of MN patches. Once applied at superficial tumor sites, DOX and ICG were quickly released by dissolution of the MN tips in the interstitial fluid. The combination of chemotherapy and PTT was activated under NIR irradiation to further enhance the benefit [315]. In another work, black phosphorus (BP)-loaded separable MNs were employed as responsive oxygen delivery carriers for wound healing. Specifically, MNs composed of a polyvinyl acetate (PVA) backing layer and gelatin methacryloyl (GelMA) tips were loaded with BP QDs and hemoglobin (Hb). After the MNs were applied to the wound, the PVA rapidly dissolved and the noncytotoxic, biocompatible GelMA tips were left inside the skin. After generating heat from BP QDs under irradiation from a near-infrared ray, the oxygen reversibly bound with Hb was released, thereby treating the full-thickness cutaneous wound [316].

Besides treating diabetes and superficial diseases, another attractive application of combining MN and nanoparticles technologies lies in the area of vaccine delivery. Microneedles were shown to not only improve the skin penetration of the vaccine, but also promote the interaction between the large network of resident APCs and antigen to induce an efficient immune response [317–319]. Quan and coworkers found that low-dose influenza virus-like particle (VLP) administered by microneedles were more immunogenic than the same dose intramuscular (IM) injection and similarly immunogenic as high-dose IM injection in a mouse model [320]. Gu and co-workers reported a self-degradable MN patch, which was loaded with ketal-modified dextran-based nanoparticles encapsulating anti-programmed cell death receptor 1 antibody (anti-PD-1) and glucose oxidases (GOx) for cancer. After topical application of MNs, the encapsulated GOx converted glucose into gluconic acid, which induced dissociation of dextran and release of anti-PD-1 mAb in the metastatic melanoma. Importantly, the infiltration of $CD8^+$ T cells in the metastatic tumor was enhanced as well as their activity, which inhibited the formation of tumor metastasis [99].

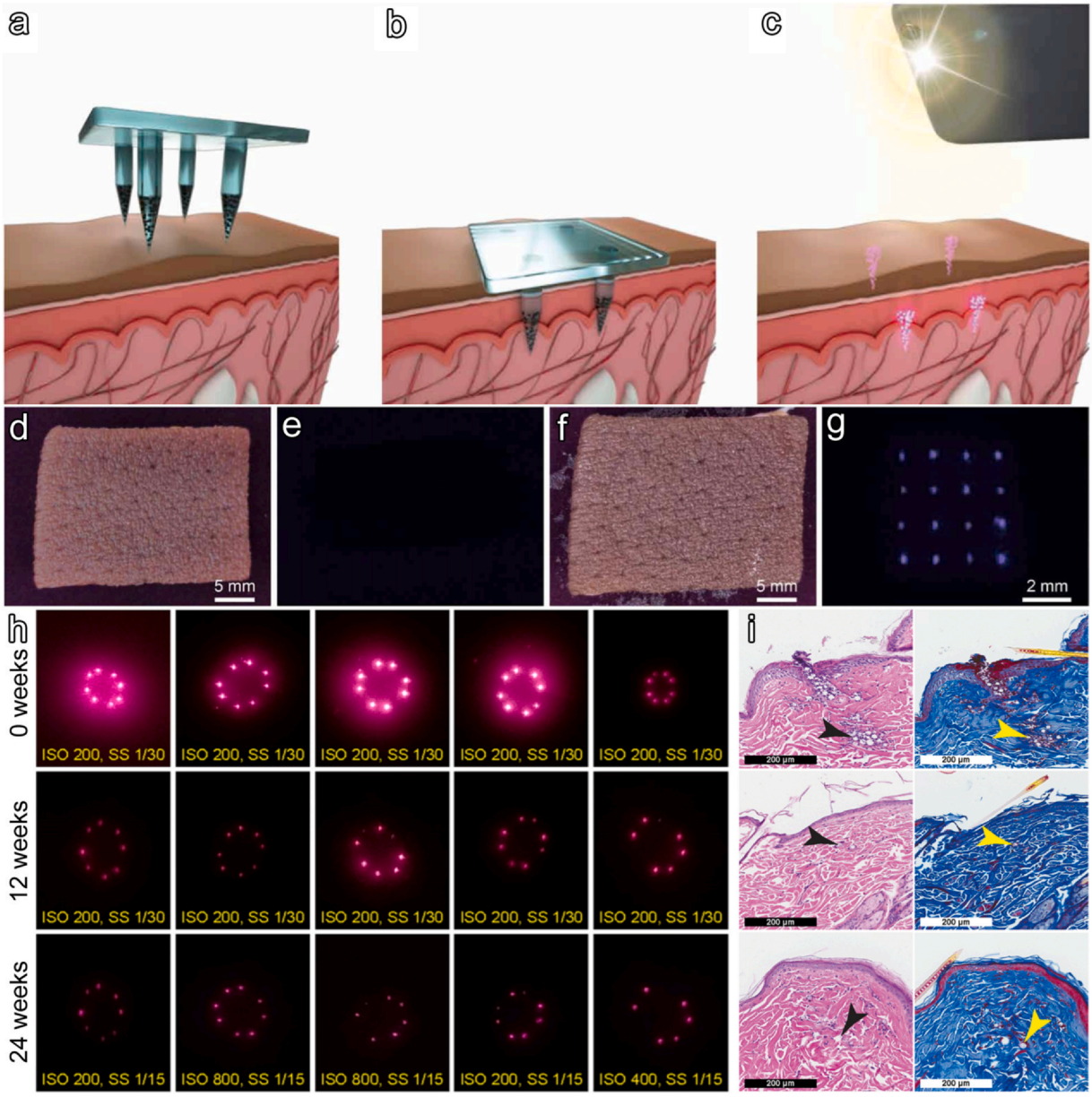


Fig. 9. (a) Fluorescent microparticles are distributed through an array of dissolvable microneedles in a distinct spatial pattern. (b) Microneedles are applied to the skin for 2–5 min, resulting in the dissolution of the microneedle matrix and retention of fluorescent microparticles. (c) A NIR LED and adapted smartphone are used to image patterns of fluorescent microparticles retained within the skin. By selectively embedding microparticles within microneedles used to deliver a vaccine, the resulting pattern of fluorescence detected in the skin can be used as an on-patient record of an individual's vaccination history. Adapted smartphone images of pigmented human skin before microneedle application (d) without and (e) with the 850-nm long-pass filters. Smartphone images of human skin after application (f) without and (g) with the 850-nm long-pass filters. (h) Cropped, but otherwise raw, smartphone images collected from a fixed distance showing the intradermal NIR signal from PMMA-encapsulated QDs delivered via microneedle patches on rats 0, 12, and 24 weeks after administration. (i) Representative histological samples collected from rats receiving microneedle-delivered PMMA particles containing QDs (top) 1 day, (medium) 2 weeks, and (bottom) 4 weeks after administration stained with hematoxylin and eosin or Masson's trichrome, respectively. Arrows indicate the location of microparticles. Reproduced with permission [309]. Copyright 2019, American Association for the Advancement of Science.

Moreover, the combination of MNs and targeted nanoparticles can provide an alternative route to deliver drugs to specific cells or tissues. This specific targeting of immune cells that lie in the dermis has been shown to enhance the immune response. For example, Huang and coworkers using CPP-PEI1800-Man nanoparticles delivered by microneedles as a Trp-2 DNA vaccine delivery system for cancer immunotherapy. This epidermal DC-targeting DNA vaccine delivery system successfully elicited both protective and therapeutic immune responses. The mechanism of antitumor activity was likely based on the recruitment of $CD4^+$ and $CD8^+$ T cells and the induction of IFN-γ and IL-12 cytokine production [321].

Overall, MNs combined with nanotechnology is promising for clinical transdermal drug delivery because of their substantial advantages over conventional injection and tremendous success in preclinical studies. Nevertheless, some issues should be considered carefully. First, due to the potential risk of infections and irritation of the skin, it is necessary to ensure the healing behavior of the skin after MNs application, especially for the MNs systems served as long-term administration tools. Second, skin permeability and painlessness should be balanced. If longer needles are used, the nanomaterials or drug formulations can be delivered at a deeper level, but also increase the possibility to stimulate pain receptors

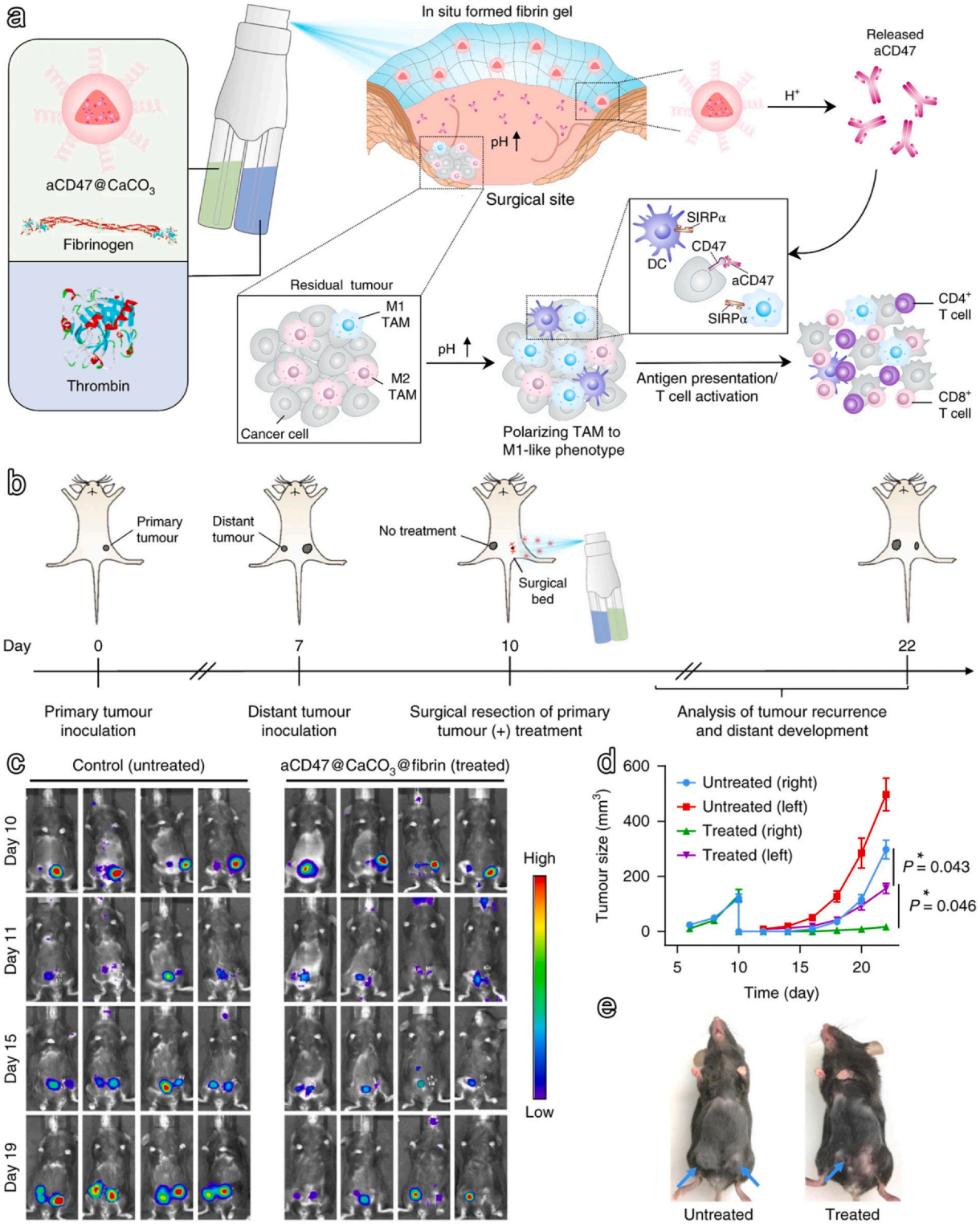


Fig. 10. (a) Schematic showing the in situ sprayed bioresponsive fibrin gel containing aCD47@$CaCO_3$ nanoparticles within the post-surgery tumor bed. aCD47@$CaCO_3$ nanoparticles encapsulated in fibrin scavenge H^+ in the surgical wound site and release aCD47, thus promoting both polarization of TAMs to an M1-like phenotype and blockade of the 'don't eat me' signal in cancer cells. (b) Schematic illustrating aCD47@$CaCO_3$ @fibrin therapy in a mouse model of incomplete tumor resection and distant tumor. Tumors on the right side were designated as 'primary tumors' with aCD47@$CaCO_3$ @fibrin treatment, and those on the left side were designated as 'distant tumors' without any treatment. (c) In vivo bioluminescence imaging of B16F10 tumors in response to local aCD47@$CaCO_3$ @fibrin treatment. Images associated with day 10 were taken before surgery. Experiments were repeated three times. (d) Growth curves for left and right tumors in untreated and treated mice. (e) Mice photographs at day 22. Reproduced with permission [338]. Copyright 2019, Nature Publishing Group.

located in the dermis. In spite of these limitations, the MN technology offers substantial potential synergy with nanomaterials with strong potential for clinical translation.

Daubing and spraying on the surface of skin or wounds

Due to various irritants such as microbes, pollutants, radiation, or other environmental insults, skin diseases, including acne, allergic dermatitis, eczema, fungal infection, are quite common [322,323]. Topical drugs that are applied externally through daubing or spraying administration are among the most common type in our daily lives. It is generally accepted that topical administration on the skin surface has fewer and generally less severe side effects than other administration routes [324]. Therefore, although the in vivo biosafety of nanotherapeutics is worrying in the aforementioned administration routes, such concerns might be minimized if used externally, which has motivated work in this area [324,325]. However, the stratum corneum of the skin prevents most of the macromolecules from entering, only small molecules (< 600 Da) can freely penetrate the skin [300]. To address this issue, the adjustment of the physicochemical properties of nano-formulations such as size, surface charge, and hydrophilicity/hydrophobicity, can significantly promote transport across the skin [326]. For example, several nanoparticle-based treatments have already been approved by FDA, such as Estrasorb (micellar nanoparticles) for topical menopause therapy. Besides, due to the lipids and lipoproteins that exist beneath the stratum corneum, lipophilic nanomedicines can be employed as a topical drug carrier. These are currently being developed and seem very promising for clinical use [327]. Recent investigations have revealed that omega 3 fatty acids can be delivered by means of nanocarriers like nanoemulsion to treat psoriasis via topical administration. These studies also showed that targeted nanopharmaceuticals can provide stability against oxidation and improve the absorption of omega 3 fatty acids in the skin [328].

Apart from being simply administered to the surface of normal skin, some nano-formulations are also designed to be applied to cover wounds and accelerate the healing process. Impaired wound healing is a major complication of several disease processes, such as diabetes. These wounds are hampered by a wide variety of processes including hypoxia, inflammation, infection, and disruption by ROS [329]. Owing to the complexity of the wound bed, the efficacy of conventional therapies that only target single parameters is limited, especially when attempting to promote the closure of slow-healing wounds [330]. Nanomaterials can target specific cells to affect the physiological processes involved in wound healing and repair wounds through the integration of multiple pathways, resulting in rapid and effective recovery [331]. Annabi and coworkers developed an adhesive hydrogel for the local delivery of microRNAs (miR-223 *) encapsulated in hyaluronic acid (HA)-based nanoparticles. The hydrogel precursor can be readily delivered to wounds and photocrosslinked in situ under visible light. HA-based NPs loaded with miR-223 * were able to efficiently induce the polarization of M1 macrophages toward the anti-inflammatory M2 state, thus driving wound healing by triggering the resolution of the inflammatory phase and promoting the formation of new vascularized skin [332]. In a separate study, Zhou showed that several derivatives can help cell migration, induce wound closure in human skin explants, and greatly accelerate wound healing in vivo, which has the potential to be employed as a wound healing formulation [333]. More recently, Yan and coworkers reported a sprayable in situ forming hydrogel composed of a copolymer of PEP and Ag@rGO nanosheets to respond to skin temperature, which can irreversibly crosslink on the wound to form a stable dressing. This sprayable hydrogel is conducive to the careful treatment of patients with large burns, as well as deep penetration into sharp wound gaps to completely seal the wound, leading to suture-less repair and the promotion of healing. Further, this hydrogel also exhibited antibacterial properties and the ability to prevent infection by methicillin-resistant Staphylococcus aureus (MRSA) in vitro and in vivo, which is highly attractive for clinical use [334]. In addition to promoting the healing of chronic wounds, externally applied nanomaterials can also be employed to treat surgical wounds. Taguchi designed an advanced sprayable wound dressing consisting of multifunctional hydrophobized microparticles (hMPs) for accelerated wound healing treatment after endoscopic submucosal dissection (ESD), which successfully suppressed fibrosis and accelerated wound healing in swine gastric ESD models [335].

As mentioned in Section 2.1, the complete surgical removal of a solid tumor is exceptionally challenging even if using IGS technology to identify the tumor margin. Although some additional treatments such as chemotherapy and immunotherapy have been employed in combination with postoperative treatment, tumor recurrence after resection is still a frequent problem. The residual tumor cells at the carcinoma boundary or single cells that escaped the local tumor can lead to regrowth at local or distant sites; therefore, new approaches are needed to detect and destroy these cells [336]. Cha and coworkers proposed a sprayable adhesive nanoparticle-based drug delivery system using a bioengineered mussel adhesive protein (MAP) for effective locoregional cancer therapy. After spraying on the excised wound of the tumor, DOX loaded in MAP NPs was released in cancer cells due to the acidic tumor microenvironment, which significantly inhibited tumor growth in vivo [337]. In another work, Gu and co-workers reported a sprayed bioresponsive immunotherapeutic fibrin gel that has been engineered to not only promote wound healing by creating a temporary shield to connect and protect injured tissue, but also inhibit local tumor recurrence and the development of distant tumors following surgery (Fig. 10). The fibrinogen solution containing anti-CD47 antibody-loaded $CaCO_3$ nanoparticles (aCD47 @$CaCO_3$) and thrombin solution can be quickly sprayed and mixed within the tumor resection cavity after surgery to form an immunotherapeutic fibrin gel in situ. In the acidic and inflamed microenvironment, $CaCO_3$ nanoparticles can gradually dissolve and release the encapsulated aCD47, promoting the activation of M1-type TAMs, and inducing macrophage phagocytosis of cancer cells via blockade of the CD47 and SIRPα interaction as well as boosting anti-tumor T cell responses. The authors also suggest that this convenient sprayable administration method can avoid the toxic effects that the systemic administration of aCD47 can elicit, which further highlights the low toxicity and ease of application that make topically administered nanodrugs enticing for clinical use [338]. More recently, Wang and coworkers developed a nanomedicine-assembled hydrogel for post-surgical tumor treatment. The thermoresponsive, curcumin-loaded polymer nanoparticles contained within a hydrogel enabled the complete coverage of the surgical bed of primary tumor and the spatiotemporal delivery of cognate nanomedicines and encapsulated nanovaccines. This nanomedicine efficiently induced the ICD of residual cancer cells and enhanced the tumor immunogenicity via the formation of tumor neoantigen-specific T cells. This study provided a nanomedicine-based approach for post-surgical tumor immunotherapy through in situ administration [339]. Similarly, Tao found that exfoliated Ge nanosheets (NSs) exhibited a high drug-loading capacity and multi-responsive drug release, which can be triggered by pH or light exposure from a NIR laser for multimodal imaging-guided treatment. By combining these nanomaterials with a hydrogel, the developed drug-loaded Ge@hydrogel can be coated on the postoperative wound after tumor resection. With the help of NIR irradiation, the generated local hyperthermia induces drug release to eliminate residual tumor cells and kill the surrounding bacteria, while the hydrogel served as a therapeutic reservoir for long-term both antitumor and antibacterial effects [340].

These works reflect the advantages of external nanodrugs in medical applications. To ensure the desired efficacy and low side

effects in clinical translation, larger animal models and larger amounts of validation results are required, which will also help to further determine the precise modalities of applications.

Conclusions and future perspectives

The careful selection of nanoparticle properties and administration route is critical to developing theranostic probes that can diagnose diseases and provide therapeutic effects in a manner that is clinically relevant. When designed appropriately, these nanoparticles can increase the accumulation in the target disease site and then be excreted from the body owing to their small size, paving the way for more sensitive detection that accelerates disease detection and improves treatment efficacy. However, despite major advances in theranostic probes, their clinical use remains hindered by potential toxicity concerns due to off-target effects in healthy tissues/organs. To fully realize the potential of these theranostic nanomaterials and bridge the gap between potential and actual clinical-grade performance, additional improvements are necessary.

Intravenously administered nanoparticles may be recognized by the immune system and are largely captured by the RES, e.g., liver and spleen, potentially leading to long-term retention in the body and chronic toxicity, raising concerns for clinical translation. Currently, our understanding of the metabolism pathways by which theranostic nanoparticles are processed remains very limited. In principle, it is generally easier to monitor the biodistribution of nanoparticles with the elements that are absent in the body, yet these materials may themselves cause adverse effects. Alternatively, elements naturally found in the human diet remain challenging to accurately trace their fate within the body due to the existence of background signal. To battle this problem, several strategies may hold promise; (1) reduce the size to enable their quick renal clearance and slow down RES uptake during circulation; (2) construct responsive nanosystems that provide their theranostic function as a result of small particles assembling within tumors in response to stimuli but then degrade into small pieces to promote elimination; (3) develop biodegradable nanoparticles to reduce the retention and suppress chronic exposure risk.

Orally delivered nanoprobes have experienced the most clinical success thus far, with an FDA-approved contrast agent. This is due, in large part, to the reduced requirements necessary for their safe and effective use. Particles that remain in the GI tract are cleared with normal digestion, thereby avoiding potential toxicity in the kidneys or liver. The GI tract is also far more tolerant to materials and may enable the safe dosing of materials that exhibit poor biocompatibility when injected. However, inconsistent GI passage time and variable environmental pH that can vary between individuals and also within an individual based on food status can make consistent targeting and diagnosis more difficult. Alternatively, when nanoprobes are designed to penetrate the intestinal epithelium rather than just release drug or serve as a contrast agent, they must meet the same stringent biocompatibility and clearance requirements as nanoprobes injected intravenously.

Locoregional delivery is another potentially attractive route of administration for some diseases. By providing a localized depot in the vicinity of the target, the on-target diagnostic signal or therapeutic effect can be concentrated and acute off-target effects can be mitigated. This administration route could also be valuable to achieve nanoprobe localization in regions that are not well-vascularized (e.g., cartilage), for which intravenous delivery would not be very efficient. Ultimately, however, the combination of locoregional administration and targeted nanoprobes may have limited applications. Since the particles are administered to the site of their target already, engineered targeting moieties may be unnecessary. Instead, this type of delivery method may be best suited for nanoprobes engineered to non-invasively characterize a site or release a therapeutic.

In addition to addressing biosafety concerns, imaging sensitivity and treatment efficacy must also be considered. For example, creating formulations that exhibit rapid renal clearance may lead to an insufficient blood circulation time for targeting the disease and thus limit their imaging and/or treatment performance. Therefore, multiple factors including particle size, renal clearance rate, and practical performance need to be properly characterized and balanced to meet the needs of a particular application, especially for intravenously administered nanoparticles. One promising approach is to construct multimodal nanoparticles, where the advantages of different modalities can be integrated to improve diagnostic sensitivity and accuracy.

There is a huge reservoir of literature describing functional materials that use NIR light for biomedical applications, including nanomaterials with built-in functions that combine NIR light-based diagnostic and therapeutic technologies. In this respect, nanotheranostic technologies enable the non-invasive, accurate identification of disease location and real-time monitoring of subsequent therapeutic effects. This combination of properties is appealing for many applications, although systemic toxicity, inferior bioavailability, insufficient targeting specificity, and unsatisfied diagnostic/therapeutic efficacy vary by disease. In the future, nanomaterial performance and safety will need to be rationally optimized for the specific administration route of interest to be clinically viable.

The clinical translation of the theranostic nanomaterials that offer superior properties to the current standard of care are warmly awaited by the clinic, yet very challenging to create in practice. Regardless of the administration route, the full array of effects that nanoparticles have on the body remains unknown and still needs to be determined with extensive safety studies. For example, the interaction of small nanoparticles and biomacromolecules such as serum proteins is related to their metabolic behavior and biological effects in vivo, but the mechanisms underlying this relationship remain unclear. Moreover, it also needs to be determined whether nanoparticles excreted through the kidney will temporarily burden the kidney or cause irreversible damage.

Another major challenge is the difficulty in comparing the theranostic performance and pharmacokinetic behaviors of the nanoprobes prepared by different research labs due to the large varieties of size, shape, surface composition, and other properties. Moreover, the choice of animal models also significantly affects the accumulation, theranostic performance, distribution, and clearance of nanomaterials in vivo. In fact, frequently used small animal models such as mice or rats may yield results that are ultimately not indicative of potential human clinical outcomes. However, the use of potentially more representative species introduces additional cost, feasibility, and perhaps even ethical concerns. As a result, it remains difficult to draw reliable conclusions about the effects of a single variable on the downstream performance for diagnostics, therapeutics, biodistribution, clearance pathway, etc.

Apart from that, the large-scale production of theranostic nanomaterials with highly reproducible physicochemical features that would be necessary for in vivo applications remains difficult. Because nanoparticles are synthesized in solution, the particle size is not only determined by synthetic parameters but also strongly affected by heat transduction and mass transduction of nuclei. All these aspects make the reproducibility and quality control of high-quality nanoprobes very challenging, especially at industrial production scales. In spite of the safety concerns and difficulties in large-scale production of multi-functional inorganic nanomaterials, disease diagnosis and treatment could realize their potential in the near future upon the development of advanced nanoprobes that exhibit low adverse effects and remarkable therapeutic performance.

In summary, it is clear that emerging nanotheranostics hold great promise for revolutionizing the diagnosis and treatment of many diseases. The ultimate goal of precision nanomedicine is to select a subset of patients with a common biological basis of disease who are most likely to benefit from a particular nanotheranostic. To accelerate progress towards this goal, it would be beneficial if the field agreed upon consensus experiments and models to enable the comparison of nanoprobes created by different groups. Specifically, it would be extremely beneficial if pharmacokinetic studies, toxicology studies, methods to ensure reproducibility during synthesis, and animal models were broadly agreed upon. Hopefully, with the development of advanced theranostic probes, precise biomarkers, new immunotherapeutic strategies, and more proper preclinical models, precision nanotheranostics will revolutionize future disease diagnosis and therapy.

CRediT authorship contribution statement

Peisen Zhang: Conceptualization, Investigation, Writing-Original Draft. **Yingying Li**: Investigation, Visulization, Writing-Original Draft. **Wen Tang**: Investigation, Visulization. **Jie Zhao**: Writing-Original Draft. **Lihong Jing**: Supervision, Conceptualization, Writing-Review & Editing, Funding acquisition. **Kevin McHugh**: Supervision, Writing-Review & Editing, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors thank the financial support from National Natural Science Foundation of China (NSFC) (22177115, 81671755, 81771902), the Youth Innovation Promotion Association CAS (2018042), National Key Research and Development Program of China (2018YFA0208800), State Key Laboratory of Luminescence and Applications (SKLA-2019–01), and Cancer Prevention & Research Institute of Texas (RR190056).

References

[1] J.K. Patra, G. Das, L.F. Fraceto, E.V.R. Campos, M.D.P. Rodriguez-Torres, L.S. Acosta-Torres, L.A. Diaz-Torres, R. Grillo, M.K. Swamy, S. Sharma, S. Habtemariam, H.S. Shin, Nano based drug delivery systems: recent developments and future prospects, J. Nanobiotechnology 16 (2018) 71.
[2] B. Fadeel, A.E. Garcia-Bennett, Better safe than sorry: understanding the toxicological properties of inorganic nanoparticles manufactured for biomedical applications, Adv. Drug Deliv. Rev. 62 (2010) 362–374.
[3] N. Gong, N.C. Sheppard, M.M. Billingsley, C.H. June, M.J. Mitchell, Nanomaterials for T-cell cancer immunotherapy, Nat. Nanotechnol. 16 (2021) 25–36.
[4] C. Zhang, L. Yan, X. Wang, S. Zhu, C. Chen, Z. Gu, Y. Zhao, Progress, challenges, and future of nanomedicine, Nano Today 35 (2020) 101008.
[5] H. Chen, Z. Gu, H. An, C. Chen, J. Chen, R. Cui, S. Chen, W. Chen, X. Chen, X. Chen, Z. Chen, B. Ding, Q. Dong, Q. Fan, T. Fu, D. Hou, Q. Jiang, H. Ke, X. Jiang, G. Liu, S. Li, T. Li, Z. Liu, G. Nie, M. Ovais, D. Pang, N. Qiu, Y. Shen, H. Tian, C. Wang, H. Wang, Z. Wang, H. Xu, J.-F. Xu, X. Yang, S. Zhu, X. Zheng, X. Zhang, Y. Zhao, W. Tan, X. Zhang, Y. Zhao, Precise nanomedicine for intelligent therapy of cancer, Sci. China Chem. 61 (2018) 1503–1552.
[6] T. Ji, D.S. Kohane, Nanoscale systems for local drug delivery, Nano Today 28 (2019) 100765.
[7] L. Rong, Q. Lei, X.Z. Zhang, Recent advances on peptide-based theranostic nanomaterials, View 1 (2020) 20200050.
[8] L.H. Jing, C. Yang, P. Zhang, J. Zeng, Z. Li, M. Gao, View 1 (2020) e19.
[9] Z.F. Li, C.Z. Di, S.P. Li, X.L. Yang, G.J. Nie, Smart nanotherapeutic targeting of tumor vasculature, Acc. Chem. Res. 52 (2019) 2703–2712.
[10] I. de Lazaro, D.J. Mooney, A nanoparticle's pathway into tumours, Nat. Mater. 19 (2020) 486–487.
[11] S. Pandit, D. Dutta, S.M. Nie, Active transcytosis and new opportunities for cancer nanomedicine, Nat. Mater. 19 (2020) 478–480.
[12] T. Ji, Y. Li, X. Deng, A.Y. Rwei, A. Offen, S. Hall, W. Zhang, C. Zhao, M. Mehta, D.S. Kohane, Delivery of local anaesthetics by a self-assembled supramolecular system mimicking their interactions with a sodium channel, Nat. Biomed. Eng. 5 (2021) 1099–1109.
[13] P. Abdou, Z.J. Wang, Q. Chen, A.M. Chan, D.J.R. Zhou, V. Gunadhi, Z. Gu, Advances in engineering local drug delivery systems for cancer immunotherapy, WIREs-Nanomed. Nanobiotech. 12 (2020) e1632.
[14] X. Han, H. Li, D. Zhou, Z. Chen, Z. Gu, Local and targeted delivery of immune checkpoint blockade therapeutics, Acc. Chem. Res. 53 (2020) 2521–2533.
[15] M.A. Dobrovolskaia, S.E. McNeil, Immunological properties of engineered nanomaterials, Nat. Nanotechnol. 2 (2007) 469–478.
[16] J.F. Jin, L.L. Zhu, M. Chen, H.M. Xu, H.F. Wang, X.Q. Feng, X.P. Zhu, Q. Zhou, The optimal choice of medication administration route regarding intravenous, intramuscular, and subcutaneous injection, Patient Prefer Adherence 9 (2015) 923–942.
[17] M. Auerbach, H. Ballard, Clinical use of intravenous iron: administration, efficacy, and safety, Hematology Am Soc Hematol Educ Program 2010 (2010) 338–347.
[18] M. Saha, Nanomedicine: promising tiny machine for the healthcare in future-a review, Oman Med J. 24 (2009) 242–247.
[19] J.K. Tee, L.X. Yip, E.S. Tan, S. Santitewagun, A. Prasath, P.C. Ke, H.K. Ho, D.T. Leong, Nanoparticles' interactions with vasculature in diseases, Chem. Soc. Rev. 48 (2019) 5381–5407.
[20] B. Sumer, J. Gao, Theranostic nanomedicine for cancer, Nanomed. (Lond.) 3 (2008) 137–140.
[21] R. Qiao, R. Zhu, M. Gao, Imaging tumor metastases with molecular probes, Curr. Pharm. Des. 21 (2015) 6260–6264.
[22] T. Ji, J. Lang, J. Wang, R. Cai, Y. Zhang, F. Qi, L. Zhang, X. Zhao, W. Wu, J. Hao, Z. Qin, Y. Zhao, G. Nie, Designing liposomes to suppress extracellular matrix expression to enhance drug penetration and pancreatic tumor therapy, ACS Nano 11 (2017) 8668–8678.
[23] T. Ji, Y. Zhao, Y. Ding, J. Wang, R. Zhao, J. Lang, H. Qin, X. Liu, J. Shi, N. Tao, Z. Qin, G. Nie, Y. Zhao, Transformable peptide nanocarriers for expeditious drug release and effective cancer therapy via cancer-associated fibroblast activation, Angew. Chem. Int. Ed. 55 (2016) 1050–1055.
[24] Y. Barenholz, Doxil®–the first FDA-approved nano-drug: lessons learned, J. Control Release 160 (2012) 117–134.
[25] D. Bobo, K.J. Robinson, J. Islam, K.J. Thurecht, S.R. Corrie, Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date, Pharm. Res. 33 (2016) 2373–2387.
[26] B. Fadeel, L. Farcal, B. Hardy, S. Vazquez-Campos, D. Hristozov, A. Marcomini, I. Lynch, E. Valsami-Jones, H. Alenius, K. Savolainen, Advanced tools for the safety assessment of nanomaterials, Nat. Nanotechnol. 13 (2018) 537–543.
[27] F. Peng, M.I. Setyawati, J.K. Tee, X. Ding, J. Wang, M.E. Nga, H.K. Ho, D.T. Leong, Nanoparticles promote in vivo breast cancer cell intravasation and extravasation by inducing endothelial leakiness, Nat. Nanotechnol. 14 (2019) 279–286.
[28] H. Wang, W. Su, M. Tan, Endogenous fluorescence carbon dots derived from food items, The Innovation 1 (2020) 100009.
[29] G. Sonavane, K. Tomoda, K. Makino, Biodistribution of colloidal gold nanoparticles after intravenous administration: effect of particle size, Colloids Surf. B Biointerfaces 66 (2008) 274–280.
[30] W.H. De Jong, W.I. Hagens, P. Krystek, M.C. Burger, A.J.A.M. Sips, R.E. Geertsma, Particle size-dependent organ distribution of gold nanoparticles after intravenous administration, Biomaterials 29 (2008) 1912–1919.
[31] R. Cai, C. Chen, The crown and the scepter: roles of the protein corona in nanomedicine, Adv. Mater. 31 (2019) e1805740.
[32] S. Liu, Y. Han, R. Qiao, J. Zeng, Q. Jia, Y. Wang, M. Gao, Investigations on the interactions between plasma proteins and magnetic iron oxide nanoparticles with different surface modifications, J. Phys. Chem. C. 114 (2010) 21270–21276.
[33] D. Docter, S. Strieth, D. Westmeier, O. Hayden, M. Gao, S.K. Knauer, R.H. Stauber, No king without a crown–impact of the nanomaterial-protein corona on nanobiomedicine, Nanomedicine 10 (2015) 503–519.
[34] K. Bourzac, News feature: cancer nanomedicine, reengineered, Proc. Natl. Acad. Sci. U. S. A. 113 (2016) 12600–12603.
[35] S. Sindhwani, A.M. Syed, J. Ngai, B.R. Kingston, L. Maiorino, J. Rothschild, P. MacMillan, Y. Zhang, N.U. Rajesh, T. Hoang, J.L.Y. Wu, S. Wilhelm, A. Zilman, S. Gadde, A. Sulaiman, B. Ouyang, Z. Lin, L. Wang, M. Egeblad, W.C.W. Chan, The entry of nanoparticles into solid tumours, Nat. Mater. 19 (2020) 566–575.
[36] J. Zhang, Z. Di, H. Yan, Y. Zhao, L. Li, One-step synthesis of single-stranded DNA-bridged iron oxide supraparticles as MRI contrast agents, Nano Lett. 21 (2021) 2793–2799.
[37] W. Poon, Y.N. Zhang, B. Ouyang, B.R. Kingston, J.L.Y. Wu, S. Wilhelm, W.C.W. Chan, Elimination pathways of nanoparticles, ACS Nano 13 (2019) 5785–5798.
[38] P. Grodzinski, M. Kircher, M. Goldberg, A. Gabizon, Integrating nanotechnology into cancer care, ACS Nano 13 (2019) 7370–7376.
[39] K. Greish, A. Mathur, M. Bakhiet, S. Taurin, Nanomedicine: is it lost in translation? Ther. Deliv. 9 (2018) 269–285.
[40] M. Bjornmalm, K.J. Thurecht, M. Michael, A.M. Scott, F. Caruso, Bridging bio-nano science and cancer nanomedicine, ACS Nano 11 (2017) 9594–9613.
[41] H. Kobayashi, R. Watanabe, P.L. Choyke, The processing of faces across non-rigid facial transformation develops at 7 month of age: a fNIRS-adaptation study, Theranostics 4 (2014) 81–89.
[42] S. Taurin, H. Nehoff, K. Greish, Anticancer nanomedicine and tumor vascular permeability; where is the missing link? J. Control Release 164 (2012) 265–275.
[43] F. Danhier, To exploit the tumor microenvironment: since the EPR effect fails in the clinic, what is the future of nanomedicine, J. Control Release 244 (2016) 108–121.

[44] H. Maeda, Macromolecular therapeutics in cancer treatment: the EPR effect and beyond, J. Control Release 164 (2012) 138–144.
[45] P. Speiser, Progress in colloid & polymer science, Progr. Colloid Polym. Sci. 59 (1976) 48–54.
[46] J.J. Marty, R.C. Oppenheim, S. P, Nanoparticles–a new colloidal drug delivery system, Pharm. Acta Helv. 53 (1978) 17–23.
[47] P. Couvreur, B. Kante, V. Lenaerts, V. Scailteur, M. Roland, P. Speiser, Tissue distribution of antitumor drugs associated with polyalkylcyanoacrylate nanoparticles, J. Pharm. Sci. 69 (1980) 199–202.
[48] G. Gregoriadis, Drug entrapment in liposomes, Febs. Lett. 36 (1973) 292–296.
[49] P. Couvreur, Polyalkylcyanoacrylates as colloidal drug carriers, Crit. Rev. Ther. Drug 5 (1988) 1–20.
[50] N. Chiannilkulchai, Z. Driouich, J.P. Benoit, A.L. Parodi, P. Couvreur, Doxorubicin-loaded nanoparticles: increased efficiency in murine hepatic metastases, Sel. Cancer Ther. 5 (1989) 1–11.
[51] L.X. Tiefenauer, G. Kuhne, R.Y. Andres, Antibody-magnetite nanoparticles: in vitro characterization of a potential tumor-specific contrast agent for magnetic resonance imaging, Bioconjug Chem. 4 (1993) 347–352.
[52] R. Weissleder, Molecular imaging: exploring the next frontier, Radiology 212 (1999) 609–614.
[53] F. Hu, Y. Ran, Z. Zhou, M. Gao, Preparation of bioconjugates of CdTe nanocrystals for cancer marker detection, Nanotechnology 17 (2006) 2972–2977.
[54] Z. Li, L. Wei, M.Y. Gao, H. Lei, A particle track-repeating algorithm for proton beam dose calculation, Adv. Mater. 17 (2005) 1001–1005.
[55] F.Q. Hu, L. Wei, Z. Zhou, Y.L. Ran, Z. Li, M.Y. Gao, Preparation of biocompatible magnetite nanocrystals for in vivo magnetic resonance detection of cancer, Adv. Mater. 18 (2006) 2553–2556.
[56] Y. Hou, R. Qiao, F. Fang, X. Wang, C. Dong, K. Liu, C. Liu, Z. Liu, H. Lei, F. Wang, M. Gao, NaGdF4 nanoparticle-based molecular probes for magnetic resonance imaging of intraperitoneal tumor xenografts in vivo, ACS Nano 7 (2013) 330–338.
[57] C. Liu, Y. Qi, R. Qiao, Y. Hou, K. Chan, Z. Li, J. Huang, L.H. Jing, J. Du, M. Gao, Detection of early primary colorectal cancer with upconversion luminescent NP-based molecular probes, Nanoscale 8 (2016) 12579–12587.
[58] Y. Li, P. Zhang, H. Ning, J. Zeng, Y. Hou, L.H. Jing, C. Liu, M. Gao, Emitting/sensitizing ions spatially separated lanthanide nanocrystals for visualizing tumors simultaneously through up- and down-conversion near-infrared II luminescence in vivo, Small 15 (2019) e1905344.
[59] D.W. Baker, J. Zhou, Y.T. Tsai, K.M. Patty, H. Weng, E.N. Tang, A. Nair, W.J. Hu, L. Tang, Development of optical probes for in vivo imaging of polarized macrophages during foreign body reactions, Acta Biomater. 10 (2014) 2945–2955.
[60] Y. Zhong, Z. Ma, F. Wang, X. Wang, Y. Yang, Y. Liu, X. Zhao, J. Li, H. Du, M. Zhang, Q. Cui, S. Zhu, Q. Sun, H. Wan, Y. Tian, Q. Liu, W. Wang, K.C. Garcia, H. Dai, In vivo molecular imaging for immunotherapy using ultra-bright near-infrared-IIb rare-earth nanoparticles, Nat. Biotechnol. 37 (2019) 1322–1331.
[61] F. Ren, L. Ding, H. Liu, Q. Huang, H. Zhang, L. Zhang, J. Zeng, Q. Sun, Z. Li, M. Gao, Ultra-small nanocluster mediated synthesis of Nd3+-doped core-shell nanocrystals with emission in the second near-infrared window for multimodal imaging of tumor vasculature, Biomaterials 175 (2018) 30–43.
[62] M. Li, H. Fang, Q. Liu, Y. Gai, L. Yuan, S. Wang, H. Li, Y. Hou, M. Gao, X. Lan, Red blood cell membrane-coated upconversion nanoparticles for pretargeted multimodality imaging of triple-negative breast cancer, Biomater. Sci. 8 (2020) 1802–1814.
[63] J. Ge, Q. Zhang, J. Zeng, Z. Gu, M. Gao, Radiolabeling nanomaterials for multimodality imaging: New insights into nuclear medicine and cancer diagnosis, Biomaterials 228 (2020) 119553.
[64] T.H. Shin, Y. Choi, S. Kim, J. Cheon, Recent advances in magnetic nanoparticle-based multi-modal imaging, Chem. Soc. Rev. 44 (2015) 4501–4516.
[65] S. Liu, B. Jia, R. Qiao, Z. Yang, Z. Yu, Z. Liu, K. Liu, J. Shi, H. Ouyang, F. Wang, M. Gao, A novel type of dual-modality molecular probe for MR and nuclear imaging of tumor: preparation, characterization and in vivo application, Mol. Pharm. 6 (2009) 1074–1082.
[66] C. Liu, Z. Gao, J. Zeng, Y. Hou, F. Fang, Y. Li, R. Qiao, L. Shen, H. Lei, W. Yang, M. Gao, Magnetic/upconversion fluorescent NaGdF4:Yb,Er nanoparticle-based dual-modal molecular probes for imaging tiny tumors in vivo, ACS Nano 7 (2013) 7227–7240.
[67] K. Ding, L.H. Jing, C. Liu, Y. Hou, M. Gao, Magnetically engineered Cd-free quantum dots as dual-modality probes for fluorescence/magnetic resonance imaging of tumors, Biomaterials 35 (2014) 1608–1617.
[68] L.H. Jing, K. Ding, S.V. Kershaw, I.M. Kempson, A.L. Rogach, M.Y. Gao, Magnetically engineered semiconductor quantum dots as multimodal imaging probes, Adv. Mater. 26 (2014) 6367–6386.
[69] H. Fang, M. Li, Q. Liu, Y. Gai, L. Yuan, S. Wang, X. Zhang, M. Ye, Y. Zhang, M. Gao, Y. Hou, X. Lan, Ultra-sensitive nanoprobe modified with tumor cell membrane for UCL/MRI/PET multimodality precise imaging of triple-negative breast cancer, Nano-Micro Lett. 12 (2020) 62.
[70] T. Ma, P. Zhang, Y. Hou, H. Ning, Z. Wang, J. Huang, M. Gao, "Smart" nanoprobes for visualization of tumor microenvironments, Adv. Healthc. Mater. 7 (2018) e1800391.
[71] Y. Lu, A.A. Aimetti, R. Langer, Z. Gu, Bioresponsive materials, Nat. Rev. Mater. 2 (2016) 16075.
[72] Y. Hou, J. Zhou, Z. Gao, X. Sun, C. Liu, D. Shangguan, W. Yang, M. Gao, Protease-activated ratiometric fluorescent probe for pH mapping of malignant tumors, ACS Nano 9 (2015) 3199–3205.
[73] T. Ma, Y. Hou, J. Zeng, C. Liu, P. Zhang, L.H. Jing, D. Shangguan, M. Gao, Dual-ratiometric target-triggered fluorescent probe for simultaneous quantitative visualization of tumor microenvironment protease activity and pH in Vivo, J. Am. Chem. Soc. 140 (2018) 211–218.
[74] Z. Fan, J. Zhao, X. Chai, L. Li, A cooperatively activatable, DNA-based fluorescent reporter for imaging of correlated enzymatic activities, Angew. Chem. Int. Ed. 60 (2021) 14887–14891.
[75] P. Zhang, J. Zeng, Y. Li, C. Yang, J. Meng, Y. Hou, M. Gao, Quantitative mapping of glutathione within intracranial tumors through interlocked MRI signals of a responsive nanoprobe, Angew. Chem. Int. Ed. 60 (2021) 8130–8138.
[76] R.K. Jain, T. Stylianopoulos, Delivering nanomedicine to solid tumors, Nat. Rev. Clin. Oncol. 7 (2010) 653–664.
[77] F. Tang, L. Li, D. Chen, Mesoporous silica nanoparticles: synthesis, biocompatibility and drug delivery, Adv. Mater. 24 (2012) 1504–1534.
[78] S.-Y. Wang, X.-X. Chen, Y. Li, Y.-Y. Zhang, Application of multimodality imaging fusion technology in diagnosis and treatment of malignant tumors under the precision medicine plan, Chin. Med. J. -Peking. 129 (2016) 2991–2997.
[79] S. Zhang, C. Sun, J. Zeng, Q. Sun, G. Wang, Y. Wang, Y. Wu, S. Dou, M. Gao, Z. Li, Ambient aqueous synthesis of ultrasmall PEGylated Cu2-x Se nanoparticles as a multifunctional theranostic agent for multimodal imaging guided photothermal therapy of cancer, Adv. Mater. 28 (2016) 8927–8936.
[80] X. Jiang, S. Zhang, F. Ren, L. Chen, J. Zeng, M. Zhu, Z. Cheng, M. Gao, Z. Li, Ultrasmall magnetic CuFeSe2 ternary nanocrystals for multimodal imaging guided photothermal therapy of cancer, ACS Nano 11 (2017) 5633–5645.
[81] F. Mao, L. Wen, C. Sun, S. Zhang, G. Wang, J. Zeng, Y. Wang, J. Ma, M. Gao, Z. Li, Ultrasmall biocompatible Bi2Se3 nanodots for multimodal imaging-guided synergistic radiophotothermal therapy against cancer, ACS Nano 10 (2016) 11145–11155.
[82] C. Chi, Y. Du, J. Ye, D. Kou, J. Qiu, J. Wang, J. Tian, X. Chen, Intraoperative imaging-guided cancer surgery: from current fluorescence molecular imaging methods to future multi-modality imaging technology, Theranostics 4 (2014) 1072–1084.
[83] K.J. McHugh, L.H. Jing, A.M. Behrens, S. Jayawardena, W. Tang, M.Y. Gao, R. Langer, A. Jaklenec, Biocompatible semiconductor quantum dots as cancer imaging agents, Adv. Mater. 30 (2018) 1706356.
[84] C. Li, Y. Zhang, M. Wang, Y. Zhang, G. Chen, L. Li, D. Wu, Q. Wang, In vivo real-time visualization of tissue blood flow and angiogenesis using Ag2S quantum dots in the NIR-II window, Biomaterials 35 (2014) 393–400.
[85] C. Li, L. Cao, Y. Zhang, P. Yi, M. Wang, B. Tan, Z. Deng, D. Wu, Q. Wang, Preoperative detection and intraoperative visualization of brain tumors for more precise surgery: a new dual-modality MRI and NIR nanoprobe, Small 11 (2015) 4517–4525.
[86] S. Mura, J. Nicolas, P. Couvreur, Stimuli-responsive nanocarriers for drug delivery, Nat. Mater. 12 (2013) 991–1003.
[87] P. Zhang, Y. Hou, J. Zeng, Y. Li, Z. Wang, R. Zhu, T. Ma, M. Gao, Coordinatively unsaturated Fe3+ based activatable probes for enhanced MRI and therapy of tumors, Angew. Chem. Int. Ed. 58 (2019) 11088–11096.
[88] H. Li, Z. Wang, Z. Chen, T. Ci, G. Chen, D. Wen, R. Li, J. Wang, H. Meng, R. Bryan Bell, Z. Gu, G. Dotti, Z. Gu, Disrupting tumour vasculature and recruitment of aPDL1-loaded platelets control tumour metastasis, Nat. Commun. 12 (2021) 2773.
[89] Z. Geng, F. Chen, X. Wang, L. Wang, Y. Pang, J. Liu, Combining anti-PD-1 antibodies with Mn2+-drug coordinated multifunctional nanoparticles for enhanced cancer therapy, Biomaterials 275 (2021) 120897.
[90] D. Jiao, S. Yang, Overcoming resistance to drugs targeting KRASG12C mutation, The Innovation 1 (2020) 100035.
[91] D.M. Pardoll, The blockade of immune checkpoints in cancer immunotherapy, Nat. Rev. Cancer 12 (2012) 252–264.
[92] R.S. Riley, C.H. June, R. Langer, M.J. Mitchell, Delivery technologies for cancer immunotherapy, Nat. Rev. Drug Discov. 18 (2019) 175–196.
[93] Z. Geng, L. Wang, K. Liu, J. Liu, W. Tan, Enhancing anti-PD-1 immunotherapy by nanomicelles self-assembled from multivalent aptamer drug conjugates, Angew. Chem. Int. Ed. 60 (2021) 15459–15465.
[94] Q. Hu, H. Li, E. Archibong, Q. Chen, H. Ruan, S. Ahn, E. Dukhovlinova, Y. Kang, D. Wen, G. Dotti, Z. Gu, Inhibition of post-surgery tumour recurrence via a hydrogel releasing CAR-T cells and anti-PDL1-conjugated platelets, Nat. Biomed. Eng. 5 (2021) 1038–1047.
[95] Q. Hu, W. Sun, J. Wang, H. Ruan, X. Zhang, Y. Ye, S. Shen, C. Wang, W. Lu, K. Cheng, G. Dotti, J.F. Zeidner, J. Wang, Z. Gu, Conjugation of haematopoietic stem cells and platelets decorated with anti-PD-1 antibodies augments anti-leukaemia efficacy, Nat. Biomed. Eng. 2 (2018) 831–840.
[96] Q. Chen, M. Chen, Z. Liu, Local biomaterials-assisted cancer immunotherapy to trigger systemic antitumor responses, Chem. Soc. Rev. 48 (2019) 5506–5526.
[97] L. Luo, M.Z. Iqbal, C. Liu, J. Xing, O.U. Akakuru, Q. Fang, Z. Li, Y. Dai, A. Li, Y. Guan, A. Wu, Engineered nano-immunopotentiators efficiently promote cancer immunotherapy for inhibiting and preventing lung metastasis of melanoma, Biomaterials 223 (2019) 119464.
[98] M.S. Goldberg, Improving cancer immunotherapy through nanotechnology, Nat. Rev. Cancer 19 (2019) 587–602.
[99] C. Wang, Y. Ye, G.M. Hochu, H. Sadeghifar, Z. Gu, Enhanced cancer immunotherapy by microneedle patch-assisted delivery of anti-PD1 antibody, Nano Lett. 16 (2016) 2334–2340.
[100] P. Zhang, J. Meng, Y. Li, C. Yang, Y. Hou, W. Tang, K. McHugh, L.H. Jing, Nanotechnology-enhanced immunotherapy for metastatic cancer, The Innovation 2 (2021) 100174.
[101] S.G. Crich, E. Terreno, S. Aime, Nano-sized and other improved reporters for magnetic resonance imaging of angiogenesis, Adv. Drug Deliv. Rev. 119 (2017) 61–72.

[102] W.J. Kelley, H. Safari, G. Lopez-Cazares, O. Eniola-Adefeso, Vascular-targeted nanocarriers: design considerations and strategies for successful treatment of atherosclerosis and other vascular diseases, WIREs Nanomed. Nanobiotech. 8 (2016) 909–926.

[103] R.R. Edelman, H.P. Mattle, D.J. Atkinson, H.M. Hoogewoud, MR angiography, Am. J. Roentgenol. 154 (1990) 937–946.

[104] H. Zhang, M.R. Prince, Renal MR angiography, Magn. Reson. Imaging Clin. N. Am. 12 (2004) 487–503 (vi).

[105] K. Chan, W. Wong, Small molecular gadolinium(III) complexes as MRI contrast agents for diagnostic imaging, Coord. Chem. Rev. 251 (2007) 2428–2451.

[106] A.A. Bogdanov, R. Weissleder, H.W. Frank, A.V. Bogdanova, N. Nossif, B.K. Schaffer, E. Tsai, M.I. Papisov, T.J. Brady, A new macromolecule as a contrast agent for MR angiography: preparation, properties, and animal studies, Radiology 187 (1993) 701–706.

[107] M. Allard, D. Doucet, P. Kien, B. Bonnemain, J.M. Caille, Experimental study of DOTA-gadolinium. Pharmacokinetics and pharmacologic properties, Invest. Radiol. 23 (Suppl 1) (1988) S271–S274.

[108] Y.H. Lin, R.M. Hwang, B.B. Chen, C.Y. Hsu, C.W. Yu, J.H. Kao, H.S. Lee, P.C. Liang, S.Y. Wei, T.T. Shih, Vascular and hepatic enhancements at MR imaging: comparison of Gd-EOB-DTPA and Gd-DTPA in the same subjects, Clin. Imaging 38 (2014) 287–291.

[109] K. Peldschus, M. Hamdorf, P. Robert, M. Port, G. Adam, C.U. Herborn, Comparison of the high relaxivity Gd chelates P1152 and Gd-BOPTA for contrast-enhanced MR angiography in rabbits at 1.5 Tesla and 3.0 Tesla, J. Magn. Reson. Imaging 32 (2010) 459–465.

[110] R.E. Port, M.V. Knopp, G. Brix, Dynamic contrast-enhanced MRI using Gd-DTPA: interindividual variability of the arterial input function and consequences for the assessment of kinetics in tumors, Magn. Reson. Med. 45 (2001) 1030–1038.

[111] P. Zhang, Z. Wang, Y. Wang, Y. Wang, C. Liu, K. Cao, Y. Lu, L. Behboodpour, Y. Hou, M. Gao, An MRI contrast agent based on a zwitterionic metal-chelating polymer for hepatorenal angiography and tumor imaging, J. Mater. Chem. B 8 (2020) 6956–6963.

[112] A.S. Gupta, Nanomedicine approaches in vascular disease: a review, Nanomedicine 7 (2011) 763–779.

[113] R. Naccache, P. Chevallier, J. Lagueux, Y. Gossuin, S. Laurent, L. Vander Elst, C. Chilian, J.A. Capobianco, M.-A. Fortin, High relaxivities and strong vascular signal enhancement for NaGdF4 nanoparticles designed for dual MR/optical imaging, Adv. Healthc. Mater. 2 (2013) 1478–1488.

[114] J. Zeng, L.H. Jing, Y. Hou, M. Jiao, R. Qiao, Q. Jia, C. Liu, F. Fang, H. Lei, M. Gao, Anchoring group effects of surface ligands on magnetic properties of Fe_3O_4 nanoparticles: towards high performance MRI contrast agents, Adv. Mater. 26 (2014) 2694–2698.

[115] M. Jiao, L.H. Jing, X. Wei, C. Liu, X. Luo, M. Gao, The Yin and Yang of coordinating co-solvents in the size-tuning of Fe3O4 nanocrystals through flow synthesis, Nanoscale 9 (2017) 18609–18612.

[116] Z. Gao, T. Ma, E. Zhao, D. Docter, W. Yang, R.H. Stauber, M. Gao, Small is smarter: nano MRI contrast agents - advantages and recent achievements, Small 12 (2016) 556–576.

[117] T. Wang, Y. Hou, B. Bu, W. Wang, T. Ma, C. Liu, L. Lin, L. Ma, X. Lou, M. Gao, Timely visualization of the collaterals formed during acute ischemic stroke with Fe3 O4 nanoparticle-based MR imaging probe, Small 14 (2018) e1800573.

[118] F. Hu, Q. Jia, Y. Li, M. Gao, Facile synthesis of ultrasmall PEGylated iron oxide nanoparticles for dual-contrast T1- and T2-weighted magnetic resonance imaging, Nanotechnology 22 (2011) 245604.

[119] T.-H. Shin, P.K. Kim, S. Kang, J. Cheong, S. Kim, Y. Lim, W. Shin, J.-Y. Jung, J.D. Lah, B.W. Choi, J. Cheon, High-resolution T1 MRI via renally clearable dextran nanoparticles with an iron oxide shell, Nat. Biomed. Eng. 5 (2021) 252–263.

[120] B.H. Kim, N. Lee, H. Kim, K. An, Y.I. Park, Y. Choi, K. Shin, Y. Lee, S.G. Kwon, H.B. Na, J.G. Park, T.Y. Ahn, Y.W. Kim, W.K. Moon, S.H. Choi, T. Hyeon, Large-scale synthesis of uniform and extremely small-sized iron oxide nanoparticles for high-resolution T1 magnetic resonance imaging contrast agents, J. Am. Chem. Soc. 133 (2011) 12624–12631.

[121] Y. Lu, Y.J. Xu, G.B. Zhang, D. Ling, M.Q. Wang, Y. Zhou, Y.D. Wu, T. Wu, M.J. Hackett, B. Hyo Kim, H. Chang, J. Kim, X.T. Hu, L. Dong, N. Lee, F. Li, J.C. He, L. Zhang, H.Q. Wen, B. Yang, S. Hong Choi, T. Hyeon, D.H. Zou, Iron oxide nanoclusters for T 1 magnetic resonance imaging of non-human primates, Nat. Biomed. Eng. 1 (2017) 637–643.

[122] K. Welsher, S.P. Sherlock, H. Dai, Deep-tissue anatomical imaging of mice using carbon nanotube fluorophores in the second near-infrared window, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 8943–8948.

[123] G. Hong, A.L. Antaris, H. Dai, Near-infrared fluorophores for biomedical imaging, Nat. Biomed. Eng. 1 (2017) 0010.

[124] G. Hong, J.C. Lee, J.T. Robinson, U. Raaz, L. Xie, N.F. Huang, J.P. Cooke, H. Dai, Multifunctional in vivo vascular imaging using near-infrared II fluorescence, Nat. Med. 18 (2012) 1841–1846.

[125] Y. Zhong, Z. Ma, S. Zhu, J. Yue, M. Zhang, A.L. Antaris, J. Yuan, R. Cui, H. Wan, Y. Zhou, W. Wang, N.F. Huang, J. Luo, Z. Hu, H. Dai, Boosting the down-shifting luminescence of rare-earth nanocrystals for biological imaging beyond 1500 nm, Nat. Commun. 8 (2017) 737.

[126] A. Romero-Corral, V.M. Montori, V.K. Somers, J. Korinek, R.J. Thomas, T.G. Allison, F. Mookadam, F. Lopez-Jimenez, Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies, Lancet 368 (2006) 666–678.

[127] K.H. Bønaa, I. Njølstad, P.M. Ueland, H. Schirmer, A. Tverdal, T. Steigen, H. Wang, J.E. Nordrehaug, E. Arnesen, K. Rasmussen, Homocysteine lowering and cardiovascular events after acute myocardial infarction, N. Engl. J. Med. 354 (2006) 1578–1588.

[128] N. Balu, J. Wang, L. Dong, F. Baluyot, H. Chen, C. Yuan, Current techniques for MR imaging of atherosclerosis, Top. Magn. Reson Imaging 20 (2009) 203–215.

[129] C. Yuan, J. Wang, N. Balu, High-field atherosclerotic plaque magnetic resonance imaging, Neuroimaging Clin. N. Am. 22 (2012) 271–284.

[130] G. Bala, B. Cosyns, Recent advances in visualizing vulnerable plaque: focus on noninvasive molecular imaging, Curr. Cardiol. Rep. 16 (2014) 520.

[131] M. Magnoni, E. Ammirati, P.G. Camici, Non-invasive molecular imaging of vulnerable atherosclerotic plaques, J. Cardiol. 65 (2015) 261–269.

[132] R. Qiao, X. Huang, Y. Qin, Y. Li, T.P. Davis, C.E. Hagemeyer, M. Gao, Recent advances in molecular imaging of atherosclerotic plaques and thrombosis, Nanoscale 12 (2020) 8040–8064.

[133] E.A. Osborn, F.A. Jaffer, Imaging atherosclerosis and risk of plaque rupture, Curr. Atheroscler. Rep. 15 (2013) 359.

[134] H. Qiao, Y. Wang, R. Zhang, Q. Gao, X. Liang, L. Gao, Z. Jiang, R. Qiao, D. Han, Y. Zhang, Y. Qiu, J. Tian, M. Gao, F. Cao, MRI/optical dual-modality imaging of vulnerable atherosclerotic plaque with an osteopontin-targeted probe based on Fe3O4 nanoparticles, Biomaterials 112 (2017) 336–345.

[135] R. Qiao, H. Qiao, Y. Zhang, Y. Wang, C. Chi, J. Tian, L. Zhang, F. Cao, M. Gao, Molecular imaging of vulnerable atherosclerotic plaques in vivo with osteopontin-specific upconversion nanoprobes, ACS Nano 11 (2017) 1816–1825.

[136] Y. Wang, Y. Zhang, Z. Wang, J. Zhang, R.R. Qiao, M. Xu, N. Yang, L. Gao, H. Qiao, M. Gao, F. Cao, Optical/MRI dual-modality imaging of M1 macrophage polarization in atherosclerotic plaque with MARCO-targeted upconversion luminescence probe, Biomaterials 219 (2019) 119378.

[137] Y. Zhang, A. Koradia, D. Kamato, A. Popat, P.J. Little, H.T. Ta, Treatment of atherosclerotic plaque: perspectives on theranostics, J. Pharm. Pharm. 71 (2019) 1029–1043.

[138] J.Y. Choi, J. Ryu, H.J. Kim, J.W. Song, J.H. Jeon, D.H. Lee, D.J. Oh, D.G. Gweon, W.Y. Oh, H. Yoo, K. Park, J.W. Kim, Therapeutic effects of targeted $PPAR_{\gamma}$ activation on inflamed high-risk plaques assessed by serial optical imaging in vivo, Theranostics 8 (2018) 45–60.

[139] T.D. Brown, K.A. Whitehead, S. Mitragotri, Materials for oral delivery of proteins and peptides, Nat. Rev. Mater. 5 (2019) 127–148.

[140] J. Liu, Y. Pang, S. Zhang, C. Cleveland, X. Yin, L. Booth, J. Lin, Y.-A. Lucy Lee, H. Mazdiyasni, S. Saxton, A.R. Kirtane, Tv Erlach, J. Rogner, R. Langer, G. Traverso, Triggerable tough hydrogels for gastric resident dosage forms, Nat. Commun. 8 (2017) 124.

[141] W. Hou, J. Li, Z. Cao, S. Lin, C. Pan, Y. Pang, Decorating bacteria with a therapeutic nanocoating for synergistically enhanced biotherapy, J. Liu, Small 17 (2021) e2101810.

[142] S. Lin, S. Mukherjee, J. Li, W. Hou, C. Pan, J. Liu, Mucosal immunity–mediated modulation of the gut microbiome by oral delivery of probiotics into Peyer's patches, Sci. Adv. 7 (2021) eabf0677.

[143] Y. Zhang, M. Li, G. Du, X. Chen, X. Sun, Advanced oral vaccine delivery strategies for improving the immunity, Adv. Drug Deliv. Rev. 177 (2021) 113928.

[144] R. Wang, L. Zhou, W. Wang, X. Li, F. Zhang, In vivo gastrointestinal drug-release monitoring through second near-infrared window fluorescent bioimaging with orally delivered microcarriers, Nat. Commun. 8 (2017) 14702.

[145] A. Abramson, M.R. Frederiksen, A. Vegge, B. Jensen, M. Poulsen, B. Mouridsen, M.O. Jespersen, R.K. Kirk, J. Windum, F. Hubalek, J.J. Water, J. Fels, S.B. Gunnarsson, A. Bohr, E.M. Straarup, M.W.H. Ley, X. Lu, J. Wainer, J. Collins, S. Tamang, K. Ishida, A. Hayward, P. Herskind, S.T. Buckley, N. Roxhed, R. Langer, U. Rahbek, G. Traverso, Oral delivery of systemic monoclonal antibodies, peptides and small molecules using gastric auto-injectors, Nat. Biotechnol. (2021), https://doi.org/10.1038/s41587-41021-01024-41580

[146] A. Abramson, E. Caffarel-Salvador, M. Khang, D. Dellal, D. Silverstein, Y. Gao, M.R. Frederiksen, A. Vegge, F. Hubalek, J.J. Water, A.V. Friderichsen, J. Fels, R.K. Kirk, C. Cleveland, J. Collins, S. Tamang, A. Hayward, T. Landh, S.T. Buckley, N. Roxhed, U. Rahbek, R. Langer, G. Traverso, An ingestible self-orienting system for oral delivery of macromolecules, Science 363 (2019) 611–615.

[147] A. Abramson, E. Caffarel-Salvador, V. Soares, D. Minahan, R.Y. Tian, X. Lu, D. Dellal, Y. Gao, S. Kim, J. Wainer, J. Collins, S. Tamang, A. Hayward, T. Yoshitake, H.-C. Lee, J. Fujimoto, J. Fels, M.R. Frederiksen, U. Rahbek, N. Roxhed, R. Langer, G. Traverso, A luminal unfolding microneedle injector for oral delivery of macromolecules, Nat. Med. 25 (2019) 1512–1518.

[148] D.J. Drucker, Advances in oral peptide therapeutics, Nat. Rev. Drug Discov. 19 (2020) 277–289.

[149] X. Yang, C. Ma, Z. Chen, J. Liu, F. Liu, R. Xie, H. Zhao, G. Deng, A.T. Chen, N. Gong, L. Yao, P. Zuo, K. Zhi, J. Wang, X. Gao, J. Wang, L. Fan, J. Zhou, Single small molecule-assembled nanoparticles mediate efficient oral drug delivery, Nano Res. 12 (2019) 2468–2476.

[150] Z. Zhang, F. Gao, S. Jiang, L. Ma, Y. Li, Nano-based drug delivery system enhances the oral absorption of lipophilic drugs with extensive presystemic metabolism, Curr. Drug Metab. 13 (2012) 1110–1118.

[151] A. Bernkop-Schnurch, T. Schmitz, Presystemic metabolism of orally administered peptide drugs and strategies to overcome it, Curr. Drug Metab. 8 (2007) 509–517.

[152] R. Pandey, Z. Ahmad, S. Sharma, G.K. Khuller, Nano-encapsulation of azole antifungals: potential applications to improve oral drug delivery, Int. J. Pharm. 301 (2005) 268–276.

[153] A. Mahapatro, D.K. Singh, Biodegradable nanoparticles are excellent vehicle for site directed in-vivo delivery of drugs and vaccines, J. Nanobiotechnology 9 (2011) 55.

[154] T. Sim, C. Lim, N.H. Hoang, H. Joo, J.W. Lee, D.-W. Kim, E.S. Lee, Y.S. Youn, J.O. Kim, K.T. Oh, Nanomedicines for oral administration based on diverse nanoplatform, J. Pharm. Investig. 46 (2016) 351–362.
[155] X. Cui, L. Bao, X. Wang, C. Chen, The nano-intestine interaction: understanding the location-oriented effects of engineered nanomaterials in the intestine, Small 16 (2020) e1907665.
[156] M. Duran-Lobato, Z. Niu, M.J. Alonso, Oral delivery of biologics for precision medicine, Adv. Mater. 32 (2020) e1901935.
[157] R.C. Haldemann Heusler, E. Wight, B. Marincek, Oral superparamagnetic contrast agent (ferumoxsil): tolerance and efficacy in MR imaging of gynecologic diseases, J. Magn. Reson. Imaging 5 (1995) 385–391.
[158] M.G. Panthani, T.A. Khan, D.K. Reid, D.J. Hellebusch, M.R. Rasch, J.A. Maynard, B.A. Korgel, In vivo whole animal fluorescence imaging of a microparticle-based oral vaccine containing (CuInSe(x)S(2-x))/ZnS core/shell quantum dots, Nano Lett. 13 (2013) 4294–4298.
[159] W. Huang, R. Chen, Y. Peng, F. Duan, Y. Huang, W. Guo, X. Chen, L. Nie, In vivo quantitative photoacoustic diagnosis of gastric and intestinal dysfunctions with a broad pH-responsive sensor, ACS Nano 13 (2019) 9561–9570.
[160] M.D. Bhavsar, M.M. Amiji, Polymeric nano- and microparticle technologies for oral gene delivery, Expert Opin. Drug Deliv. 4 (2007) 197–213.
[161] B. Mishra, S. Chaurasia, Design of novel chemotherapeutic delivery systems for colon cancer therapy based on oral polymeric nanoparticles, Ther. Deliv. 8 (2017) 29–47.
[162] S. Hua, E. Marks, J.J. Schneider, S. Keely, Advances in oral nano-delivery systems for colon targeted drug delivery in inflammatory bowel disease: selective targeting to diseased versus healthy tissue, Nanomed.: Nanotechnol., Biol. Med. 11 (2015) 1117–1132.
[163] R.L. Siegel, K.D. Miller, A. Goding Sauer, S.A. Fedewa, L.F. Butterly, J.C. Anderson, A. Cercek, R.A. Smith, A. Jemal, Colorectal cancer statistics, 2020, CA: A Cancer J. Clin. 70 (2020) 145–164.
[164] L. Lu, G. Chen, Y. Qiu, M. Li, D. Liu, D. Hu, X. Gu, Z. Xiao, Supplementary motor area deactivation impacts the recovery of hand function from severe peripheral nerve injury, Sci. Bull. 61 (2016) 670–681.
[165] M. Naeem, U.A. Awan, F. Subhan, J. Cao, S.P. Hlaing, J. Lee, E. Im, Y. Jung, J.-W. Yoo, Advances in colon-targeted nano-drug delivery systems: challenges and solutions, Arch. Pharm. Res. 43 (2020) 153–169.
[166] S. Hua, E. Marks, J.J. Schneider, S. Keely, Advances in oral nano-delivery systems for colon targeted drug delivery in inflammatory bowel disease: selective targeting to diseased versus healthy tissue, Nanomedicine 11 (2015) 1117–1132.
[167] T. Zhang, G. Zhu, B. Lu, Q. Peng, Oral nano-delivery systems for colon targeting therapy, Pharm. Nanotechnol. 5 (2017) 83–94.
[168] M.Y. Shen, T.I. Liu, T.W. Yu, R. Kv, W.H. Chiang, Y.C. Tsai, H.H. Chen, S.C. Lin, H.C. Chiu, Hierarchically targetable polysaccharide-coated solid lipid nanoparticles as an oral chemo/thermotherapy delivery system for local treatment of colon cancer, Biomaterials 197 (2019) 86–100.
[169] Y. Sun, B. Duan, H. Chen, X. Xu, A novel strategy for treating inflammatory bowel disease by targeting delivery of methotrexate through glucan particles, Adv. Health Mater. 9 (2020) e1901805.
[170] J. Xie, C. Wang, N. Wang, S. Zhu, L. Mei, X. Zhang, Y. Yong, L. Li, C. Chen, C. Huang, Z. Gu, Y. Li, Y. Zhao, Graphdiyne nanoradioprotector with efficient free radical scavenging ability for mitigating radiation-induced gastrointestinal tract damage, Biomaterials 244 (2020) 119940.
[171] C. Wang, J. Xie, X. Dong, L. Mei, M. Zhao, Z. Leng, H. Hu, L. Li, Z. Gu, Y. Zhao, Clinically approved carbon nanoparticles with oral administration for intestinal radioprotection via protecting the small intestinal crypt stem cells and maintaining the balance of intestinal flora, Small 16 (2020) 1906915.
[172] C.A. Schoener, N.A. Peppas, pH-responsive hydrogels containing PMMA nanoparticles: an analysis of controlled release of a chemotherapeutic conjugate and transport properties, J. Biomater. Sci. Polym. Ed. 24 (2013) 1027–1040.
[173] C. Li, Y. Zhao, J. Cheng, J. Guo, Q. Zhang, X. Zhang, J. Ren, F. Wang, J. Huang, H. Hu, R. Wang, J. Zhang, A proresolving peptide nanotherapy for site-specific treatment of inflammatory bowel disease by regulating proinflammatory microenvironment and gut microbiota, Adv. Sci. 6 (2019) 1900610.
[174] Q. Zhang, H. Tao, Y. Lin, Y. Hu, H. An, D. Zhang, S. Feng, H. Hu, R. Wang, X. Li, J. Zhang, A superoxide dismutase/catalase mimetic nanomedicine for targeted therapy of inflammatory bowel disease, Biomaterials 105 (2016) 206–221.
[175] C. Li, Y. Zhao, J. Cheng, J. Guo, Q. Zhang, X. Zhang, J. Ren, F. Wang, J. Huang, H. Hu, R. Wang, J. Zhang, A proresolving peptide nanotherapy for site-specific treatment of inflammatory bowel disease by regulating proinflammatory microenvironment and gut microbiota, Adv. Sci. 6 (2019) 1900610.
[176] H.H. Guo, C. Ma, W.S. Zheng, Y. Luo, C. Li, X.L. Li, X.L. Ma, C.L. Feng, T.T. Zhang, Y.X. Han, Z.G. Luo, Y. Zhan, R. Li, L.L. Wang, J.D. Jiang, Dual-stimuli-responsive gut microbiota-targeting berberine-cs/pt-nps improved metabolic status in obese hamsters, Adv. Funct. Mater. 29 (2019) 1808197.
[177] B. Kumar, S. Kulanthaivel, A. Mondal, S. Mishra, B. Banerjee, A. Bhaumik, I. Banerjee, S. Giri, Mesoporous silica nanoparticle based enzyme responsive system for colon specific drug delivery through guar gum capping, Colloids Surf. B Biointerfaces 150 (2017) 352–361.
[178] W. Li, D. Liu, H. Zhang, A. Correia, E. Mäkilä, J. Salonen, J. Hirvonen, H.A. Santos, Microfluidic assembly of a nano-in-micro dual drug delivery platform composed of halloysite nanotubes and a pH-responsive polymer for colon cancer therapy, Acta Biomater. 48 (2017) 238–246.
[179] L.B. Vong, T. Yoshitomi, H. Matsui, Y. Nagasaki, Development of an oral nanotherapeutics using redox nanoparticles for treatment of colitis-associated colon cancer, Biomaterials 55 (2015) 54–63.
[180] D.W. Zheng, X. Dong, P. Pan, K.W. Chen, J.X. Fan, S.X. Cheng, X.Z. Zhang, Phage-guided modulation of the gut microbiota of mouse models of colorectal cancer augments their responses to chemotherapy, Nat. Biomed. Eng. 3 (2019) 717–728.
[181] J.-W. Yoo, M. Naeem, J. Cao, M. Choi, W. Kim, H.R. Moon, B.L. Lee, M.-S. Kim, Y. Jung, Enhanced therapeutic efficacy of budesonide in experimental colitis with enzyme/pH dual-sensitive polymeric nanoparticles, Int. J. Nanomed. (2015) 4565.
[182] M. Naeem, J. Bae, M.A. Oshi, M.-S. Kim, H.R. Moon, B.L. Lee, E. Im, Y. Jung, J.-W. Yoo, Colon-targeted delivery of cyclosporine A using dual-functional Eudragit® FS30D/PLGA nanoparticles ameliorates murine experimental colitis, Int. J. Nanomed. 13 (2018) 1225–1240.
[183] J.H. Kang, J.Y. Hwang, J.W. Seo, H.S. Kim, U.S. Shin, Small intestine- and colon-specific smart oral drug delivery system with controlled release characteristic, Mater. Sci. Eng. C. Mater. Biol. Appl. 91 (2018) 247–254.
[184] A. American Diabetes, Diabetes. Care, 33 Suppl 1 (2010) S62–69.
[185] E.B. Souto, S.B. Souto, J.R. Campos, P. Severino, T.N. Pashirova, L.Y. Zakharova, A.M. Silva, A. Durazzo, M. Lucarini, A.A. Izzo, A. Santini, Nanoparticle delivery systems in the treatment of diabetes complications, Molecules 24 (2019) 4209.
[186] K.G.M.M. Alberti, P.Z. Zimmet, Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation, Diabet. Med. 15 (1998) 539–553.
[187] G.P. Carino, E. Mathiowitz, Oral insulin delivery, Adv. Drug Deliv. Rev. 35 (1999) 249–257.
[188] A. Gedawy, J. Martinez, H. Al-Salami, C.R. Dass, Oral insulin delivery: existing barriers and current counter-strategies, J. Pharm. Pharm. 70 (2018) 197–213.
[189] Y.B. Miao, W.Y. Pan, K.H. Chen, H.J. Wei, F.L. Mi, M.Y. Lu, Y. Chang, H.W. Sung, Engineering a nanoscale Al-MOF-armored antigen carried by a “trojan horse”-like platform for oral vaccination to induce potent and long-lasting immunity, Adv. Funct. Mater. 29 (2019) 1904828.
[190] N. Shrestha, M.-A. Shahbazi, F. Araújo, E. Mäkilä, J. Raula, E.I. Kauppinen, J. Salonen, B. Sarmento, J. Hirvonen, H.A. Santos, Multistage pH-responsive mucoadhesive nanocarriers prepared by aerosol flow reactor technology: a controlled dual protein-drug delivery system, Biomaterials 68 (2015) 9–20.
[191] H.R. Lakkireddy, M. Urmann, M. Besenius, U. Werner, T. Haack, P. Brun, J. Alie, B. Illel, L. Hortala, R. Vogel, D. Bazile, Oral delivery of diabetes peptides - comparing standard formulations incorporating functional excipients and nanotechnologies in the translational context, Adv. Drug Deliv. Rev. 106 (2016) 196–222.
[192] M. Safari, Y. Kamari, M. Ghiaci, H. Sadeghi-Aliabadi, M. Mirian, Synthesis and characterization of insulin/zirconium phosphate@TiO2 hybrid composites for enhanced oral insulin delivery applications, Drug Dev. Ind. Pharm. 43 (2017) 862–870.
[193] H.M. Joshi, D.R. Bhumkar, K. Joshi, V. Pokharkar, M. Sastry, Gold nanoparticles as carriers for efficient transmucosal insulin delivery, Langmuir 22 (2006) 300–305.
[194] W. Deng, Q. Xie, H. Wang, Z. Ma, B. Wu, X. Zhang, Selenium nanoparticles as versatile carriers for oral delivery of insulin: Insight into the synergic antidiabetic effect and mechanism, Nanomedicine 13 (2017) 1965–1974.
[195] Y. Kamari, P. Ghiaci, M. Ghiaci, Study on montmorillonite/insulin/TiO2 hybrid nanocomposite as a new oral drug-delivery system, Mater. Sci. Eng. C. Mater. Biol. Appl. 75 (2017) 822–828.
[196] J. Florek, R. Caillard, F. Kleitz, Evaluation of mesoporous silica nanoparticles for oral drug delivery - current status and perspective of MSNs drug carriers, Nanoscale 9 (2017) 15252–15277.
[197] A. Diaz, A. David, R. Perez, M.L. Gonzalez, A. Baez, S.E. Wark, P. Zhang, A. Clearfield, J.L. Colon, Nanoencapsulation of insulin into zirconium phosphate for oral delivery applications, Biomacromolecules 11 (2010) 2465–2470.
[198] Y. Zhang, L. Zhang, Q. Ban, J. Li, C.H. Li, Y.Q. Guan, Preparation and characterization of hydroxyapatite nanoparticles carrying insulin and gallic acid for insulin oral delivery, Nanomedicine 14 (2018) 353–364.
[199] N.A. Peppas, Y. Huang, Nanoscale technology of mucoadhesive interactions, Adv. Drug Deliv. Rev. 56 (2004) 1675–1687.
[200] Z.H. Zhang, S. Abbad, R.R. Pan, A.Y. Waddad, L.L. Hou, H.X. Lv, J.P. Zhou, N-octyl-N-Arginine chitosan micelles as an oral delivery system of insulin, J. Biomed. Nanotechnol. 9 (2013) 601–609.
[201] E.V. Batrakova, A.V. Kabanov, Pluronic block copolymers: evolution of drug delivery concept from inert nanocarriers to biological response modifiers, J. Control Release 130 (2008) 98–106.
[202] C. Durrer, J.M. Irache, F. Puisieux, D. Duchêne, G. Ponchel, Mucoadhesion of latexes. I. Analytical methods and kinetic studies, Pharm. Res 11 (1994) 674–679.
[203] C. Durrer, J.M. Irache, F. Puisieux, D. Duchene, G. Ponchel, Mucoadhesion of latexes. II. Adsorption isotherms and desorption studies, Pharm. Res 11 (1994) 680–683.
[204] C.M. Lehr, J.A. Bouwstra, W. Kok, A.B. Noach, A.G. de Boer, H.E. Junginger, Bioadhesion by means of specific binding of tomato lectin, Pharm. Res. 9 (1992) 547–553.
[205] C.-M. Lehr, Lectin-mediated drug delivery: the second generation of bioadhesives, J. Control Release 65 (2000) 19–29.
[206] E.M. Pridgen, F. Alexis, T.T. Kuo, E. Levy-Nissenbaum, R. Karnik, R.S. Blumberg, R. Langer, O.C. Farokhzad, Transepithelial transport of Fc-targeted nanoparticles by the neonatal fc receptor for oral delivery, Sci. Transl. Med. 5 (2013) 213ra167.

[207] J. Mudassir, Y. Darwis, P.K. Khiang, Prerequisite characteristics of nanocarriers favoring oral insulin delivery: nanogels as an opportunity, Int. J. Polym. Mater. Polym. Biomater. 64 (2014) 155–167.
[208] N.G. Lamson, A. Berger, K.C. Fein, K.A. Whitehead, Anionic nanoparticles enable the oral delivery of proteins by enhancing intestinal permeability, Nat. Biomed. Eng. 4 (2020) 84–96.
[209] P. Li, H.M. Nielsen, A. Mullertz, Impact of lipid-based drug delivery systems on the transport and uptake of insulin across caco-2 cell monolayers, J. Pharm. Sci. 105 (2016) 2743–2751.
[210] X. Han, Y. Lu, J. Xie, E. Zhang, H. Zhu, H. Du, K. Wang, B. Song, C. Yang, Y. Shi, Z. Cao, Controlled fabrication of gold nanotip arrays by nanomolding-necking technology, Nat. Nanotechnol. 31 (2020) 144001-614.
[211] S. Sharma, Patient selection for oral chemotherapy, Oncology (Williston Park) 15 (2001) 33–35.
[212] M.E. Royce, P.M. Hoff, R. Pazdur, Novel oral chemotherapy agents, Curr. Oncol. Rep. 2 (2000) 31–37.
[213] T.R. Halfdanarson, A. Jatoi, Oral cancer chemotherapy: the critical interplay between patient education and patient safety, Curr. Oncol. Rep. 12 (2010) 247–252.
[214] H. Liu, F. Ren, H. Zhang, Y. Han, H. Qin, J. Zeng, Y. Wang, Q. Sun, Z. Li, M. Gao, Oral administration of highly bright Cr3+ doped ZnGa2O4 nanocrystals for in vivo targeted imaging of orthotopic breast cancer, J. Mater. Chem. B 6 (2018) 1508–1518.
[215] Q. Song, C. Zheng, J. Jia, H. Zhao, Q. Feng, H. Zhang, L. Wang, Z. Zhang, Y. Zhang, A probiotic spore-based oral autonomous nanoparticles generator for cancer therapy, Adv. Mater. 31 (2019) e1903793.
[216] S.S. Feng, L. Zhao, J. Tang, Nanomedicine for oral chemotherapy, Nanomed. (Lond.) 6 (2011) 407–410.
[217] C.K. Lin, M.Y. Bai, T.M. Hu, Y.C. Wang, T.K. Chao, S.J. Weng, R.L. Huang, P.H. Su, H.C. Lai, Preclinical evaluation of a nanoformulated antihelminthic, niclosamide, in ovarian cancer, Oncotarget 7 (2016) 8993–9006.
[218] K.-H. Chen, Y.-B. Miao, C.-Y. Shang, T.-Y. Huang, Y.-T. Yu, C.-N. Yeh, H.-L. Song, C.-T. Chen, F.-L. Mi, K.-J. Lin, H.-W. Sung, A bubble bursting-mediated oral drug delivery system that enables concurrent delivery of lipophilic and hydrophilic chemotherapeutics for treating pancreatic tumors in rats, Biomaterials 255 (2020) 120157.
[219] N. Marasini, M. Skwarczynski, I. Toth, Oral delivery of nanoparticle-based vaccines, Expert Rev. Vaccin. 13 (2014) 1361–1376.
[220] Y. Shi, T. Lammers, Combining Nanomedicine and Immunotherapy, ACS Chem. Res. 52 (2019) 1543–1554.
[221] Y. Ding, Z. Li, A. Jaklenec, Q. Hu, Vaccine delivery systems toward lymph nodes, Adv. Drug Deliv. Rev. (2021) 113914.
[222] T. Ye, F. Li, G. Ma, W. Wei, Enhancing therapeutic performance of personalized cancer vaccine via delivery vectors, Adv. Drug Deliv. Rev. 177 (2021) 113927.
[223] L. Miao, L. Li, Y. Huang, D. Delcassian, J. Chahal, J. Han, Y. Shi, K. Sadtler, W. Gao, J. Lin, J.C. Doloff, R. Langer, D.G. Anderson, Delivery of mRNA vaccines with heterocyclic lipids increases anti-tumor efficacy by STING-mediated immune cell activation, Nat. Biotechnol. 37 (2019) 1174–1185.
[224] M. Luo, H. Wang, Z. Wang, H. Cai, Z. Lu, Y. Li, M. Du, G. Huang, C. Wang, X. Chen, M.R. Porembka, J. Lea, A.E. Frankel, Y.X. Fu, Z.J. Chen, J. Gao, A STING-activating nanovaccine for cancer immunotherapy, Nat. Nanotechnol. 12 (2017) 648–654.
[225] Z. Lu, Z. Peng, C. Liu, Z. Wang, Y. Wang, X. Jiao, J. Li, L. Shen, Current status and future perspective of immunotherapy in gastrointestinal cancers, The Innovation 1 (2020) 100041.
[226] Y. Tang, W. Fan, G. Chen, M. Zhang, X. Tang, H. Wang, P. Zhao, Q. Xu, Z. Wu, X. Lin, Y. Huang, Recombinant cancer nanovaccine for targeting tumor-associated macrophage and remodeling tumor microenvironment, Nano Today 40 (2021) 101244.
[227] Q. Zhu, J. Talton, G. Zhang, T. Cunningham, Z. Wang, R.C. Waters, J. Kirk, B. Eppler, D.M. Klinman, Y. Sui, S. Gagnon, I.M. Belyakov, R.J. Mumper, J.A. Berzofsky, Large intestine-targeted, nanoparticle-releasing oral vaccine to control genitorectal viral infection, Nat. Med. 18 (2012) 1291–1296.
[228] Y. Huang, R. Fayad, A. Smock, A.M. Ullrich, L. Qiao, Induction of mucosal and systemic immune responses against human carcinoembryonic antigen by an oral vaccine, Cancer Res. 65 (2005) 6990–6999.
[229] W. Ge, Y. Li, Z.S. Li, S.H. Zhang, Y.J. Sun, P.Z. Hu, X.M. Wang, Y. Huang, S.Y. Si, X.M. Zhang, Y.F. Sui, The antitumor immune responses induced by nanoemulsion-encapsulated MAGE1-HSP70/SEA complex protein vaccine following peroral administration route, Cancer Immunol. Immunother. 58 (2009) 201–208.
[230] Z. Liu, D. Lv, S. Liu, J. Gong, D. Wang, M. Xiong, X. Chen, R. Xiang, X. Tan, Alginic acid-coated chitosan nanoparticles loaded with legumain DNA vaccine: effect against breast cancer in mice, PLoS One 8 (2013) e60190.
[231] P. Bergqvist, A. Stensson, L. Hazanov, A. Holmberg, J. Mattsson, R. Mehr, M. Bemark, N.Y. Lycke, Re-utilization of germinal centers in multiple Peyer's patches results in highly synchronized, oligoclonal, and affinity-matured gut IgA responses, Mucosal Immunol. 6 (2012) 122–135.
[232] O. Pabst, A.M. Mowat, Oral tolerance to food protein, Mucosal Immunol. 5 (2012) 232–239.
[233] S. Wilhelm, A.J. Tavares, Q. Dai, S. Ohta, J. Audet, H.F. Dvorak, W.C.W. Chan, Analysis of nanoparticle delivery to tumours, Nat. Rev. Mater. 1 (2016) 16014.
[234] G. Toffoli, G. Corona, B. Basso, M. Boiocchi, Pharmacokinetic optimisation of treatment with oral etoposide, Clin. Pharmacokinet. 43 (2004) 441–466.
[235] A. Habib, K. Desai, R. Hickey, B. Thornburg, R. Lewandowski, R. Salem, Locoregional therapy of hepatocellular carcinoma, Clin. Liver Dis. 19 (2015) 401–420.
[236] J.M. Llovet, T. De Baere, L. Kulik, P.K. Haber, T.F. Greten, T. Meyer, R. Lencioni, Locoregional therapies in the era of molecular and immune treatments for hepatocellular carcinoma, Nat. Rev. Gastroenterol. Hepatol. 18 (2021) 293–313.
[237] C. Weldon, T. Ji, M.-T. Nguyen, A. Rwei, W. Wang, Y. Hao, C. Zhao, M. Mehta, B.Y. Wang, J. Tsui, R.P. Marini, D.S. Kohane, Nanoscale bupivacaine formulations to enhance the duration and safety of intravenous regional anesthesia, ACS Nano 13 (2019) 18–25.
[238] S. GuhaSarkar, K. Pathak, N. Sudhalkar, P. More, J.S. Goda, V. Gota, R. Banerjee, Synergistic locoregional chemoradiotherapy using a composite liposome-in-gel system as an injectable drug depot, Int. J. Nanomed. 11 (2016) 6435–6448.
[239] C. Hotz, T.R. Wagenaar, F. Gieseke, D.S. Bangari, M. Callahan, H. Cao, J. Diekmann, M. Diken, C. Grunwitz, A. Hebert, K. Hsu, M. Bernardo, K. Karikó, S. Kreiter, A.N. Kuhn, M. Levit, N. Malkova, S. Masciari, J. Pollard, H. Qu, S. Ryan, A. Selmi, J. Schlereth, K. Singh, F. Sun, B. Tillmann, T. Tolstykh, W. Weber, L. Wicke, S. Witzel, Q. Yu, Y.-A. Zhang, G. Zheng, J. Lager, G.J. Nabel, U. Sahin, D. Wiederschain, Local delivery of mRNA-encoded cytokines promotes antitumor immunity and tumor eradication across multiple preclinical tumor models, Sci. Transl. Med. 13 (2021) eabc7804.
[240] W. Gao, Y. Chen, Y. Zhang, Q. Zhang, L. Zhang, Nanoparticle-based local antimicrobial drug delivery, Adv. Drug Deliv. Rev. 127 (2018) 46–57.
[241] D. Zheng, D.A. Giljohann, D.L. Chen, M.D. Massich, X.Q. Wang, H. Iordanov, C.A. Mirkin, A.S. Paller, Topical delivery of siRNA-based spherical nucleic acid nanoparticle conjugates for gene regulation, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) 11975–11980.
[242] B.V. Bonifacio, P.B. Silva, M.A. Ramos, K.M. Negri, T.M. Bauab, M. Chorilli, Nanotechnology-based drug delivery systems and herbal medicines: a review, Int. J. Nanomed. 9 (2014) 1–15.
[243] R. Xing, K. Liu, T. Jiao, N. Zhang, K. Ma, R. Zhang, Q. Zou, G. Ma, X. Yan, An injectable self-assembling collagen-gold hybrid hydrogel for combinatorial antitumor photothermal/photodynamic therapy, Adv. Mater. 28 (2016) 3669–3676.
[244] C.M. Jewell, S.C. Lopez, D.J. Irvine, In situ engineering of the lymph node microenvironment via intranodal injection of adjuvant-releasing polymer particles, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 15745–15750.
[245] A. Albanese, P.S. Tang, W.C. Chan, The effect of nanoparticle size, shape, and surface chemistry on biological systems, Annu. Rev. Biomed. Eng. 14 (2012) 1–16.
[246] K.M. Tsoi, S.A. MacParland, X.-Z. Ma, V.N. Spetzler, J. Echeverri, B. Ouyang, S.M. Fadel, E.A. Sykes, N. Goldaracena, J.M. Kaths, J.B. Conneely, B.A. Alman, M. Selzner, M.A. Ostrowski, O.A. Adeyi, A. Zilman, I.D. McGilvray, W.C.W. Chan, Mechanism of hard-nanomaterial clearance by the liver, Nat. Mater. 15 (2016) 1212–1221.
[247] H. Han, Y. Hou, X. Chen, P. Zhang, M. Kang, Q. Jin, J. Ji, M. Gao, Metformin-induced stromal depletion to enhance the penetration of gemcitabine-loaded magnetic nanoparticles for pancreatic cancer targeted therapy, J. Am. Chem. Soc. 142 (2020) 4944–4954.
[248] R. Qiao, Q. Jia, S. Huwel, R. Xia, T. Liu, F. Gao, H.J. Galla, M. Gao, Receptor-mediated delivery of magnetic nanoparticles across the blood-brain barrier, ACS Nano 6 (2012) 3304–3310.
[249] K.W. Li, W. Dang, B.M. Tyler, G. Troiano, T. Tihan, H. Brem, K.A. Walter, Polilactofate microspheres for Paclitaxel delivery to central nervous system malignancies, Clin. Cancer Res. 9 (2003) 3441–3447.
[250] G. Pradilla, P.P. Wang, P. Gabikian, K. Li, C.A. Magee, K.A. Walter, H. Brem, Local intracerebral administration of Paclitaxel with the paclimer delivery system: toxicity study in a canine model, J. Neurooncol. 76 (2006) 131–138.
[251] E. Nance, C. Zhang, T.Y. Shih, Q. Xu, B.S. Schuster, J. Hanes, Brain-penetrating nanoparticles improve paclitaxel efficacy in malignant glioma following local administration, ACS Nano 8 (2014) 10655–10664.
[252] S. Gupta, P.K. Gupta, G. Dharanivasan, R.S. Verma, Current prospects and challenges of nanomedicine delivery in prostate cancer therapy, Nanomed. (Lond.) 12 (2017) 2675–2692.
[253] M. Laprise-Pelletier, J. Lagueux, M.F. Cote, T. LaGrange, M.A. Fortin, Low-dose prostate cancer brachytherapy with radioactive palladium-gold nanoparticles, Adv. Healthc. Mater. 6 (2017) 1601120.
[254] M.G. Wientjes, J.H. Zheng, L. Hu, Y. Gan, J.L. Au, Intraprostatic chemotherapy: distribution and transport mechanisms, Clin. Cancer Res. 11 (2005) 4204–4211.
[255] C. Zhao, Q. Feng, Z. Dou, W. Yuan, C. Sui, X. Zhang, G. Xia, H. Sun, J. Ma, Local targeted therapy of liver metastasis from colon cancer by galactosylated liposome encapsulated with doxorubicin, PLoS One 8 (2013) e73860.
[256] Z. Meng, Y. Chao, X. Zhou, C. Liang, J. Liu, R. Zhang, L. Cheng, K. Yang, W. Pan, M. Zhu, Z. Liu, Near-infrared-triggered in situ gelation system for repeatedly enhanced photothermal brachytherapy with a single dose, ACS Nano 12 (2018) 9412–9422.
[257] N. Gerwin, C. Hops, A. Lucke, Intraarticular drug delivery in osteoarthritis, Adv. Drug Deliv. Rev. 58 (2006) 226–242.
[258] G.S. Firestein, Evolving concepts of rheumatoid arthritis, Nature 423 (2003) 356–361.
[259] I.B. McInnes, G. Schett, The pathogenesis of rheumatoid arthritis, N. Engl. J. Med. 365 (2011) 2205–2219.
[260] D.L. Scott, F. Wolfe, T.W.J. Huizinga, Rheumatoid arthritis, Lancet 376 (2010) 1094–1108.
[261] L. Terslev, S. Torp-Pedersen, E. Qvistgaard, B. Danneskiold-Samsoe, H. Bliddal, Estimation of inflammation by doppler ultrasound: quantitative changes after intra-articular treatment in rheumatoid arthritis, Ann. Rheum. Dis. 62 (2003) 1049–1053.

[262] J. Song, C.H. Suh, Y.B. Park, S.H. Lee, N.C. Yoo, J.D. Lee, K.H. Kim, S.K. Lee, A phase I/IIa study on intra-articular injection of holmium-166-chitosan complex for the treatment of knee synovitis of rheumatoid arthritis, Eur. J. Nucl. Med. 28 (2001) 489–497.
[263] M. Qindeel, D. Khan, N. Ahmed, S. Khan, R. Asim Ur, Surfactant-free, self-assembled nanomicelles-based transdermal hydrogel for safe and targeted delivery of methotrexate against rheumatoid arthritis, ACS Nano 14 (2020) 4662–4681.
[264] Q. Zhang, D. Dehaini, Y. Zhang, J. Zhou, X. Chen, L. Zhang, R.H. Fang, W. Gao, L. Zhang, Neutrophil membrane-coated nanoparticles inhibit synovial inflammation and alleviate joint damage in inflammatory arthritis, Nat. Nanotechnol. 13 (2018) 1182–1190.
[265] J. Yeo, Y.M. Lee, J. Lee, D. Park, K. Kim, J. Kim, J. Park, W.J. Kim, Nitric oxide-scavenging nanogel for treating rheumatoid arthritis, Nano Lett. 19 (2019) 6716–6724.
[266] Y. Yan, T. Sun, H. Zhang, X. Ji, Y. Sun, X. Zhao, L. Deng, J. Qi, W. Cui, H.A. Santos, H. Zhang, Euryale feroxseed-inspired superlubricated nanoparticles for treatment of osteoarthritis, Adv. Funct. Mater. 29 (2019) 1807559.
[267] R. Liang, J. Zhao, B. Li, P. Cai, X.J. Loh, C. Xu, P. Chen, D. Kai, L. Zheng, Implantable and degradable antioxidant poly(ε-caprolactone)-lignin nanofiber membrane for effective osteoarthritis treatment, Biomaterials 230 (2020) 119601.
[268] Q. Wang, Y. Shen, G. Mi, D. He, Y. Zhang, Y. Xiong, T.J. Webster, J. Tu, Fumaryl diketopiperazine based effervescent microparticles to escape macrophage phagocytosis for enhanced treatment of pneumonia via pulmonary delivery, Biomaterials 228 (2020) 119575.
[269] F.R. Brennan, L.D. Morton, S. Spindeldreher, A. Kiessling, R. Allenspach, A. Hey, P.Y. Muller, W. Frings, Safety and immunotoxicity assessment of immunomodulatory monoclonal antibodies, J. Sims, MAbs 2 (2010) 233–255.
[270] L. Milling, Y. Zhang, D.J. Irvine, Delivering safer immunotherapies for cancer, Adv. Drug Deliv. Rev. 114 (2017) 79–101.
[271] M.W. Tibbitt, J.E. Dahlman, R. Langer, Emerging frontiers in drug delivery, J. Am. Chem. Soc. 138 (2016) 704–717.
[272] G.M. Lynn, R. Laga, C.M. Jewell, Induction of anti-cancer T cell immunity by in situ vaccination using systemically administered nanomedicines, Cancer Lett. 459 (2019) 192–203.
[273] M. Feng, Y. Pan, R. Kong, S. Shu, Therapy of primary liver cancer, The Innovation 1 (2020) 100032.
[274] A. Gardner, B. Ruffell, Dendritic cells and cancer immunity, Trends Immunol. 37 (2016) 855–865.
[275] L. Wang, X. Wang, F. Yang, Y. Liu, L. Meng, Y. Pang, M. Zhang, F. Chen, C. Pan, S. Lin, X. Zhu, K.W. Leong, J. Liu, Systemic antiviral immunization by virus-mimicking nanoparticles-decorated erythrocytes, Nano Today 40 (2021) 101280.
[276] Y. Sakai, B.J. Morrison, J.D. Burke, J.M. Park, M. Terabe, J.E. Janik, G. Forni, J.A. Berzofsky, J.C. Morris, Vaccination by genetically modified dendritic cells expressing a truncated neu oncogene prevents development of breast cancer in transgenic mice, Cancer Res. 64 (2004) 8022–8028.
[277] K. Palucka, J. Banchereau, Cancer immunotherapy via dendritic cells, Nat. Rev. Cancer 12 (2012) 265–277.
[278] J. Xiang, L. Xu, H. Gong, W. Zhu, C. Wang, J. Xu, L. Feng, L. Cheng, R. Peng, Z. Liu, Antigen-loaded upconversion nanoparticles for dendritic cell stimulation, tracking, and vaccination in dendritic cell-based immunotherapy, ACS Nano 9 (2015) 6401–6411.
[279] S.-Y. Kim, H. Phuengkham, Y.-W. Noh, H.-G. Lee, S.H. Um, Y.T. Lim, Immune complexes mimicking synthetic vaccine nanoparticles for enhanced migration and cross-presentation of dendritic cells, Adv. Funct. Mater. 26 (2016) 8072–8082.
[280] J. Sprooten, J. Ceusters, A. Coosemans, P. Agostinis, S. De Vleeschouwer, L. Zitvogel, G. Kroemer, L. Galluzzi, A.D. Garg, Trial watch: dendritic cell vaccination for cancer immunotherapy, Oncoimmunology 8 (2019) e1638212.
[281] K.F. Bol, G. Schreibelt, W.R. Gerritsen, I.J. de Vries, C.G. Figdor, Dendritic cell-based immunotherapy: state of the art and beyond, Clin. Cancer Res. 22 (2016) 1897–1906.
[282] M.A. Cheever, C.S. Higano, PROVENGE (Sipuleucel-T) in prostate cancer: the first FDA-approved therapeutic cancer vaccine, Clin. Cancer Res. 17 (2011) 3520–3526.
[283] A. de Titta, M. Ballester, Z. Julier, C. Nembrini, L. Jeanbart, A.J. van der Vlies, M.A. Swartz, J.A. Hubbell, Nanoparticle conjugation of CpG enhances adjuvancy for cellular immunity and memory recall at low dose, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 19902–19907.
[284] Y. Tao, E. Ju, Z. Li, J. Ren, X. Qu, Engineered CpG-antigen conjugates protected gold nanoclusters as smart self-vaccines for enhanced immune response and cell imaging, Adv. Funct. Mater. 24 (2014) 1004–1010.
[285] R. Yang, J. Xu, L. Xu, X. Sun, Q. Chen, Y. Zhao, R. Peng, Z. Liu, Cancer cell membrane-coated adjuvant nanoparticles with mannose modification for effective anticancer vaccination, ACS Nano 12 (2018) 5121–5129.
[286] F. Li, W. Nie, F. Zhang, G. Lu, C. Lv, Y. Lv, W. Bao, L. Zhang, S. Wang, X. Gao, W. Wei, H.-Y. Xie, Engineering magnetosomes for high-performance cancer vaccination, ACS Cent. Sci. 5 (2019) 796–807.
[287] J. Wang, J. Meng, W. Ran, R.J. Lee, L. Teng, P. Zhang, Y. Li, Hepatocellular carcinoma growth retardation and PD-1 blockade therapy potentiation with synthetic high-density lipoprotein, Nano Lett. 19 (2019) 5266–5276.
[288] S. Ahn, I.-H. Lee, S. Kang, D. Kim, M. Choi, P.E. Saw, E.-C. Shin, S. Jon, Gold nanoparticles displaying tumor-associated self-antigens as a potential vaccine for cancer immunotherapy, Adv. Healthc. Mater. 3 (2014) 1194–1199.
[289] Y. Chao, L. Xu, C. Liang, L. Feng, J. Xu, Z. Dong, L. Tian, X. Yi, K. Yang, Z. Liu, Combined local immunostimulatory radioisotope therapy and systemic immune checkpoint blockade imparts potent antitumour responses, Nat. Biomed. Eng. 2 (2018) 611–621.
[290] Y. Liu, W.N. Crowe, L. Wang, Y. Lu, W.J. Petty, A.A. Habib, D. Zhao, An inhalable nanoparticulate STING agonist synergizes with radiotherapy to confer long-term control of lung metastases, Nat. Commun. 10 (2019) 5108.
[291] J.L. Perry, S. Tian, N. Sengottuvel, E.B. Harrison, B.K. Gorentla, C.H. Kapadia, N. Cheng, J.C. Luft, J.P. Ting, J.M. DeSimone, C.V. Pecot, Pulmonary delivery of nanoparticle-bound toll-like receptor 9 agonist for the treatment of metastatic lung cancer, ACS Nano 14 (2020) 7200–7215.
[292] Y.-N. Zhang, J. Lazarovits, W. Poon, B. Ouyang, L.N.M. Nguyen, B.R. Kingston, W.C.W. Chana, Nanoparticle size influences antigen retention and presentation in lymph node follicles for humoral immunity, Nano Lett. 19 (2019) 7226–7235.
[293] B. Yin, C.K.W. Chan, S. Liu, H. Hong, S.H.D. Wong, L.K.C. Lee, L.W.C. Ho, L. Zhang, K.C. Leung, P.C. Choi, L. Bian, X.Y. Tian, M.N. Chan, C.H.J. Choi, Intrapulmonary cellular-level distribution of inhaled nanoparticles with defined functional groups and its correlations with protein corona and inflammatory response, ACS Nano 13 (2019) 14048–14069.
[294] W.G. Kreyling, W. Moller, U. Holzwarth, S. Hirn, A. Wenk, C. Schleh, M. Schaffler, N. Haberl, N. Gibson, J.C. Schittny, Age-dependent rat lung deposition patterns of inhaled 20 nanometer gold nanoparticles and their quantitative biokinetics in adult rats, ACS Nano 12 (2018) 7771–7790.
[295] T. Sheng, B. Luo, W. Zhang, X. Ge, J. Yu, Y. Zhang, Z. Gu, Microneedle-mediated vaccination: innovation and translation, Adv. Drug Deliv. Rev. (2021) 113919, https://doi.org/10.1016/j.addr.2021.113919
[296] M.R. Prausnitz, R. Langer, Transdermal drug delivery, Nat. Biotechnol. 26 (2008) 1261–1268.
[297] M.R. Prausnitz, S. Mitragotri, R. Langer, Current status and future potential of transdermal drug delivery, Nat. Rev. Drug Discov. 3 (2004) 115–124.
[298] P. Makvandi, R. Jamaledin, G.J. Chen, Z. Baghbantaraghdari, E.N. Zare, C. Di Natale, V. Onesto, R. Vecchione, J. Lee, F.R. Tay, P. Netti, V. Mattoli, A. Jaklenec, Z. Gu, R. Langer, Stimuli-responsive transdermal microneedle patches, Mater. Today 47 (2021) 206–222.
[299] J. Yu, J. Wang, Y. Zhang, G. Chen, W. Mao, Y. Ye, A.R. Kahkoska, J.B. Buse, R. Langer, Z. Gu, Glucose-responsive insulin patch for the regulation of blood glucose in mice and minipigs, Nat. Biomed. Eng. 4 (2020) 499–506.
[300] L. Xie, H. Zeng, J. Sun, W. Qian, Engineering microneedles for therapy and diagnosis: a Survey, Micromachines (Basel), Micromachines (Basel) 11 (2020), p. 271.
[301] M.R. Prausnitz, Microneedles for transdermal drug delivery, Adv. Drug Deliv. Rev. 56 (2004) 581–587.
[302] Y. Zhang, Q. Liu, J. Yu, S. Yu, J. Wang, L. Qiang, Z. Gu, Locally induced adipose tissue browning by microneedle patch for obesity treatment, ACS Nano 11 (2017) 9223–9230.
[303] G. Chen, Z. Chen, D. Wen, Z. Wang, H. Li, Y. Zeng, G. Dotti, R.E. Wirz, Z. Gu, Transdermal cold atmospheric plasma-mediated immune checkpoint blockade therapy, Proc. Natl. Acad. Sci. U. S. A. 117 (2020) 3687–3692.
[304] T. Jiang, G. Xu, G. Chen, Y. Zheng, B. He, Z. Gu, Progress in transdermal drug delivery systems for cancer therapy, Nano Res 13 (2020) 1810–1824.
[305] Y. Zeng, J. Wang, Z. Wang, G. Chen, J. Yu, S. Li, Q. Li, H. Li, D. Wen, Z. Gu, Z. Gu, Colloidal crystal microneedle patch for glucose monitoring, Nano Today 35 (2020) 100984.
[306] P. Singh, A. Carrier, Y. Chen, S. Lin, J. Wang, S. Cui, X. Zhang, Polymeric microneedles for controlled transdermal drug delivery, J. Control Release 315 (2019) 97–113.
[307] K. Ita, Transdermal delivery of drugs with microneedles-potential and challenges, Pharmaceutics 7 (2015) 90–105.
[308] Z. Zhang, P.C. Tsai, T. Ramezanli, B.B. Michniak-Kohn, Polymeric nanoparticles-based topical delivery systems for the treatment of dermatological diseases, Wiley Inter. Rev. Nanomed. Nanobiotechnol 5 (2013) 205–218.
[309] K.J. McHugh, L.H. Jing, S.Y. Severt, M. Cruz, M. Sarmadi, H.S.N. Jayawardena, C.F. Perkinson, F. Larusson, S. Rose, S. Tomasic, T. Graf, S.Y. Tzeng, J.L. Sugarman, D. Vlasic, M. Peters, N. Peterson, L. Wood, W. Tang, J. Yeom, J. Collins, P.A. Welkhoff, A. Karchin, M. Tse, M. Gao, M.G. Bawendi, R. Langer, A. Jaklenec, Biocompatible near-infrared quantum dots delivered to the skin by microneedle patches record vaccination, Sci. Transl. Med. 11 (2019) eaay7162.
[310] A. GhavamiNejad, J. Li, B. Lu, L. Zhou, L. Lam, A. Giacca, X.Y. Wu, Glucose-responsive composite microneedle patch for hypoglycemia-triggered delivery of native glucagon, Adv. Mater. 31 (2019) e1901051.
[311] J. Yu, C. Qian, Y. Zhang, Z. Cui, Y. Zhu, Q. Shen, F.S. Ligler, J.B. Buse, Z. Gu, Hypoxia and H2O2 dual-sensitive vesicles for enhanced glucose-responsive insulin delivery, Nano Lett. 17 (2017) 733–739.
[312] J. Yu, Y. Zhang, Y. Ye, R. DiSanto, W. Sun, D. Ranson, F.S. Ligler, J.B. Buse, Z. Gu, Microneedle-array patches loaded with hypoxia-sensitive vesicles provide fast glucose-responsive insulin delivery, Proc. Natl. Acad. Sci. U. S. A. 112 (2015) 8260–8265.
[313] Y. Ye, J. Yu, C. Wang, N.Y. Nguyen, G.M. Walker, J.B. Buse, Z. Gu, Microneedles integrated with pancreatic cells and synthetic glucose-signal amplifiers for smart insulin delivery, Adv. Mater. 28 (2016) 3115–3121.
[314] W. Chen, R. Tian, C. Xu, B.C. Yung, G. Wang, Y. Liu, Q. Ni, F. Zhang, Z. Zhou, J. Wang, G. Niu, Y. Ma, L. Fu, X. Chen, Microneedle-array patches loaded with dual mineralized protein/peptide particles for type 2 diabetes therapy, Nat. Commun. 8 (2017) 1777.

[315] P. Pei, F. Yang, J. Liu, H. Hu, X. Du, N. Hanagata, S. Zhao, Y. Zhu, Composite-dissolving microneedle patches for chemotherapy and photothermal therapy in superficial tumor treatment, Biomater. Sci. 6 (2018) 1414–1423.
[316] X. Zhang, G. Chen, Y. Liu, L. Sun, L. Sun, Y. Zhao, Black phosphorus-loaded separable microneedles as responsive oxygen delivery carriers for wound healing, ACS Nano 14 (2020) 5901–5908.
[317] S.A. Coulman, A. Anstey, C. Gateley, A. Morrissey, P. McLoughlin, C. Allender, J.C. Birchall, Microneedle mediated delivery of nanoparticles into human skin, Int. J. Pharm. 366 (2009) 190–200.
[318] H. Vallhov, W. Xia, H. Engqvist, A. Scheynius, Bioceramic microneedle arrays are able to deliver OVA to dendritic cells in human skin, J. Mater. Chem. B 6 (2018) 6808–6816.
[319] M. del Pilar Martin, W.C. Weldon, V.G. Zarnitsyn, D.G. Koutsonanos, H. Akbari, I. Skountzou, J. Jacob, M.R. Prausnitz, R.W. Compans, Local response to microneedle-based influenza immunization in the skin, mBio 3 (2012) e00012-12.
[320] F.S. Quan, Y.C. Kim, R.W. Compans, M.R. Prausnitz, S.M. Kang, Dose sparing enabled by skin immunization with influenza virus-like particle vaccine using microneedles, J. Control Release 147 (2010) 326–332.
[321] Y. Hu, B. Xu, J. Xu, D. Shou, E. Liu, J. Gao, W. Liang, Y. Huang, Microneedle-assisted dendritic cell-targeted nanoparticles for transcutaneous DNA immunization, Polym. Chem. 6 (2015) 373–379.
[322] P.M. Elias, The skin barrier as an innate immune element, Semin. Immunopathol. 29 (2007) 3–14.
[323] C. Robert, T.S. Kupper, Inflammatory skin diseases, T cells, and immune surveillance, N. Engl. J. Med. 341 (1999) 1817–1828.
[324] M. Rahman, S. Akhter, S. Beg, Nanomedicine advances in topical infective and non-infective skin diseases therapy, Recent Pat. Antiinfect Drug Disco 13 (2018) 104.
[325] R. Saraceno, A. Chiricozzi, M. Gabellini, S. Chimenti, Emerging applications of nanomedicine in dermatology, Ski. Res Technol. 19 (2013) e13–e19.
[326] B. Baroli, Penetration of nanoparticles and nanomaterials in the skin: fiction or reality? J. Pharm. Sci. 99 (2010) 21–50.
[327] O. Perumal, B. Michniak-Kohn, E. Touitou, M.S. Roberts, A special issue on skin nanotechnology, J. Biomed. Nanotechnol. 6 (2010) 405–407.
[328] M. Rahman, S. Beg, M.Z. Ahmad, I. Kazmi, A. Ahmed, Z. Rahman, F.J. Ahmad, S. Akhter, Omega-3 fatty acids as pharmacotherapeutics in psoriasis: current status and scope of nanomedicine in its effective delivery, Curr. Drug Targets 14 (2013) 708–722.
[329] L.M. Morton, T.J. Phillips, Wound healing and treating wounds: differential diagnosis and evaluation of chronic wounds, J. Am. Acad. Dermatol. 74 (2016) 589–605 quiz 605-586.
[330] R.G. Frykberg, J. Banks, Challenges in the treatment of chronic wounds, Adv. Wound Care 4 (2015) 560–582.
[331] R. Cortivo, V. Vindigni, L. Iacobellis, G. Abatangelo, P. Pinton, B. Zavan, Nanoscale particle therapies for wounds and ulcers, Nanomed. (Lond.) 5 (2010) 641–656.
[332] B. Saleh, H.K. Dhaliwal, R. Portillo-Lara, E. Shirzaei Sani, R. Abdi, M.M. Amiji, N. Annabi, Local immunomodulation using an adhesive hydrogel loaded with mirna-laden nanoparticles promotes wound healing, Small 15 (2019) e1902232.
[333] Z. Zhou, S. Joslin, A. Dellinger, M. Ehrich, B. Brooks, Q. Ren, U. Rodeck, R. Lenk, C.L. Kepley, A novel class of compounds with cutaneous wound healing properties, J. Biomed. Nanotechnol. 6 (2010) 605–611.
[334] X. Yan, W.W. Fang, J. Xue, T.C. Sun, L. Dong, Z. Zha, H. Qian, Y.H. Song, M. Zhang, X. Gong, Y. Lu, T. He, Thermoresponsive in situ forming hydrogel with sol-gel irreversibility for effective methicillin-resistant staphylococcus aureus infected wound healing, ACS Nano 13 (2019) 10074–10084.
[335] A. Nishiguchi, F. Sasaki, H. Maeda, M. Kabayama, A. Ido, T. Taguchi, Multifunctional hydrophobized microparticles for accelerated wound healing after endoscopic submucosal dissection, Small 15 (2019) e1901566.
[336] R. Liebers, D. Jager, Surgical wound immunotherapy, Nat. Nanotechnol. 14 (2019) 7–8.
[337] Y. Jeong, Y.K. Jo, B.J. Kim, B. Yang, K.I. Joo, H.J. Cha, Sprayable adhesive nanotherapeutics: mussel-protein-based nanoparticles for highly efficient locoregional cancer therapy, ACS Nano 12 (2018) 8909–8919.
[338] Q. Chen, C. Wang, X. Zhang, G. Chen, Q. Hu, H. Li, J. Wang, D. Wen, Y. Zhang, Y. Lu, G. Yang, C. Jiang, J. Wang, G. Dotti, Z. Gu, In situ sprayed bioresponsive immunotherapeutic gel for post-surgical cancer treatment, Nat. Nanotechnol. 14 (2019) 89–97.
[339] X. Liu, Z. Feng, C. Wang, Q. Su, H. Song, C. Zhang, P. Huang, X.J. Liang, A. Dong, D. Kong, W. Wang, Co-localized delivery of nanomedicine and nanovaccine augments the postoperative cancer immunotherapy by amplifying T-cell responses, Biomaterials 230 (2020) 119649.
[340] C. Feng, J. Ouyang, Z.M. Tang, N. Kong, Y. Liu, L.Y. Fu, X.Y. Ji, T. Xie, O.C. Farokhzad, W. Tao, Germanene-based theranostic materials for surgical adjuvant treatment: inhibiting tumor recurrence and wound infection, Matter 3 (2020) 127–144.

Dr. Peisen Zhang is a postdoctoral Fellow in Guangzhou First People's Hospital since 2020. He received his B.Sc. in applied chemistry (2015) from Central South University and Ph.D. in physical chemistry (2020) from the Institute of Chemistry, Chinese Academy of Sciences. His major research focuses on the synthesis and bioapplications of functional nanomaterials.

Dr. Lihong Jing is an associate professor in the Institute of Chemistry, Chinese Academy of Sciences. She received her PhD degree in Physical Chemistry (2011) under the supervision of Prof. Mingyuan Gao. She worked as a research assistant (2011)/associate (2013)/fellow (2016) in Prof. Andrey Rogach lab from City University of Hong Kong. She worked in Prof. Robert Langer lab from Koch Institute for Integrative Cancer Research at Massachusetts Institute of Technology (MIT) from 2017 to 2018. She is a "Member of Youth Innovation Promotion Association CAS". Her major research focuses on the synthesis and applications of multifunctional luminescent nanomaterials.

Dr. Kevin McHugh is an Assistant Professor and CPRIT Scholar in Cancer Research in the Department of Bioengineering at Rice University. Dr. McHugh received his bachelor's degree in Biomedical Engineering from Case Western Reserve University, his master's degree and Ph.D. from Boston University, and was a Postdoctoral Fellow in Robert Langer's laboratory at the Massachusetts Institute of Technology (MIT) where his research aimed to create vaccine-delivery systems for low-resource settings. His lab currently focuses on the development of biomaterial platforms for drug delivery and tissue engineering with an emphasis on advanced fabrication techniques, biodegradable polymers, and bioorthogonal click chemistry.