MINI-REVIEW

The recent progress of inorganic-based intelligent responsive nanoplatform for tumor theranostics

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Abstract

Inorganic nanoplatform exhibits great potentials in drug delivery and responsive release attributed to its inherent physicochemical properties, good biocompatibility, surface modification, and easy synthesis. In this review, the recent progresses on the inorganic smart bio-responsive nanoplatforms for tumor theranostics are summarized, which could be triggered by either endogenous tumor microenvironment (TME) or the exogenous physical and hopeful to achieve safe, precise, and high efficacy for tumor therapy. Notably, these nanoplatforms generally are dependent on the intelligent and multifunctional design of nanocarriers, including mesoporous silica nanoparticles (MSNs), black phosphorus (BP), Prussian blue (PB), and other inorganic-based nanoparticles. Finally, the perspectives and challenges of inorganic nanoplatform in the future translational medicine are proposed.

KEYWORDS

drug delivery, inorganic nanoplatform, intelligent response, tumor theranostics

1 | INTRODUCTION

Rapid, safe, and effective therapy of malignant tumors has always been the goal pursued by researchers. However, the traditional cancer treatments, including surgery, radiotherapy (RT), and chemotherapy, are still unsatisfactory.¹ For instance, cancer recurrence and metastasis are generally the main factors that induce the failure of surgical excision.³ The high-energy X-ray in RT is inevitable cause of damage to normal tissues,⁴ and the severe multidrug resistance (MDR) and side effects extremely limit the application of traditional chemotherapy.⁵ As a result, to improve the poor prognosis of monotherapy, numerous intelligent nanoplatforms have been developed for satisfactory diagnostic and therapeutic effects.⁶ For example, an intelligent nanoplatform has been fabricated that can respond to near-infrared (NIR) photothermal to release NO gas and chemotherapy drugs. The generation of NO...
gas is demonstrated to relieve the MDR by inhibiting the activity of P-glycoprotein (P-gp) and further enhances the toxicity of chemotherapy against MDR tumor. Moreover, high-Z elements combined with catalase-like activity of precious metal elements to form an X-ray sensitized generator could be employed to trigger endogenous H$_2$O$_2$ into O$_2$, relieving tumor hypoxia and enhancing RT, as well as reducing the radiation dose of X-ray and exhibiting a lower damage to normal tissues. As expected, these nanoplatforms can effectively compensate for the side effects of traditional cancer treatments, to greatly enhance high efficacy of tumor theranostics. 

There has been rapid development of nanotechnology, and the progress of biomedical nanomaterials has been greatly promoted. Organic materials such as liposomes and self-assembly micelles have been extensively investigated for drug delivery, which exhibit promising prospect of results because of the favorable biocompatibility and loading capacity. Nevertheless, organic nanomaterials are liable to appear in unpredictable dimensional variations when placed in physiological environments or loaded with therapeutic cargo. Comparably, inorganic materials have been widely favored due to their good biocompatibility, easy synthesis, uniform and controllable particle size, and surface modification, which show a great potential in drug delivery and responsive release. 

Attributed to the unique physicochemical structure of inorganic nanoparticles, wide applications in imaging, magnetocaloric, detection, and therapy (e.g., hyperthermal therapy, radiotherapy, sonodynamic therapy) have been achieved. Typically, to achieve the precise treatment in lesion regions, these inorganic-based nanoplatforms are often designed to be activated by endogenous tumor microenvironment (TME) or exogenous stimuli (e.g., light, ultrasound [US], X-ray, magnetism, heat). The activators of TME include weak acid, reactive oxygen species (ROS), glutathione (GSH), and special active protease, and so forth.

Herein, we focused on the recent research progresses on some typical inorganic-based intelligent responsive nanoplatforms; for example, mesoporous silica nanoparticles (MSNs), black phosphorus (BP), Prussian blue (PB), and so forth, and for tumor theranostics and outlook, the current opportunities and challenges are summarized in Figure 1 and Table 1.

2 MSN-BASED NANOPLATFORMS

Attributed to the high pore volume, large surface area, tunable pore and nanostructure, abundant surface chemical property, and good biocompatibility, MSNs have been extensively explored for drug delivery and controlled release, bio-imaging, and synergistic tumor therapy. 

The porous structure of MSNs provides cavities that can host and release a great variety of biomolecules and therapeutic agents. In fact, the versatility of MSNs in size, morphology, and texture has fueled their application as controlled drug-delivery nanocarriers. Modification with the multifunctional groups or doping with active metal ions could endow MSN the carrier targeting and drug-responsive release, achieving highly therapeutic activity of MSN-based nanoplatforms.

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Lv and coworkers used folate (FA) as an active ligand to modify the surface of MSN endowing with the tumor-targeting capability of MSN (MSN-FA). After loaded with chemotherapy drug...
TABLE 1  Summary of various inorganic-based intelligent responsive nanoplatforms

| Platforms | Nanoparticles          | Stimulus | Tumor model | References |
|-----------|------------------------|----------|-------------|------------|
| MSNs      | I/D@MSN               | NIR      | 4T1         | 31         |
|           | MSN-FA-TAN-MB         | US       | H22         | 34         |
|           | CM@MON@DOX            | X-ray    | 4T1         | 39         |
|           | L-Arg-HMON-GOx        | Glucose/H2O2 | U87MG     | 40         |
|           | MSN-S-S-HFn-DOX       | GSH      | PANC-1      | 41         |
|           | GPDC-MSNs             | pH       | Huh-7       | 42         |
| BP        | BPN/MnO2/DOX          | NIR      | HeLa        | 43         |
|           | Au/BP@MS              | US       | MCF-7       | 55         |
|           | RGD-Ir@BP             | X-ray    | CNE-2       | 44         |
|           | Cy5-dHeme-BPNS-FA     | H2O2/NIR | HeLa        | 57         |
|           | BP@ZIF-8@DOX          | pH       | HCT-116     | 59         |
| PB        | DTX@m-PB-NO           | NIR      | 4T1         | 65         |
|           | LMWHA-MPB/HMME        | US       | 4T1         | 67         |
|           | HMPB/Bi2S3            | X-ray/H2O2 | MCF-7     | 68         |
|           | mGPB                  | H2O2/NIR | 4T1        | 69         |
|           | DCF@PVP/Cu-HMPB       | pH       | 4T1        | 70         |
| Others    | Apt-pHEMA(CA)@UCNP    | NIR      | Raji        | 74         |
|           | ZGO@TiO2@ALP-NEs      | US       | GBM         | 45         |
|           | DOX@Fe(III)@WS2-PVP   | H2O2     | HT29        | 80         |
|           | IR780/DOX@ZIF-DH      | pH       | HeLa        | 83         |

Tanshinone IIA (TAN), the MSN-FA was further encapsulated in a microbubble (MSN-FA-TAN-MB) to realize tumor-targeting and US-responsive release of the drug under US image monitoring. Moreover, it is reported that US can trigger the N,N'-di-sec-butyl-N,N'-dinitroso-1,4-phenylenediamine (BNN6, NO donor) to generate NO gas, which can combine with superparamagnetic iron oxide nanoparticles (SPION) to achieve magnetic resonance imaging (MRI)-guided US-responsive NO gas therapy (BNN6-SPION@hMSN).

X-ray owns an extremely high penetration depth in vivo, and low-dose X-ray radiation can potentially trigger the release of drug both temporally and spatially without any additives. For instance, in order to achieve on-demand release of chemotherapy drug and tumor-targeting, Shao et al. synthesized cancer cell membrane-coated mesoporous organosilica nanoparticles (CM@MON@DOX), which could realize homology targeting and controlled release DOX via cleavage of diselenide bonds under low-dose X-ray radiation, resulting in DOX-mediated chem-immunotherapy.

Besides exogenous stimuli-responsive drug release, endogenous stimuli-responsiveness (e.g., weak acidity, H2O2, GSH, active enzyme) can further realize the intelligent and precise therapy of nanomedicines. Fan et al. reported a glucose-H2O2 cascade-responsive NO release nanoplatform (L-Arg-HMON-GOx), which was based on L-Arg and glucose oxidase (GOx) co-loaded into HMON. Moreover, to improve drug targeting and endogenous responsive release, Zink and coworkers used MSN as carrier to load DOX and functionalized with 2-2’ dithiodipyridine to bond human H chain ferritin (HFn) as nanovalve for intracellular redox-triggered drug release (MSN-S-S-HFn-DOX). The nanovalve can be autonomously activated by reduction of the disulfide bonds, which results in HFn dissociation and drug release when exposed to glutathione (GSH). Similarly, our group previously fabricated a GSH-responsive MONs, which loaded DOX and were effectively activated by disulfide bonds for release drugs (Figure 2A).

3 | BLACK PHOSPHORUS-BASED NANOPLATFORMS

Black phosphorus (BP) nanosheets have been widely employed for tumor treatment due to good...
biodegradability, biocompatibility, photosensitivity, and photothermal efficiency. As known to all, biosafety is a major issue for the in vivo application of nanoagents, as a large amount of nanobiomaterials still suffer from poor biodegradability. The excretion from body is incomplete, and the accumulation of nanobiomaterials may cause risks of long-term toxicity in human body. It is noted that the most significant advantage of BP is that they can be degraded into nontoxic phosphates, and P is an important element in human body, which could effectively circumvent the long-term accumulation issue in vivo. Benefiting to its high NIR photothermal conversion efficiency, BP could be served as an effective photosensitizer (PS) to generate ROS, and has attracted enormous attention in photothermal therapy (PTT) and photodynamic therapy (PDT). In addition, as a nonmetallic layered semiconductor, BP owns a higher specific surface area compared to other two-dimensional materials, which endows it with excellent drug loading capacity due to its pleated lattice configuration. Interestingly, BP can be responsive to TME and exogenous stimuli for drug release, enabling it to be an ideal nanocarrier candidate for precise therapy of cancer.

NIR light is shown to be an exogenous stimulus that has been widely utilized in PTT and PDT, attributed to its less tissue invasiveness, low side effect, and deep tissue penetration depth. Wang et al. reported a class of compact MnO2-loaded BP nanostructure for delivering drug (DOX) and tumor-specific diagnosis (BPN/MnO2/DOX).
Interestingly, the obtained BPN/MnO$_2$/DOX nanosponge exhibited a catalase-like activity that catalyzed the endogenous H$_2$O$_2$ to generate O$_2$ for enhancing PDT. Meanwhile, such BP-based nanoplatforms show an intelligent drug-release behavior under the exogenous NIR irradiation in tumor lesions, combined with its high photothermal performance to achieve good synergistic PDT and chemotherapy (Figure 2C). Similarly, Shi’s group developed an intelligent nanoplatform via integrating biocompatible photosynthetic cyanobacteria with BP nanosheets to form Cyan@BPNSs, which could in situ generate O$_2$ through photosynthesis by cyanobacteria under laser irradiation, combined with the photosensitization of BP to enhance the generation of $^1$O$_2$, resulting in strong cancer cell killing effect.\(^4\)

It is well known that US and X-ray can obtain the deeper tissue-penetrating depth in comparison with NIR, showing a great advantage of treatment in deep tumor. Attributing to the piezoelectric properties of BP nanosheet, Mei’s group coated MnO$_2$ on Au nanoparticle-anchored BP nanosheets and decorated with soybean phospholipid to construct a sonoactivated oxidative stress amplification nanoplatform (Au/BP@MS).\(^5\) Briefly, the Au/BP@MS exhibited increased ROS generation efficiency under US irradiation in tumor region due to BP-based nanosensitizer-induced improvement of hole–electron separation as well as MnO$_2$-mediated O$_2$ generation, thus leading to high efficient cancer cell apoptosis. Moreover, Yang et al. innovatively constructed a covalently functionalized few-layer BP nanosheets that not only boosted the generation of ROS by US, but also decreased the cytotoxicity relative to the pristine BP.\(^6\) Additionally, BP nanosheets also can be activated by X-ray to produce ROS that exhibit great potential in radiosensitization. Chen and coworkers employed the unsaturated iridium complex to coordinate with BP nanosheet to obtain two-dimensional layered nanoparticles (RGD-Ir@BP NPs).\(^4\) Intriguingly, the Ir complex played an important role in enhancing the photoelectric properties and photoinduced charge carrier dynamics of BP, thus RGD-Ir@BP NPs produce obviously enhanced ROS after X-ray irradiation (Figure 2D).

Generally, catalyzing tumor endogenous H$_2$O$_2$ to generate O$_2$ is a promising strategy for alleviating tumor hypoxia as well as sensitizing PDT, RT, sonodynamic therapy (SDT), or immunotherapy. Lei and coworkers used the BP nanosheet as both photosensitizer and nanocarrier that loaded with folate and a blocker DNA duplex of 5’-Cy5-aptamer-heme/3’-heme-labeled oligonucleotides (Cy5-dHeme-BPNS-FA).\(^5\) This nanoplatform could convert endogenous H$_2$O$_2$ to O$_2$ via the in situ decomposition reaction by Heme, thus enhancing the generation of $^1$O$_2$ after the irradiation by NIR laser. Furthermore, catalase-like platinum (Pt) nanoparticles were developed as nanoenzyme to anchor onto the surface of BP nanosheet, conjugated with Ce6 and PEGylation to obtain BP/Pt-Ce6@PEG NSs.\(^5\) The prepared BP/Pt-Ce6@PEG NSs could catalyze H$_2$O$_2$ into O$_2$ in situ to relieve tumor hypoxia and boost the production of ROS. Inspired by the weak acidic TME, a pH-sensitive drug-delivery system was designed by Zhang’s group.\(^5\) The BP nanosheets were encapsulated into ZIF-8 and subsequently loaded with DOX to form BP@ZIF-8@DOX nanoplatform, which were responsive to the low pH to release DOX and combined with PTT for synergistic therapy.

4 | PRUSSIAN BLUE-BASED NANOPLATFORMS

PB is a mixed-valence iron hexacyanoferrate (Fe$_4$[Fe(CN)$_6$]$_3$) with high biocompatibility and has been approved for the clinical treatment of radioactive poisoning by Food and Drug Administration (FDA).\(^5\) Typically, PB nanoparticles were utilized as a drug carrier for controlled drug release due to its controllable morphology and easy surface functionalization, which were also reported as a fluorescent nanoprobe by simply integrating fluorescein isothiocyanate (FITC) into hollow mesoporous PB for specific detection of HClO in cancer cells.\(^6\) Specifically, the charge transfer between Fe$^{3+}$ and Fe$^{2+}$ in the structure of PB endows its strong near-infrared absorption in the 600–1000 nm range, exhibiting a great potential in PTT and photoacoustic (PA) imaging.\(^5\) More interestingly, PB NPs could be served as a versatile nanozyme with multiple enzyme-like activities to scavenge ROS against ROS-related disease as well as to catalyze tumor endogenous H$_2$O$_2$ into O$_2$ to relieve tumor hypoxia. Additionally, PB NPs were reported to act as a novel photosensitizer with efficient production of $^1$O$_2$, via NIR irradiation-induced energy transfer for cancer therapy.\(^6\)

Our group previously reported that Gd$^{3+}$-doped PB endowed PB with tunable localized surface plasmon resonance (LSPRs) from 710 to 910 nm, which provides a powerful nanoplatform for more precise diagnosis and higher therapeutic efficiency for tumors.\(^6\) In order to design a NIR laser-controlled drug release nanoplatform, Zhang and coworkers prepared sodium nitroprusside (SNP)-doped mesoporous PB, followed by loading anticancer drug docetaxel (DTX) to form DTX@m-PB-NO NPs.\(^6\) The result showed that DTX@m-PB-NO NPs exhibited an excellent NIR laser-responsive NO release behavior that can be controlled by adjusting the laser intensity and irradiation time. Additionally, Shen’s group demonstrated for the first time that PB could be served as a novel photosensitizer with efficient generation of $^1$O$_2$ under NIR-induced energy transfer.\(^6\)
As an effective drug carrier, mesoporous PB exhibits efficient drug loading capacity and subsequently utilized for US or X-ray stimulus-response for tumor therapy. For instance, our group constructed a US/PA imaging guided and NIR triggered synergistic thermo-chemotherapy by using perfluoropentane (PFP) and DOX co-loading into hollow mesoporous PB (HMPB).\cite{66} Moreover, Zhang et al. prepared mesoporous PB that integrated with low molecular weight hyaluronic acid (LMWHA) surface modification and sonosensitizer hematoporphyrin monomethyl ether (HMME) to obtain LMWHA-MPB/HMME NPs, which acted as catalase to decompose endogenous H2O2 into O2 and further enhanced the generation of ROS via US.\cite{67} Additionally, Li and coworkers synthesized Bi2S3 quantum dot-doped HMPB (HMPB/Bi2S3) for amplified tumor oxidative stress by PB-based Fenton reaction and a consumer of GSH, augmenting Bi2S3-mediated RT.\cite{68}

The unique properties of the TME enable nanomedicines to achieve specific responses and acquire high efficient cancer treatment.\cite{51} Specifically, Zhang’s group reported an intelligent nanozyme that was designed to target tumor cell via camouflaged homologous tumor cell membrane and glucose (GOx)-loaded HMPB (mGPB) NPs.\cite{69} Interestingly, the nanozyme acted as catalase-like to catalyze H2O2 into O2 in the dark, while played as peroxidase and oxidase to utilize H2O2 to generate 1O2 and OH under NIR irradiation. Wu et al. designed an HMPB-based therapeutic nanoplatform, which was constructed by encapsulating drug disulfiram (DSF) into copper-enriched and polyvinylpyrrolidone (PVP)-decorated HMPB (DSF@PVP/Cu-HMPB) NPs.\cite{70} They found that DSF@PVP/Cu-HMPB NPs were responsive to the endogenous weak acidity in TME, following by co-release of DSF and Cu2+ to form cytotoxic bis(N,N-diethyl dithiocarbamato) copper(II) complexes (CuL2) via DSF-Cu2+ chelating reaction, thus remarkably inducing tumor apoptosis. Meanwhile, our group developed an Mn-containing PB (MnPBA) shell-coated HMPB core to form core–shell HMPB@MnPBA. A good positive correlation between pH-responsive MRI intensity and DOX release was found, enabling MRI-monitored drug release for efficient tumor chemotherapy.\cite{71}

## 5 OTHER INORGANIC-BASED NANOPROTOCOLS

In addition to above-mentioned intelligent responsive nanoplatforms, the intrinsic physiochemical property of some other inorganic nanoparticles can also enable them to be smart nanosystems for diseases theranostics. As a typical paradigm, upconversion luminescent nanoparticles (UCNPs) can convert low-energy long-wavelength NIR light into high-energy short-wavelength ultraviolet (UV) or visible light via the anti-Stokes effect. The emission spectrum of UCNPs exhibits high continuity, good stability, no photofading and photochemical degradation, especially suitable for fluorescent labeling, deep tumor fluorescence imaging, NIR-based PTT, and PDT.\cite{73} Du et al. inspired by the NIR up-conversion of UCNPs, modified poly (2-hydroxyethyl methacrylate) with pendants of cinnamate groups (CA) on the surface of UCNPs, followed by functionalization with anti-CD20 aptamer to form Apt-pHEMA(CA)@UCNP.\cite{74} Notably, with the irradiation of 980 nm laser, UCNPs could convert it into UV light and induce the cross-linking of CA groups, leading the aggregation of CD20 receptor and cell apoptosis. In parallel, Yan and coworkers utilized the heterostructure of core–shell UCNP@porphyrinic metal–organic frameworks (MOFs) to generate ROS via energy transfer from UCNP core to the MOF shell under NIR irradiation, and synergy against cancer with tirapazamine-mediated chemotherapy was achieved (Figure 2F).\cite{46}

TiO2 is an excellent inorganic sonosensitizer that can produce high cytotoxic ROS via US cavitation for SDT.\cite{75} In order to surmount blood–brain-barrier (BBB) and tumor heterogeneity, Li and coworkers fabricated a neutrophil-delivered nanosensitizer for US-boosted chemo/immunotherapy for glioblastoma, which was composed of ZnGa2O4:Cr3+ (ZGO) core and hollow TiO2 shell and then encapsulated with paclitaxel (PTX)-loaded liposome to form ZGO@TiO2@ALP (Figure 2E).\cite{45} The obtained nanoplatform could penetrate through BBB for glioblastoma accumulation, followed by ROS generation and liposome destruction for PTX release to augment therapy under US irradiation. Furthermore, Zhang et al. constructed novel core–shell nanoparticles (TiO2@Cap NPs), with enhanced ROS generation and controllable release of Ca2+ in weak acidic TME upon US irradiation.\cite{76} This nanosensitizer could effectively induce mitochondrial dysfunction through overloading intracellular Ca2+ ions and further synergizing with SDT.

Recently, intelligent Fe-based nanoplatforms have attracted much focus. Fe species cannot only be employed as MRI contrast agents, but also acted as nanozyme, showing versatile applications, such as bio-detection, bio-imaging, and cancer treatment.\cite{79} For example, an interesting DOX@Fe(III) species-WS2–PVP nanoplatform with self-circulating redox capability was developed. Therein, Fe(III) species could react with WS2 to form Fe2+ and WO42–, accelerating Fe2+-mediated Fenton to produce ROS, while accompanying with the biodegradation of nanosystem. Moreover, the NIR triggered WS2 to produce temperature rise, further boosting ROS generation beneficial for the synergistic CDT, PTT, and chemotherapy of tumor.\cite{80} Generally speaking, the simpler the composition...
of the nanosystem, the better is the potential of clinical transformation. Therefore, those nanoplatforms with simple components but powerful therapeutic functions are much attractive. Very recently, our group developed a simple composition with multifunctional Fe1−xS-PVP NPs, which could respond to the endogenous \( \text{H}_2\text{O}_2 \) via Fenton reaction to produce ROS, and their high photothermal performance further facilitated the process (Figure 2G).15 More importantly, Fe1−xS-PVP NPs could in situ produce \( \text{H}_2\text{S} \) in the weakly acidic TME and effectively inhibit cellular respiration through suppressing the enzyme cytochrome c oxidase (COX IV) expression, demonstrating the excellent antitumor effect by synergistic \( \text{H}_2\text{S}/\text{PTT}/\text{CDT} \).

It is known that MOFs exhibit great potential application in nanomedicine due to the advantages of large specific surface area, uniform pore structure, and high biocompatibility.82 Thereinto, zeolitic imidazolate framework (ZIF) as one kind of MOFs system, which owns its inherent superiority of pH sensitivity and high drug-loading capacity has become one of the ideal carriers of intelligent responsive nanoplatforms. Recently, our group reported an acidic sensitive ZIF-based nanoplatform, which co-loaded DOX and photosensitizer IR780 to form \( \text{IR780/DOX}@\text{ZIF} \), followed by coating a spermine-modified acetalated dextran (SAD) shell to avoid premature drug release from ZIF, which could response TME to release IR780 and DOX within tumor region, exhibiting the high effective synergy of chemotherapy/PDT.83 In order to achieve more efficacy for tumor treatment, we further constructed a dual-responsive drug delivery nanoplatform with co-loading of ribonuclease A (RA) and DOX to obtain \( \text{ZIF-DOX/RA}@\text{DG} \). Specifically, the dextran polymer shell (DG) with \( \gamma \)-glutamyl transpeptidase (GGT) and pH dual-response function was coated on the surface of ZIF carrier.47 Once the negatively charged \( \text{ZIF-DOX/RA}@\text{DG} \) came in contact with the highly expressed GGT and weak acidic TME, cationization and structural dissociation occurred in the DG shell, leading to the precise co-delivery of two drugs to the deep tissue of the tumor by charge reversal and endocytosis, thus greatly improving the synergistic antitumor therapy (Figure 2H).

6 | CONCLUSION

To utilize the unique physicochemical properties, many kinds of inorganic nanoparticles have been employed in the biomedicine field in the recent years. Notably, some typical inorganic-based intelligent responsive nanoplatforms generally endow with inherent advantages, such as good biocompatibility, easy for synthesis and surface modification, presenting great potentials in drug delivery and responsive release. For example, owning to the high pore volume and large surface area, MSNs were taken as one of the most attractive drug delivery nanocarriers in tumor therapy. Moreover, black phosphorous (BP) and PB with excellent NIR photothermal conversion efficiency have aroused enormous attention in PTT, and has been utilized as drug carriers for NIR-responsive release. Meanwhile, BP and PB could also be employed as effective photosensitizer and sonosensitizer for photodynamic therapy (PDT) and sonodynamic therapy (SDT), respectively. Similarly, other nanoplatforms based on upconversion luminescent nanoparticles (UCNPs), \( \text{TiO}_2 \), Fe-based nanoparticles, and ZIF, and so forth could be intelligently activated by exogenous or endogenous stimuli, to exert excellent anticancer effect ascribed to their unique intrinsic functionality.

It should be noted that compared with pure inorganic nanoparticles, those inorganic nanoparticles modified with protein or organic functional molecules could exhibit more attractive advantages in future applications, especially for those nanoplatforms with simple composition but multifunctionality. Protein and organic molecules can efficiently improve the hemocompatibility and degradability of inorganic nanoparticle, as well as prolong the blood circulation to aggregate in the targeted region. Nevertheless, it is still urgent to tackle the issue of facile and stable mass production of these intelligent nanoplatforms to meet the basic requirement of clinical translation.

Despite some encouraging preclinical results so far, these inorganic nanoplatforms still encounter many challenges. Typically, although inorganic nanoparticles exhibit good biocompatible and low systemic toxicity to a certain extent, the long-term biosafety puzzle is urgent to be resolved before entering the clinical translation. Besides, the exact biological mechanism of these multifunctional nanoplatforms demands to be further verified. How to accurately judge the therapeutic mechanism of nanoparticles against cancer in a complex and changeable body is an extremely vital link in future clinical applications. Moreover, facilitating the accumulation of nanoparticles in tumor region via ingenious design of nanosystems and escaping capture by reticuloendothelial system are the prerequisites for improving the therapeutic effect. With the continuous advances in nanotechnology and nanomedicine, more interesting inorganic-based intelligent responsive nanoplatforms, as we believe, will be expected to achieve clinical transformation in the future.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

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