The potential biomedical platforms based on the functionalized Gd@C\textsubscript{82} nanomaterials

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Funding information
National Natural Science Foundation of China, Grant/Award Number: 51902313; National Major Scientific Instruments and Equipments Development Project, Grant/Award Number: ZDYZ2015-2

Abstract
Gadolinium metallofullerene (Gd@C\textsubscript{82}), a novel star carbonaceous material, has allured considerable attention due to its attractive properties. Increasing evidence exhibits that functionalized Gd@C\textsubscript{82} nanomaterials have great potential in various biomedical applications. Except for the earliest bioapplication as the next-generation of magnetic resonance imaging contrast agent, Gd@C\textsubscript{82} nanomaterials perform excellent anti-cancer activities. Functionalized Gd@C\textsubscript{82} nanomaterials could inhibit tumor growth by suppressing tumor angiogenesis, cutting off the existing tumor vasculature under radiofrequency irradiation or modulating immune cells. In addition, Gd@C\textsubscript{82} nanomaterials could be adjuvant agents to lower the toxicity of chemotherapeutic drugs and alleviate drug resistance. In particular, Gd@C\textsubscript{82} nanomaterials are demonstrated to regulate glucose and lipid metabolism, presenting superior anti-type 2 diabetes mellitus effects. With no detectable toxicity and pleiotropic biological effects, Gd@C\textsubscript{82} nanomaterials could be promising biomedical platforms in the future.

KEYWORDS
Antineoplastic activities, Functionalized Gd@C\textsubscript{82} nanomaterials, Metabolic disease regulators, MRI contrast agents, Vascular disrupting agents

1 | INTRODUCTION

With the booming development of nanotechnology, engineered nanoparticles, including carbon nanomaterials, are emerging as excellent platforms for biomedical application.\textsuperscript{1,2} As a unique class of carbon allotropes, fullerenes have allured a great deal of attention and been studied intensively since their discovery. Endohedral metallofullerene is formed when many metal atoms or metal clusters are put inside fullerenes.\textsuperscript{3,4} Derived from the unique structures of the outer fullerene cages and encaged metal clusters, metallofullerenes possess superb properties, such as excellent stability, para-magnetism, the large surface area, the unsaturated double bands on the surface, and the special surface easy to be functionalized.\textsuperscript{5} It has been reported that metallofullerenes could be modified by physical modification with polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), cyclodextrin, and so on, as well as chemical reactions by functional groups, presenting biological and pharmacological activity.\textsuperscript{5–8}

Gd@C\textsubscript{82} is a common gadolinium metallofullerene (gadofullerene), consisting of a core of gadolinium (Gd) atom and a closed outer sheath of 82 carbon atoms.\textsuperscript{3,9} After modified by functional groups of hydroxy, carboxyl, amino groups, and so on, Gd@C\textsubscript{82} exhibited high potential in biomedicine, such as...
magnetic resonance imaging (MRI) contrast, antitumor therapeutics, adjuvant therapeutic agents, metabolic diseases modulation, and so forth (Figure 1).10–20 In this review, we briefly summarize the recent progresses achieved in these potential biomedical applications of the functionalized Gd@C_{82} nanomaterials.

2 | TUMOR DIAGNOSIS AND TREATMENT BY FUNCTIONALIZED Gd@C_{82} Nanomaterials

2.1 | MRI contrast agents

The biomedical application of functionalized Gd@C_{82} materials stemmed from the seminal early works, in which Gd@C_{82} was polyhydroxylated as a potential new nanoplatfor for next-generation MRI contrast agents.21,22 And in recent years, these applications have been extensively investigated due to the high proton relaxivity and low toxicity of Gd@C_{82} nanomaterials.23–26 To be applied in vivo, gadofullerene was commonly modified by various functional groups, mainly including polyhydroxylated, carboxylated, and PEGylated-hydroxylated modification.27–29 And the differences in the type and number of groups on the surface of fullerene cages can result in different relaxivities. The most common methods to convert the gadofullerenes to hydrophilic materials are hydroxylation. Numerous studies indicated that polyhydroxylated Gd@C_{82} (Gd@C_{82}(OH)_m) exhibited a much higher r1 relaxivity, up to 12–14 folds at 0.5 T and six to eight times at 7.0 T compared with the commercial Magnevist.22,23 After modified by carboxylated groups, the Gd@C_{82}O_6(OH)_{16}(NHCH2CH2COOH)_8 was up to 1.02–1.15 times as much as Gd-DTPA (Magnevist) at 1.5 T. And the higher the pH values, the larger the relative intensity of MR signals, as the higher the pH values, the more aggregates.25 In addition, an organophosphonate functionalized Gd@C_{82} nanomaterial, Gd@C_{82}O_2(OH)_{16}(C(PO_3Et_2)_2)_{10}, exhibited the r1 value 6.5-folds as much as Gd-DTPA at 0.35 T.30 Studies also demonstrated that Gd@C_{82}O_x(OH)_y with more hemiketal groups presented much more higher relaxivities than those with fewer hemiketal groups, possibly resulting from the effects of the conversion between hemiketal groups and ketone analogs on the aggregation behavior of the Gd@C_{82} nanomaterials.31

Not just for MRI contrast agents, the Gd@C_{82} nanomaterials are applied to multimodal imaging with certain functionalization. After modified with an anti-GFP biotin, the Gd@C_{82} derivative not only exhibited high relaxivity, but also served as a fluorescence probe.32 Studies demonstrated that amino acid functionalized Gd@C_{82} derivative was modified by 64Cu labelling to realize the MRI/positron emission tomography (PET) hybrid imaging modalities.11 These all provide a great potential for developing novel next generation MRI contrast agents based on metallofullerenes.

2.2 | Angiogenesis inhibitors

It has been recognized that the neovasculature plays an essential role in tumor growth, survival, and metastasis, thus, the therapeutics targeting tumor angiogenesis have been thriving.33 Nowadays, various tumor angiogenesis inhibitors (TAI) were developed, which commonly act by inhibiting angiogenic stimulators, endothelial proliferation, proteolysis of extracellular matrix (ECM) and integrins.34

In 2005, it was demonstrated that the functionalized Gd@C_{82} nanoparticles, Gd@C_{82}(OH)_{22} (f-NPs), could prevent tumor growth in H22 hepatocellular carcinoma.35 And then, the tumor inhibition mechanisms were explored. The f-NPs, whose size is approximately 70 nm with 22 hydroxy groups on the carbon cages (Figure 2A), could suppress tumor angiogenesis by downregulating more than 10 angiogenic factors (Figure 2B), leading to the significant reduction of microvessel density and the insufficiency of tumor blood perfusion, and thus yielding a marked tumor growth inhibition with a tumor inhibitory rate much higher than the common tumor chemotherapeutic drug paclitaxel.20 Furthermore, f-NPs could also inhibit tumor angiogenesis by impairing matrix metalloproteinase (MMPs) activities (Figure 2C), as activated MMPs (specifically, MMP-2 and MMP-9) are responsible for proteolysis of the ECM, which is a prerequisite...
FIGURE 2  The tumor angiogenesis inhibition by Gd@C_{82}(OH)_{22} (f-NPs). (A) The synthesis and SEM image of f-NPs. (B) The downregulation of angiogenic factors by f-NPs. (C) Inhibition of f-NPs on MMP-2 and MMP-9 in tumor tissues. (D) The collagen fibers at tumor site in control and f-NPs–treated animals analyzed by Van Gieson staining. It was validated that f-NPs could not only depress MMPs expressions but also inhibit their activities by indirectly interacting with MMPs by a special binding mode, and thus suppress tumor growth.

In addition, the proteolysis of ECM plays a critical role in tumor neovascularity, tumor invasion, and metastasis. Therefore, targeting tumor ECM becomes an important antitumor therapy, which focuses on the collagen, elastin, proteoglycans, fibrous matrices, and so forth. Evidence suggests that f-NPs inhibit tumor metastasis by suppressing MMP production, subsequently reducing fibrous matrix degradation. Then, the “prison” made by a thick fibrous cage confined tumor cells and cut the communication between cancer- and tumor-associated macrophages (Figure 2D). And studies reported that f-NPs can firmly bind with tropocollagen, enhance the rigidity of the native structure of collagen molecules, promote the formation of an oligomer or a microfibril, and thus suppress the malignant progression of cancer cells.

2.3 Vascular disruption agents

Different with normal vessels tumor vasculatures possess special pathophysiological features, including high vascular permeability, chaotic architecture, non-uniform surface markers, and the lack of lymphatic drainage. According to these characterizations, known as the enhanced permeability and retention (EPR) effects, many vascular disruption agents (VDAs) were designed and applied clinically, such as CA4P, ZD6126, and DMXAA. However, there are always serious side-effects occurring such as tumor pain and cardiotoxicity.

Importantly, a new kind of functionalized Gd@C_{82} nanocrystals, (Gd@C_{82})_{n}(OH)_{n} (GFNCs), were synthesized via a novel solid–liquid reaction. Different from the previous hydroxylated Gd@C_{82} nanoparticles (f-NPs), GFNCs consist of a cluster of Gd@C_{82} crystal and further modification by outer functional groups (Figure 3A). And the gadofullerenes are spherical or ellipsoid particles with an average size of 140 nm (Figure 3B). Interestingly, it was demonstrated that GFNCs exhibited superior properties such as expansion by phase transition under RF irradiation and so on (Figure 3C). Accordingly, a novel antitumor technique was presented in 2015, which could disrupt abnormal tumor vasculatures with the help of RF. This therapeutic strategy opens a new gate for antineoplastic effects of functionalized Gd@C_{82} nanoparticles. Results showed that GFNCs possessed excellent anticancer activities in various tumors like H22 (Figure 3D), 4T1, HepG2, and so forth. Tumors were
FIGURE 3  The antitumor effects of (Gd@C$_{82}$)$_n$(OH)$_n$ nanocrystals (GFNCs) via disrupting preexisting tumor blood vessels. (A) Two Gd@C$_{82}$ nanomaterials with different structure synthesized by two different methods. (B) Cryo-TEM micrograph of GFNCs. The inset is the SAED pattern. (C) Size expansion of GFNCs after 200 MHz RF irradiation for 30 min. (D) The high antitumor effect by GFNCs under RF using H22 liver tumor models. (E) Tumor vascular disruption treated by RF-assisted GFNCs by DSFC. (F) Tumor vascular disrupting mechanism by RF-assisted GFNCs$^{19,45}$

observed to induce a rapid and extensive necrosis, and finally serious inner collapses 24 hours after RF-assisted GFNCs treatment.$^{19}$ And the tumor inhibition rate was up to 88.7% calculated by hematoxylin–eosin (HE) staining.$^{44}$ Then, the detailed process of disrupting tumor blood vessels by RF-assisted GFNCs was real-time monitored using a dorsal skin flap chamber (DSFC) model, which could visually observe the vascular structure and blood flow.$^{45}$ Tumor blood vessels were broken and hemorrhages 20 minutes after treatment, leading to remarkable collapse and fragmentation of the whole tumor vascular net. As time went by, the areas of bleeding were continually increased, the shape of the vessels became unrecognizable from DSFC window, and lastly the vessels became fuzzy and then invisible (Figure 3E).$^{45}$ However, normal vessels remained undamaged after treated by RF-assisted GFNCs.

Furthermore, the dynamic contrast enhanced (DCE)-MRI, a “gold standard” method to evaluate functional characteristics of the vascular net, was performed. Results indicated that the blood perfusion and the $K_{trans}$ values (the rate of transfer of the contrast agent from the blood to the interstitial space) of tumors were greatly and persistently decreased after treatment, suggesting the considerable destruction of capillary function of the tumor.$^{45}$ Additionally, the VE-cadherin was downregulated by RF-assisted GFNCs, which was an important transmembrane adhesion protein in endothelial cells located at intercellular junctions of tumor blood vessels.$^{44}$ After intravenous injection, GFNCs would rapidly flow along the normal blood vessels and penetrate the leaks of tumor vascular endothelial cells. With the properties of size-expansion by a phase transition, GFNCs would undergo explosive volume expansion and the possible rotation when the RF is applied. And thus, the networks of endothelia cells could be destroyed and abscised from the basilemma (Figure 3F).

With further exploration, a new β-alanine functionalized gadofullerene nanocrystals, (Gd@C$_{82}$)$_n$(Ala)$_n$, were developed and applied to vascular disruption. Compared with GFNCs, this new nanoparticle presented superior physicochemical properties, which could improve the antitumor effects as vascular disrupting agents.$^{46}$ The technique based on RF-assisted functionalized gadofullerene as a new tumor vascular disrupting strategy brings a new dawn for cancer treatment.

Notably, photodynamic therapy (PDT) is an important anticancer therapy, which damage tumor cells via light induced reactive oxygen species (ROS) with the assistance of light-absorbing photosensitizers (PSs). Different from the conventional cell-oriented PDT (C-PDT), a new photodynamic therapy targeting tumor vasculature (V-PDT) was constructed based on functionalized Gd@C$_{82}$ nanomaterials.$^{47}$ The results indicated that Gd-Ala could disrupt tumor vasculature under simultaneous light irradiation.

### 2.4 Immune modulators

Tumor immunotherapy has been flourishing in recent years, which focuses on triggering effective antitumor immunity.$^{48}$ Researches demonstrated that f-NPs presented specific immunomodulatory effects on T cells and macrophages (Figure 4A), including the polarization of the cytokine balance toward Th1 (T-helper cell type 1) cytokines, the stimulation of TH0 cells to differentiate proportionately more Th1 cells, the decreased secretion of Th2 (T-helper cell type 2) cytokines, and increased production of Th1 cytokines, and thus inhibited tumor growth.$^{18}$ Additionally, it was found that f-NPs could induce phenotypic maturation of dendritic cells (DC) (Figure 4B) by promoting cytokines release and enhance TH1 immune response.$^{49}$ Other research reported that f-NPs activated macrophages (Figure 4C) and promoted the secretion of proinflammatory cytokines like IL-6, IL-1β, and TNF-α, thereby preventing tumor progression.$^{50–52}$ Moreover, f-NPs could effectively depress tumor development by regulating TNF-α-mediating cellular
Apart from f-NPs, our groups reported that photo-triggered amino acid functionalized Gd@C82 (Gd-Ala) enhanced DCs’ maturation and activated T lymphocytes, promoting tumor ablation.47 Therefore, functionalized Gd@C82 nanomaterials could be immune modulators to inhibit tumor development.

### 2.5 Adjuvant therapeutics

Although chemotherapeutics is still the present-day mainstream of cancer therapy due to its convenience and high efficiency, there are considerable adverse effects, such as serious injury to normal tissues, drug resistance, and so on.55–58 To overcome these problems, adjuvant therapeutics is a promising alternative for novel cancer treatments. The commonly used chemotherapeutic agent cyclophosphamide (CTX) exhibited serious damage to bone marrow, heart, spleen, lungs, and so on, leading to observable white blood cells (WBC) and hemoglobin (HGB) reduction. Inspiringly, GFNCs could specifically accumulate in bone marrow and balance oxidative stress, resulting in the prominent increase of mouse blood cells (WBC) and pathological improvements of the primary organs (Figure 5A,B).15 As is known that the cisplatin (CP) is a cornerstone of the chemotherapeutic regimens, but acquired resistance confines its application. As shown in Figure 5C, CP exhibited high inhibiting effects on CP-sensitive tumors, but hardly worked on CP-resistant tumors. In contrast, CP combined with f-NPs inhibited both the CP-s and CP-r tumors.59 These results demonstrated that functionalized Gd@C82 nanomaterials could be a potential adjuvant therapeutic agent with reduction of toxicity and improvement of drug resistance.

### 3 THE METABOLIC DISEASE REGULATION BY FUNCTIONALIZED Gd@C82 NANOPARTICLES

Until now, the major biomedical applications of functionalized gadofullerene nanoparticles (GFNPs) focus on the tumor diagnosis and treatment, however, the superior biochemical properties promote this star nanomaterial to be applied in other biomedical platforms. Encouragingly, our group developed a new nanoplatform for metabolic disease based on functionalized Gd@C82 nanoparticles (GFNPs), especially for type 2 diabetes mellitus (T2DM).17 After intraperitoneal injection, GFNPs could accumulate in the pancreas and liver (Figure 6A), which makes T2DM treatment possible. And the fasting blood glucose of the diabetic db/db mice was decreased to normal after GFNPs treatment, and it still remained normal glucose levels even stopping drug administration (Figure 6B). Altogether, GFNPs could not only protect pancreatic β-cells against oxidative stress and inflammation, but also improve hepatic insulin resistance by inhibiting gluconeogenesis and promoting glycogenesis (Figure 6C). These results suggest that GFNPs could regulate glucose
metabolism, significantly decreasing blood glucose without hypoglycemia and realizing a sustainability antidiabetic effect.

Additionally, it was demonstrated that GFNPs could reduce the lipid deposition in liver tissues of diabetic mice (Figure 6D), indicating that GFNPs could regulate lipid metabolism.

4 | BIODISTRIBUTION AND BIOSAFETY OF FUNCTIONALIZED Gd@C₈₂ NANOMATERIALS

It should not be neglected that the biodistribution and biosafety of nanomaterials are the prerequisites for their clinical applications. Generally, there are two commonly used methods to detect the contents of Gd@C₈₂ nanomaterials, one is inductively coupled plasma mass spectrometry (ICP), another is radiolabeling. After intravenous injection, Gd@C₈₂ nanomaterials mainly accumulated in the liver, spleen, lungs, bone, and so on.¹⁵,⁴⁶,⁴⁷ Importantly, the biodistribution was different in Gd@C₈₂ nanomaterials with different functional groups modification. By ¹³¹I radiolabeled method, GFNCs was found to mainly accumulate in the liver, stomach, bone, spleen, and kidneys.⁴³ By ⁶⁴Cu and ⁸⁹Zer radiolabeled method, Gd@C₈₂ nanomaterials mainly accumulated in the liver, spleen, and kidneys.¹¹ By intraperitoneal injection, Gd@C₈₂ nanomaterials were primarily distributed in the pancreas, liver, bone, spleen, and so on.¹⁷,⁶⁰ Therefore, the biodistribution of functionalized Gd@C₈₂ nanomaterials depends on the method of administration and functionalization. Additionally, studies also reported that Gd@C₈₂ nanomaterials could be cleared from the body over time.

Numerous studies have been explored to evaluate the biosafety of functionalized Gd@C₈₂ nanomaterials either in vitro or in vivo. Recently, evidence indicated that functionalized Gd@C₈₂ nanomaterials showed no reduction of cell abilities, but promotion of cell proliferation, such as human umbilical vein endothelial cells (HUVECs),⁴⁴ brain capillary endothelial cells (rBCECs),⁶¹ human embryonic lung fibroblast cells (MRC-5),¹⁴ human epidermal keratinocytes alpha (HEKα),¹³ L02 human hepatic cells,⁶² immune cells (B cells, T cells or macrophages),⁴⁸ hepatoma cells (HepG2),⁴⁴ and so on.

Similarly, the biosafety in vivo was also studied by many researchers. After treatment, Gd@C₈₂(OH)₂₂ showed no
apparent toxic effect on the growth, behaviors, reproductivity, stress resistance, and longevity of the nematode Caenorhabditis elegans (C. elegans). In addition, tumor-bearing mice remained normal body weight after Gd@C$_{82}$(OH)$_{22}$ administration, suggesting no detectable toxicity. To evaluate the effects of Gd@C$_{82}$ nanomaterials on liver and kidney functions, the commonly used indicators such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), alkaline phosphatase (ALP), and creatinine (Cr) were monitored. The results demonstrated that the levels of those indicators tended to normal levels in healthy mice after treatment. Interestingly, instead of inducing significant pathological injuries of main organs like the liver, spleen, kidneys, and bones of mice, Gd@C$_{82}$ nanomaterials reverse the damage of these organs induced by radiation or chemotherapeutic agents. All these results indicated that functionalized Gd@C$_{82}$ nanomaterials exhibit excellent biosafety, laying the foundation for their further biomedical or clinical application.

5 | CONCLUSIONS

Altogether, functionalized Gd@C$_{82}$ nanomaterials exhibit high potential in biomedical applications. In particular, Gd@C$_{82}$ nanomaterials could be promising MRI contrast
agents better than commercial agents. And f-NPs could inhibit tumor angiogenesis by downregulating angiogenic factors, suppressing the expressions and activities of MMPs, and reducing extracellular matrix degradation. Differently, GFNCs could disrupt the pre-existing tumor vasculature with the help of RF or light, deriving from the size expansion when it crosses the endothelial cells or ROS generation. Gd@C_{82} nanomaterials also showed great value in anticancer therapy as immunomodulators and adjuvant therapeutic agents. Additionally, GFNPs modulated glucose and lipid metabolism, exhibiting superior efficacy on T2DM treatment. Importantly, no detectable toxicity is observed in vitro or in vivo.

With the rapid development of nanotechnology, nanodrugs have been emerging with tremendous advantages in clinical use. But challenges still remain, such as the stability, controllability, pharmaceutical preparations, biosafety, biocompatibility, etc. Fortunately, evidence supports that fullerenes possess high biological effects in cancer diagnosis and treatment, glucose and lipid modulation, and some other fields. And the bio-safety evaluation in vitro and in vivo demonstrated that fullerenes were bio-compatible with low toxicity. With much more progress in exploring the most proper pharmaceutical preparations in corresponding with disease, fullerenes could be promising platforms for future biomedical application in clinical use.

CONFLICT OF INTEREST
There is no conflict of interest to declare.

ACKNOWLEDGMENT
This work is supported by the National Natural Science Foundation of China (51902313) and the National Major Scientific Instruments and Equipments Development Project (ZDYZ2015-2).

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How to cite this article: Li X, Wang C. The potential biomedical platforms based on the functionalized Gd@C_{82} nanomaterials. VIEW. 2020;1:e7. https://doi.org/10.1002/viw2.7