

# Recent developments in nitric oxide-releasing biomaterials for biomedical applications

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## Abstract

Nitric oxide (NO) is an endogenous gas with several physiological activities. Owing to the NO physiological functions, such as inhibition of platelet aggregation and adhesion, vascular muscle relaxation, modulation of inflammation and immune response, antibacterial and anticancer activity, increasing attentions have been paid to the development of biomaterials with the ability to release this medical gas. Nowadays, numerous prodrugs have been developed to release NO *in vivo*. However, due to the low payloads and non-controlled delivery of the prodrug, the NO-releasing devices do not fulfil the expectations, which restricts their widespread application. Recently, several methods have been proposed to address the issue above, including physical and chemical methods and specific designs. This review aims to briefly introduce the latest achievements with recent 3 years involving coatings which mimic the vascular endothelium to treat atherosclerosis, nanocarriers which generate NO for a sustained anticancer treatment, and a framework which modifies the prodrug as a stable cardiovascular stent or as an anticancer targeted drug.

**Key words:** nitric oxide; biomaterial; controlled release; cardiovascular disease; anti-cancer; anti-bacterial

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## INTRODUCTION

Nitric oxide (NO) is a physiological messenger molecule, which plays a regulative role in several physiological processes and exhibits exceptional therapeutic potential in different fields. It is involved in cardiovascular homeostasis, immune response, bone metabolism, neurotransmission, and cancer.<sup>1-5</sup> Physiologically, endothelial cells produce NO at a flux of 0.05–0.40 nmol/(cm<sup>2</sup>•min), which inhibits platelet adhesion, vascular smooth muscle cell proliferation, and promotes vascular vasodilation.<sup>6,7</sup> All of these turn the endothelium to an essential tissue, which guarantees the patency and homeostasis of blood vessels. Besides this, NO is also widely applied in anti-bacterial materials which is derived from its toxicity in high concentration.

The function of NO is dose-dependent, and the concentration has to be adjusted to obtain the desired therapeutic effect. For example, NO has been applied to inhibit tumor development on the basis of the “anti-Warburg effect” at a high concentration range.<sup>8</sup> However, excessively high concentrations of NO in the blood may lead to NO poisoning, whereas low concentrations of NO may support tumor cell growth.<sup>9,10</sup> Likewise, low NO levels have obviously anti-apoptotic effects, and high NO levels result in necrosis and cell death.<sup>5</sup> These results highlight the importance to control the delivery velocity and concentration of NO.

This review is based on the development of the NO-

releasing materials in recent 3 years, and takes the emphasis on the means of the control of release and new methods of the response which is in order to increase drug targeting to realize the gas therapy. The advantage of these materials have been highlighted and the prospects for development have been concluded in the end.

## NITRIC OXIDE DONOR

In order to obtain a sufficient amount of NO for the treatment, several donors, which release NO by means of different reactions, have been investigated. Up to date, the typical low-molecular-weight NO donors, which are widely applied in NO-releasing materials are divided into the following categories, N-diazoniumdiolate (NONOate), S-nitrosothiols (RSNO) and L-arginine (L-Arg).<sup>11-14</sup> NONOate is well-known as its release under physiological environment dispenses with no catalyst.<sup>15,16</sup> Different from the NONOate, RSNO is an endogenous NO donor and the physiological transporter *in vivo*. RSNO is sensitive to conditions of the environment, such as metal ions, pH, and light. Hence RSNO can be used to design systems with regulated NO release.<sup>17-19</sup> L-Arg is a natural NO donor which produces NO by the catalysis *via* inducible NO synthase. Meanwhile, L-Arg also releases NO by the oxidization of ROS which has high concentrations in inflammatory tissues or cancer, and show the great potential to address the above issue.<sup>14,20,21</sup>

## NEW DEVELOPMENTS IN THE NITRIC OXIDE-RELEASING BIOMATERIALS

Numerous designs have been applied to deliver NO donors or release NO directly by the biomaterials, to make use of the physiological functions of NO.

### Immobilization of nitric oxide donors

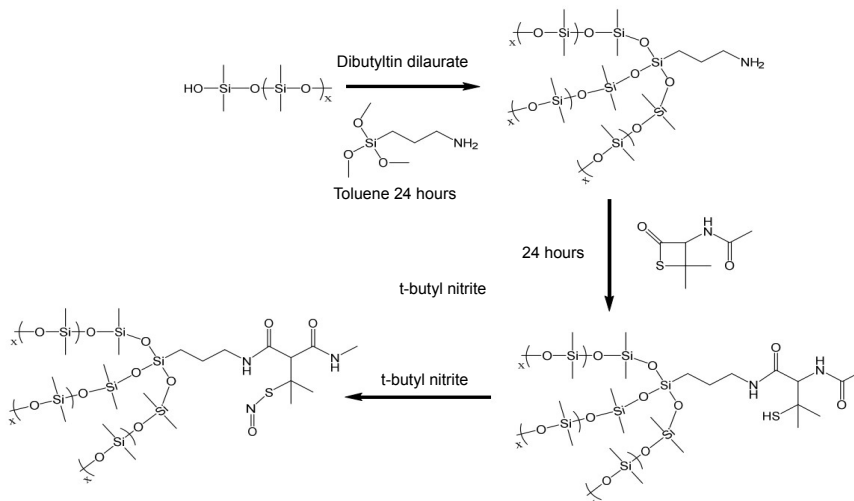
The traditional NO donor which can not release for a long period and is easy to breakdown can lead to the sudden release limits the development of NO-releasing material. Hopkins et al.<sup>22</sup> reported a method for S-nitroso-N-acetylpenicillamine (SNAP) conjugation to polydimethylsiloxane (PDMS) to achieve a long-term biocompatible silicone. As shown in **Figure 1**, the immobilization of SNAP to PDMS prevents the NO donor from direct reaction in the internal environment, and an NO release is maintained for over 125 days. Due to the continuous NO release, the new material possesses a high antibacterial potential and prevents platelet adhesion.

The release of NO is measured by chemiluminescence NO

analyzer and the samples were tested in amber reaction vessels which contains 0.01 M phosphate buffer saline with ethylenediaminetetraacetic acid at 37°C using a nitrogen bubbler and sweep gas at a combined flowrate of 200 mL/min. And the result is shown in **Figure 2**. The NO release kinetics of SNAP-PDMS films in phosphate buffer saline with ethylenediaminetetraacetic acid at 37°C measured by chemiluminescence NO analyzer which proves that the SNAP-PDMS film habits the potential of long-term NO release.

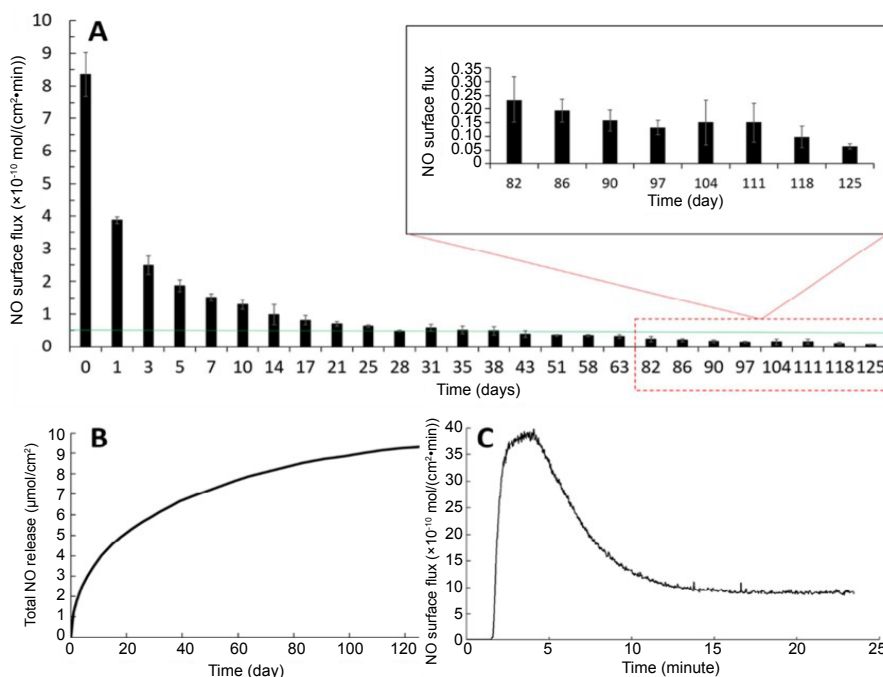
### Tailoring re-endothelialization

A normal endothelial function desires the appropriate concentrations of NO in the blood vessel to prevent thrombosis, the proliferation and adhesion of the vascular smooth muscle cells, and leukocyte activation.<sup>23</sup> However, vanishing of the endothelial cells in atherosclerotic areas and reduced activity also decreases the secretion of NO in these areas.<sup>24</sup> Hence, several approaches have been pursued to mimic the normal endothelium function to treat atherosclerosis. For



**Figure 1: Route for covalent conjugation of the SNAP molecule to hydroxyl-terminated PDMS polymer.**

Note: Reprinted with permission from Hopkins et al.<sup>22</sup> SNAP: S-nitroso-N-acetylpenicillamine; PDMS: polydimethylsiloxane.



**Figure 2: Nitric oxide (NO) release kinetics of SNAP-PDMS films.**

Note: (A) The continuous NO release flux, taken at specified days while storing the films in phosphate buffer saline with ethylenediaminetetraacetic acid at 37°C ( $n = 4$ ). The green line represents the minimum physiological level of NO flux ( $0.5 \times 10^{-10} \text{ mol}/(\text{cm}^2 \cdot \text{min})$ ). (B) Cumulative NO release over the 125-day testing period, measured and normalized per  $\text{cm}^2$  of SNAP-PDMS. (C) Representative NO release profile on day 0 from SNAP-PDMS films when placed in phosphate buffer saline with ethylenediaminetetraacetic acid at 37°C. Reprinted with permission from Hopkins et al.<sup>22</sup> SNAP: S-nitroso-N-acetylpenicillamine; PDMS: polydimethylsiloxane.

example, Yang et al.<sup>25</sup> describe a NO producing coating for multifunctional vascular stents, which is functionalized with a plasma polymerized allylamine coating and then immobilized 3,3-diselenodipropionic acid (SeDPA). SeDPA has glutathione peroxidase-like catalytic activity to generate NO from RSNOs. According to the design, NO donors, such as S-nitrosoglutathione, S-nitrosocysteine, and S-nitrosoalbumin will be decomposed by the catalysis of SeDPA *in vivo*. A such functionalized stent implanted into the vessel continuously releases NO, simulating natural endothelium and remitting the atherosclerosis (**Figure 3**).

Based on the function of the NO, the SeDPA was immobilized to an amine which bears plasma polymerized allylamine (PPAam). Then cell and animal studies with the SeDPA-PPAam coating showed a great inhibitory effect on collagen-induced platelet activation and adhesion, further on proliferation and migration of arterial smooth muscle cells. The NO-mediated effect was confirmed by analysis of intracellular cyclic guanosine monophosphate signaling pathways. The NO-catalytic bioactive coating enhanced endothelial cell migration and growth. Thus, there was cell selectivity with competitive growth of endothelial cells above smooth muscle cells. These results indicate that the NO-catalytic bioactive coating provides a new approach of an endothelium-mimetic microenvironment to promote the recovery of atherosclerosis.

#### L-arginine producing nitric oxygen via reactive oxygen species in tumor

As mentioned above, L-Arg releases NO by oxidation of reactive oxygen species (ROS), which provides a method to treat cancer. According to the free diffusion and penetration of the small molecule and the high concentration of ROS in the hypoxic tumor microenvironment,<sup>26</sup> Wan et al.<sup>27</sup> proposed a new design to achieve the gas therapy, which induces NO by

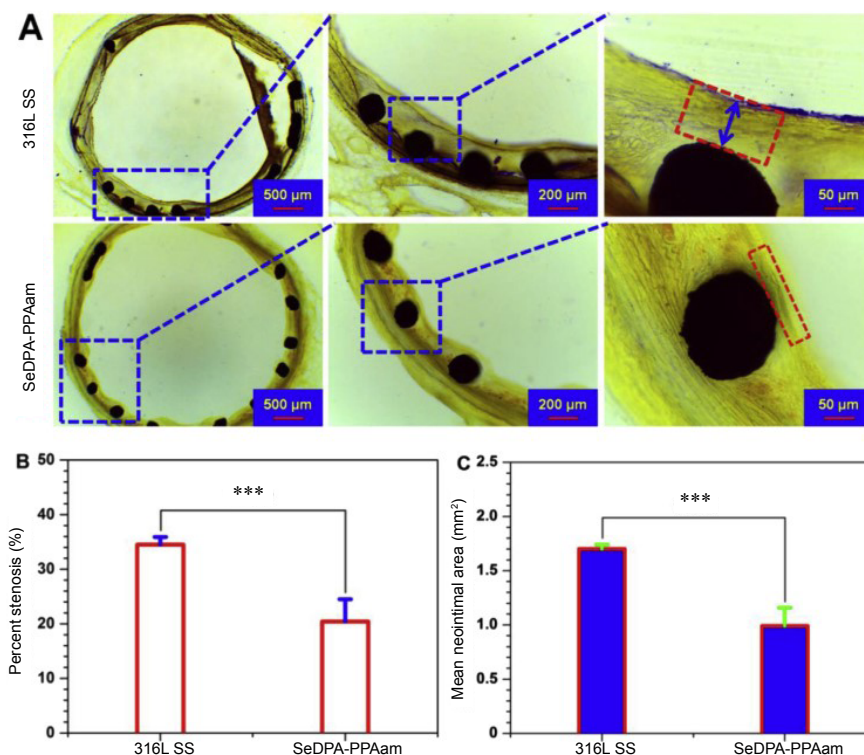
means of ROS and realizes synergistic effects.

The nanoplatform is constructed on porous coordination network (PCN), and the NO donor is coated by the cancer cell membrane (Mem), which constitute the whole material (L-Arg@PCN@Mem). With the irradiation of near-infrared light (NIR), the ROS is produced to damage the cancer cell to achieve the traditional photodynamic therapy and the ROS can converse L-Arg to NO to meet the aim of gas therapy. 2',7'-Dichlorofluorescein diacetate (DCFH-DA) is a fluorochrome which is used to measure the ROS. The production of ROS and the release of NO was measured by fluorescence spectrum under different materials and conditions and is expressed in relative fluorescence intensity, which shows that L-Arg induced NO by the ROS in **Figure 4A** and **B**, and it is also proved by **Figure 4C** which shows that the release of NO is prevented by vitamin C and controlled by the light irradiation. In order to exhibit the response of NO release under the control of NIR, the **Figure 4D** shows the condition of NO release and proves that the design meets the personal treatment requirements.

At 48 hours after injection of L-Arg@PCN@Mem and L-Arg@PCN, the tumor and issue condition is measured by fluorescence imaging and mean fluorescence intensity. According to the **Figure 5**, L-Arg@PCN@Mem with light irradiation and little tumor inhibition observed in L-Arg@PCN@Mem further confirmed biocompatibility of nanoparticles *in vivo*, which provided a possibility for further clinical research. The PCN group had an obvious tumor suppression when irradiated with 660 nm, which attributed to the effect of photodynamic therapy.

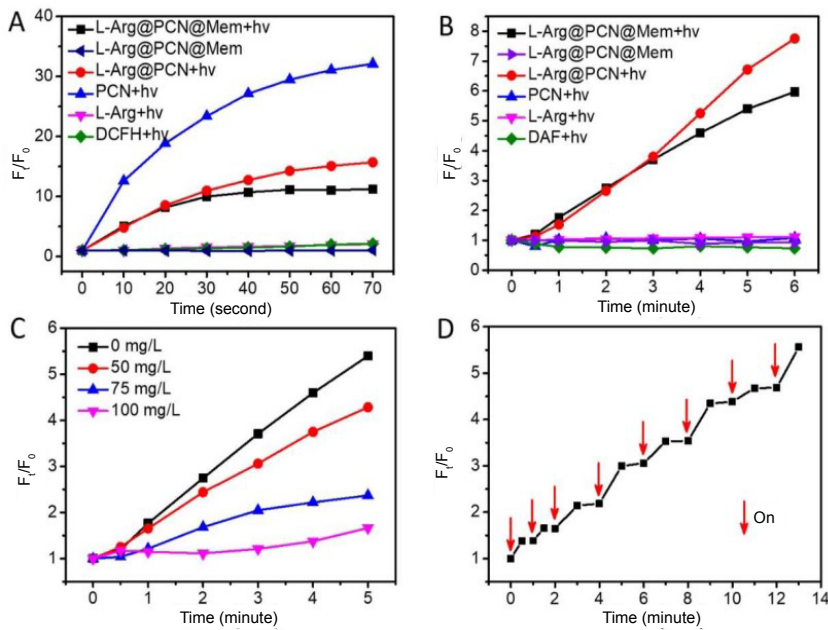
#### Fe<sub>3</sub>O<sub>4</sub> as a photoconversion agent to release nitric oxygen

Various concepts for NO releasing materials are applied in nanomedicine. As indicated above, NO has anti-cancer activity,



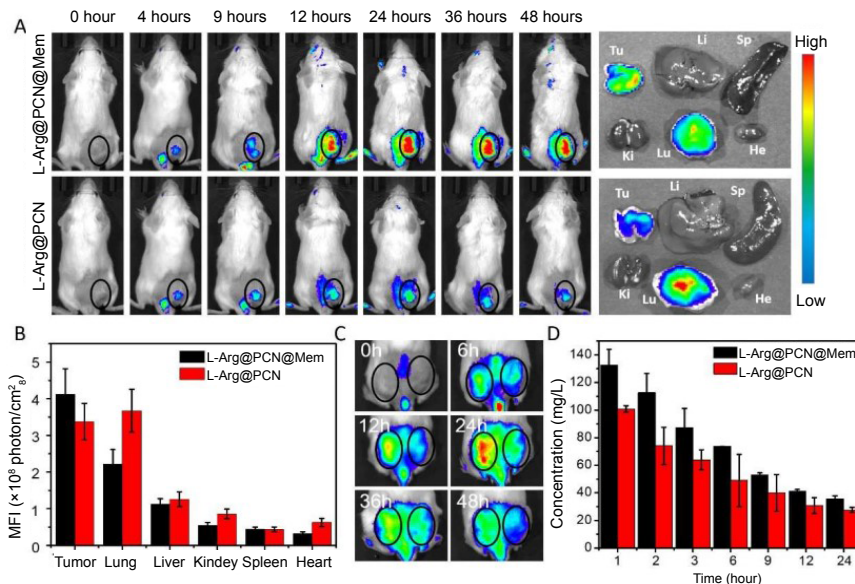
**Figure 3: The result of *in vivo* stent implantation.** Note: (A) Native 316L SS stents and SeDPA-PPAam coated stents implanted in adult New Zealand white rabbits for 28 days. Histomorphometric analysis of the in-stent restenosis. (B, C) Percent neointimal stenosis (B) and mean neointimal area analysis (C) indicated significantly reduced in-stent restenosis. Data are expressed as mean  $\pm$  SD. \*\*\* $P < 0.001$ . SS: Stainless steel; SeDPA: 3,3-diselenodipropionic acid. Reprinted with permission from Yang et al.<sup>25</sup>





**Figure 4: Production of reactive free radicals under different irradiation by fluorescence spectrum.**

Note: (A) Reactive oxygen species generation of various samples with DCFH as the probe. (B) NO generation of various samples with 4,5-diaminofluorescein as the probe. (C) The change of NO level at different concentrations of vitamin C in L-Arg@PCN@Mem. (D) NO release of L-Arg@PCN@Mem under ON-OFF irradiation. hv: Light irradiation; F<sub>t</sub>/F<sub>0</sub>: relative fluorescence intensity. DCFH: 2',7'-dichlorofluorescein; L-Arg: L-arginine; PCN: porous coordination network; Mem: cancer cell membrane; NO: nitric oxide. Reprinted with permission from Wan et al.<sup>27</sup>



**Figure 5: *In vivo* targeted imaging and pharmacokinetics.**

Note: (A) *In vivo* fluorescence imaging of 4T1 tumor-bearing mice at 0–48 hours after intravenous injection of L-Arg@PCN@Mem and L-Arg@PCN, and the fluorescence represents the materials. Right: The corresponding *ex vivo* fluorescence images of major organs and tumor tissues 48 hours post-injection. (B) The MFI value of the major organs and tumor tissues after 48 hours intravenous injection. (C) *In vivo* fluorescence imaging of 4T1 and CT26 dual tumor-bearing mouse at 0–48 hours after intravenous injection of L-Arg@PCN@Mem. Left ring: 4T1 tumor, right ring: CT26 tumor. (D) Blood concentrations of L-Arg@PCN@Mem and L-Arg@PCN after intravenous injection. He: Heart; Li: liver; Sp: spleen; Lu: lung; Ki: kidney; Tu: tumor; MFI: mean fluorescence intensity; L-Arg: L-arginine; PCN: porous coordination network; Mem: cancer cell membrane. Reprinted with permission from Wan et al.<sup>27</sup>

however, it disperses randomly in the body and does not reach effective concentrations in the tumor. Besides, the therapeutic suitability of NO is also limited by its gaseous state and short half-life. In the last few years, nanomedicine has addressed the issue. Nanomedicine attains tumor-targeted drug delivery, and numerous stimuli-triggered release ways can be designed to obtain the active drug concentration within the tumor.

Polydopamine (PDA) is widely used in antibacterial design for its great biocompatibility, biodegradability, and photoconversion efficiency. Iron oxide nanoparticles (Fe<sub>3</sub>O<sub>4</sub> NPs) is applied in bacteria treatment and separation due to its superparamagnetic property and the poly(amidoamine) (PAMAM) is a new dendrimer which can react with NO by forming NONOates. Recently, Yu et al.<sup>28</sup> have developed antibacterial materials that exhibit the ability of controlled NO release, taking advantage of Fe<sub>3</sub>O<sub>4</sub>@PDA@PAMAM@NONOate under intermittent 808 nm laser irradiation. In order to get the ability to release NO, the three generation dendritic poly(amidoamine) (PAMAM-G3) is grafted on the surface of the PDA coated iron

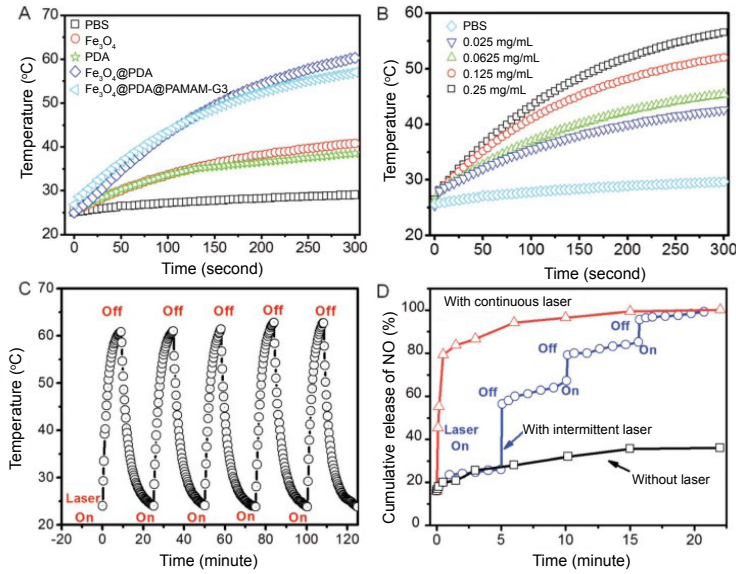
oxide nanocomposite (Fe<sub>3</sub>O<sub>4</sub>@PDA) which is after preparation and gets Fe<sub>3</sub>O<sub>4</sub>@PDA@PAMAM-G3, and then the NO is loaded with the formation of NONOate. The material causes leakage of intracellular components, which kills bacteria when it adheres to their surface and releases NO under laser irradiation with the rise of local temperature (Figure 6).

The photothermal effect, which means the continuous rise of temperature at laser irradiation, accelerates the NO release from Fe<sub>3</sub>O<sub>4</sub>@PDA@PAMAM@NONOate. NO is released in a controllable way by intermitted irradiation, which provides a method of tailored NO release flux to achieve a desired biological effect.

The synergistic actions of photothermal effect and NO treatment show a remarkable bactericidal effect (Figure 7).

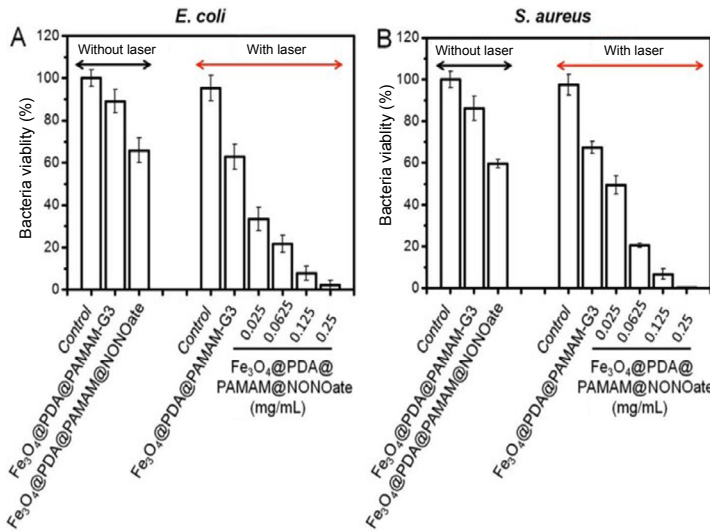
### Design of the enzyme-prodrug pair

NO is precisely controlled *in vivo* as a versatile endogenous messenger. In order to deliver NO to a specific site precisely and to make it available for clinical application, Hou et al.<sup>29</sup>



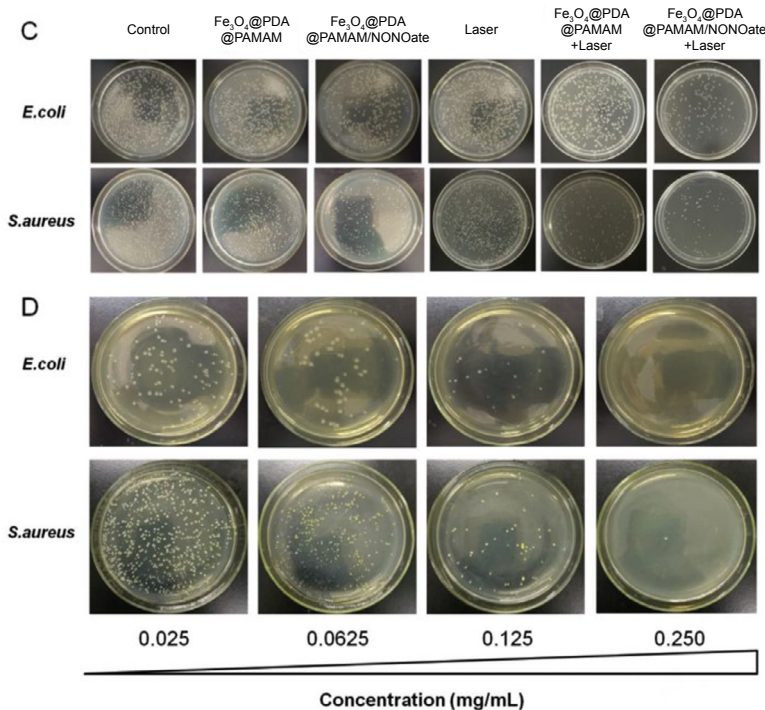
**Figure 6: The response of materials under the different environment.**

Note: (A) Photothermal effects of different nanomaterials under laser irradiation at 808 nm with a power density of 0.5 W/cm<sup>2</sup>. (B) Concentration-dependent photothermal effect of Fe<sub>3</sub>O<sub>4</sub>@PDA@PAMAM-G3 under irradiation of 808 nm laser with a power density of 0.5 W/cm<sup>2</sup>. (C) Photothermal stability evaluation of Fe<sub>3</sub>O<sub>4</sub>@PDA@PAMAM-G3 with five laser on and off cycles. (D) NO release profile of Fe<sub>3</sub>O<sub>4</sub>@PDA@PAMAM@NONOate under different laser irradiation conditions. PBS: Phosphate buffer saline; PDA: polydopamine; PAMAM: poly(amidoamine); PAMAM-G3: three generation dendritic poly(amidoamine); NO: nitric oxide. Reprinted with permission from Yu et al.<sup>28</sup>



**Figure 7: The antibacterial effect of Fe<sub>3</sub>O<sub>4</sub>@PDA@PAMAM@NONOate.**

Note: (A, B) Viability of *Escherichia coli* (*E. coli*) (A) and *Staphylococcus aureus* (*S. aureus*) (B) treated with Fe<sub>3</sub>O<sub>4</sub>@PDA@PAMAM-G3 and Fe<sub>3</sub>O<sub>4</sub>@PDA@PAMAM@NONOate under different laser irradiation conditions. (C) Colony formation of *E. coli* and *S. aureus* under different treatments. (D) Colony formation of *E. coli* and *S. aureus* treated with different concentrations of Fe<sub>3</sub>O<sub>4</sub>@PDA@PAMAM@NONOate. PDA: Polydopamine; PAMAM: poly(amidoamine); NONOate: N-diazeniumdiolate. Reprinted with permission from Yu et al.<sup>28</sup>



have proposed a bump-and-hole strategy which modifies an enzyme prodrug (pair of galactosidase galactosyl-NONOate) to accomplish a NO delivery system. In an *in vivo* near-infrared imaging assay, the NO function was measured in a hindlimb-ischemia rat model and an acute-kidney-injury mouse model and the NO delivery was highly targeted to enhance the therapeutic effect in tissue and function recovery, which also abolished the side effects on the whole body.

**Nitric oxygen nanogenerators**

The nano-gaseous-transmitters attract several researchers in the recent years to develop rapid generators of this medical gas. Guo et al.<sup>30</sup> developed phototriggered NO nanogenerators to reverse the multidrug resistance in cancer based on the use of NIR light and heat where the NO can inhibit the expression of P-glycoprotein. In this design, the nanocarriers combine with the heat-sensitive NO donor RSNO, and the photothermal conversion with heat sensitivity drives the nanogenerators to absorb the NIR light and utilizes the heat to breakdown the S-NO bonds.<sup>31</sup>

The preparation of material is shown in **Figure 8**. The nanocarriers is designed as a core-shell-shell structure (Fe<sub>3</sub>O<sub>4</sub>@PDA@mesoporous silica) and the mesoporous silica is functionalized with sulfhydryl groups which can obtain photothermal carriers.<sup>26,32</sup> Then, RSNO reacts the -SH groups to conjugate to the shell, and thiolated transferrin is linked to the material surface in the end. In order to load the doxorubicin (DOX), the phototriggered NO nanogenerators were dispersed in DOX solution for 12 hours and got the materials for the animal tests.

For cancer-cell-targeting, transferrin is conjugated to the surfaces of nanoparticles and the result of *in vivo* chemotherapy is shown in **Figure 9**. Under NIR laser irradiation, the nanogenerators produce NO, which inhibits the P-glycoprotein expressing in order to reduce the drug resistance and improve the toxicity to cancer cells.

**Liquid-infused nitric oxygen-releasing materials**

Besides the conventional chemical fixation, other designs to exploit NO for synergistic effects have been proposed. Goudie et al.<sup>33</sup> introduced a novel liquid-infused material, which can avoid platelet activation and acts as an antibacterial agent at the same time. This liquid-infused NO-releasing material was formed by blending the NO donor (SNAP) and silicone oil in silicone rubber tubing through a solvent swelling process. This work not only takes advantage of the liquid-infused materials, which present ultra-low fouling surfaces, but also prevents bacterial proliferation and platelet activation by means of NO release. In the **Figure 10**, the result shows that the liquid-infused NO-releasing materials own a great anti-bacterial potential and excellent biocompatibility.

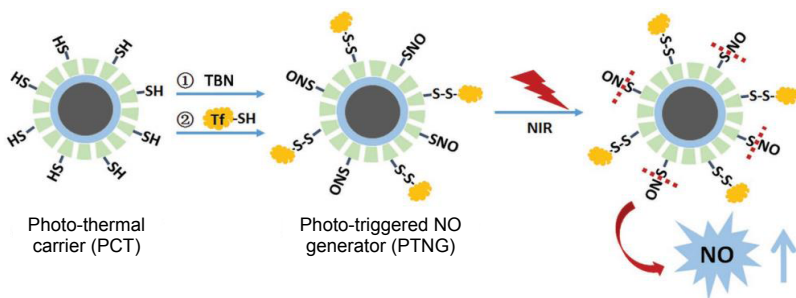
**Glucose-responsive nitric oxygen-releasing biomaterials**

As the key energy supplier and nutrient for tumors, glucose can be hydrolyzed by glucose oxidase and generate gluconic acid and H<sub>2</sub>O<sub>2</sub>.<sup>34,35</sup> As described above, H<sub>2</sub>O<sub>2</sub> has the potential to oxidize L-Arg into NO to be applied in gas therapy to treat cancer as a synergistic effect with the starving therapy.<sup>36</sup> Fan et al.<sup>21</sup> proposed a biocompatible/biodegradable nanocarrier of hollow mesoporous organosilica nanoparticles, which can be responded by glucose due to the co-delivery of glucose oxidase and L-Arg. The experiment results show a remarkable H<sub>2</sub>O<sub>2</sub> and NO cooperative anticancer effect with minimal side effects.

According to **Figure 11**, after the treatment with L-Arg-hollow mesoporous organosilica nanoparticles-glucose oxidase, the tumors did shrink remarkably. It is assumed that both the elevated H<sub>2</sub>O<sub>2</sub> concentration and the NO gas generated from L-Arg resulted in the apoptosis and necrosis of the tumor. Also a remarkable extension of survival time has been shown to prove the *in vitro* treatment efficacy.

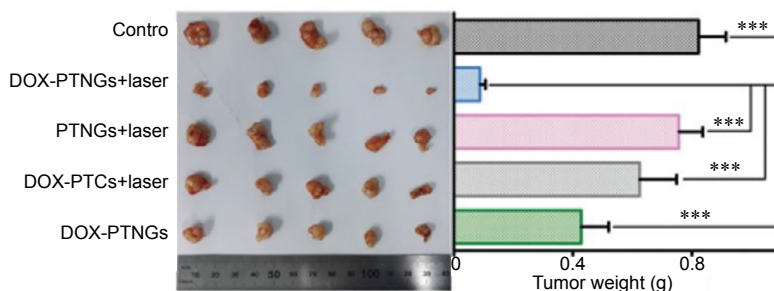
**CONCLUSIONS**

Several NO-based therapies have been developed for anti-



**Figure 8: Schematic illustration of the fabrication of phototriggered NO nanogenerators.**

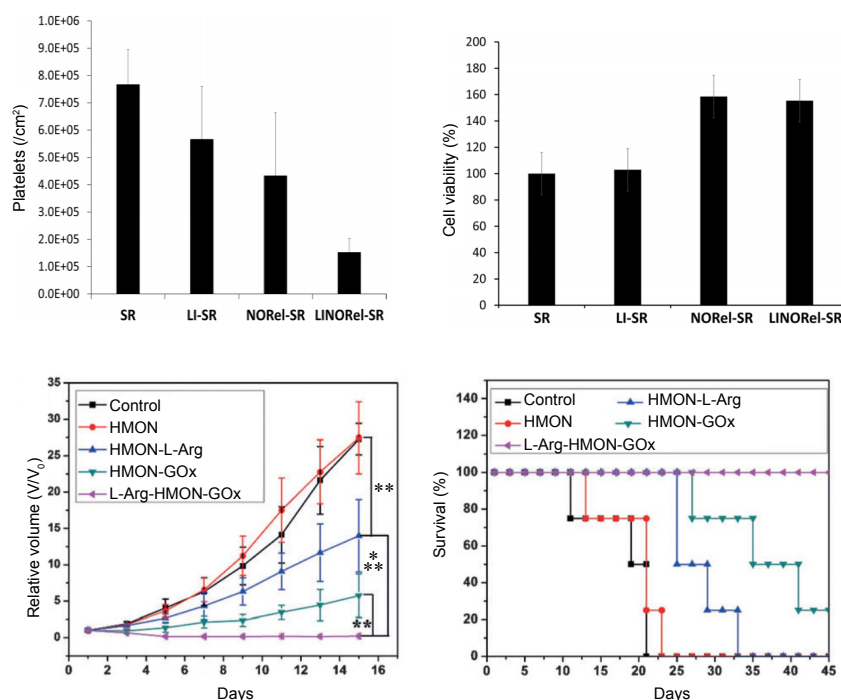
Note: NO: Nitric oxide; TBN: tert-butyl nitrite; SNO: S-nitrosothiols; NIR: near-infrared light. Reprinted with permission from Fan et al.<sup>26</sup> and Guo et al.<sup>32</sup>



**Figure 9: Photograph (left) and weights (right) of tumors after excision from each group.**

Note: Data are expressed as mean ± SD. \*\*\*P < 0.001. DOX: Doxorubicin; PTNG: phototriggered nitric oxide nanogenerator; PTC: photothermal carrier. Reprinted with permission from Fan et al.<sup>26</sup> and Guo et al.<sup>32</sup>





**Figure 10: Degree of platelet adhesion on various silicone tubings after 2 hours exposure to porcine platelet rich plasma as measured using a lactate dehydrogenase quantification assay and cytocompatibility and cell growth support of various infused SR tubing towards mouse fibroblast cells in 24 hours study.**

Note: Data are expressed as mean  $\pm$  SD. SR: The medical grade Tygon™ 3350 silicone rubber tubing; LI-SR: liquid-infused SR; NORel-SR: nitric oxide-releasing SR; LINORel-SR: liquid-infused NO-releasing SR.

**Figure 11: Tumor growth curve and survival curve of U87 tumor bearing mice after different treatments.**

Note: Data are expressed as mean ( $\pm$  SD). \*\* $P < 0.01$ , \*\*\* $P < 0.001$ . HMON: Hollow mesoporous organosilica nanoparticles; L-Arg: L-arginine; GOx: glucose oxidase. Reprinted with permission from Fan et al.<sup>21</sup>

thrombotic, antibacterial, and anticancer applications. Compared with the traditional approaches, the NO-releasing biomaterials show an immense potential to address the clinical issues. Although this review has set forth the progress in the recent years, plenty of problems are urgently needed to be solved. In some cases, the timing NO release is frequently common in normal internal environment which we need to mimicking to achieve the treatment requirements, and in the other cases, the design for anticancer or antibacterial treatment and recovery of damaged tissue should consider the toxic and protective NO concentrations, which have to be kept under precise control by the material. Further attention is needed for the completely opposite effects that different NO concentrations in cancer may have. Besides this, the order of the substrate materials which cover vascular stents, nanocarriers and prodrug or enzyme bearing compounds, should subside the toxicity. The *in vitro* experiment should be designed much more carefully in order to meet the demand of clinical application. In summary, with the development of the NO-releasing biomaterials, owing to the interoperability of the design concept, more and more medical gas related materials have gotten tremendous advance, such as hydrogen sulfide, hydrogen, and carbonic oxide. As a new delivery system of medical gas, the NO-releasing biomaterials are going to advance the area of medical gas therapeutics and become the available routine in clinical application hopefully.

#### Author contributions

HY, LXC and ZLY reviewed relative articles. HY drafted the manuscript. NH and ZLY revised the manuscript and the English. NH and ZLY guided HY and provided original creative ideals. All authors read and approved the final manuscript.

#### Conflicts of interest

The authors confirm that this article content has no conflict of interest.

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