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Photodynamic Therapy for Solid Tumor Therapy: No Longer Restricted by Hypoxia

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Abstract

Photodynamic therapy (PDT), a minimally invasive treatment modality for cancer, involving the formation of reactive oxygen species (ROS) and subsequently eradication of the tumorous cells, has received a great attention. However, its oxygen-dependent nature to certain degree limits PDT from achieving satisfactory outcomes in solid tumors because of the frequent hypoxia circumstances. To alleviate hypoxia, efforts have been made through diversified strategies, e.g., delivery of ecdemic oxygen and intracellular replenishment of oxygen during PDT. In this mini review, we further elaborate on the details of these strategies and corresponding mechanisms for better therapy efficacy.

Introduction

In recognition of its potentials for noninvasive and spatio-temporally controllable treatment of cancers, light-based therapy has been continuously explored, mainly including photodynamic therapy (PDT) [1]. and photo thermal therapy (PTT) [2]. Considering the limited therapeutic confinement, as well as the therapeutic resistance during PTT, resulting from hyperthermia-induced expression of heat shock proteins (HSPs) [3,4]. PDT, instead is seemingly a superior photo-assisted modality. During PDT, energy is transferred from photons to molecular oxygen *via* light-activated photosensitizers to form singlet oxygen ($^1O_2$) a highly reactive oxygen species (ROS) [5] which induces cell apoptosis, necrosis as well as autophagy through oxidization of lipid and proteins, damage of organelles and cell membrane [6,7]. Ongoing research on PDT is currently dominated by the $^1O_2$-producing type II photodynamic reactions.

Considerable efforts have been made to improve the therapeutic efficiency with the booming nanotechnology [8]. Given that light irradiation is essential to activate photosensitizers, photon energy was amplified with the aid of localized surface plasmon resonance of noble metal nanomaterials such as gold Nanoparticles [9,10]. Due to short lifespan of singlet oxygen and its consequent limited diffusion [11]. photosensitizer-loaded nanovehicles were accordingly designed to target mitochondria, an organelle primarily responsible for production of $^1O_2$ and more importantly for cell apoptosis [12,13]. Meanwhile, to reduce the resistance of cancer cells to $^1O_2$ cytotoxicity, $^1O_2$ scavenger glutathione (GSH) was inactivated by copper-mediated oxidation [14].

Even with the improved photo-activation and $^1O_2$-sensitive toxicity, hypoxia is still a big dilemma, which makes PDT self-limited in the long run. This could be attributed to the native hypoxia and secondary low oxygen saturation caused by PDT. Intrinsically, disorganized vasculature of most solid tumors could create regions of severe hypoxia [15]. PDT is therefore, hampered by insufficient availability of molecular oxygen. Unfortunately, PDT itself could aggravate the oxygen shortage because of the continuous consumption of intracellular molecular oxygen for producing $^1O_2$. Furthermore, PDT is also responsible for vascular damage, which diminishes the blood circulation through tumors [16]. In this case, inadequate oxygen supplement is further deteriorated along with the PDT treatment. Dramatic PDT-induced hypoxia was confirmed in both hypoxic tumor xenografts and low to non-hypoxic ones [17]. Thus, fractional PDT (intermittent light exposure) [18] and hyperbaric oxygen inhalation [19] have been accordingly proposed to address the hypoxia scenario. However, intermittent PDT virtually extends the unpleasant treating period; side effects of hyperbaric oxygen therapy cannot be neglected. To this end, the need for better solutions in order to elevate the oxygen level, especially in solid tumorous tissues, has motivated the endeavors to seek alternatives for substantially alleviating hypoxia along with amplification of PDT efficacy. Considerable progress has been made in particular relation to oxygen elevation.

Strategies to Enrich Oxygen Supply

To better address the need of decreased hypoxia and increased oxygenation, several potential strategies, including enhanced distant oxygen delivery and local oxygen supply, have been investigated.

Transportation of ecdemic oxygen

As a straightforward solution, several studies have verified the possibility of improving oxygen transportation directly into the tumorous region. Biologically, blood circulation is responsible for O_2 supply throughout the body, including the tumor tissues. In recognition, "Hot Spring" bath was employed to regulate the overall body temperature for properly accelerating the blood circulation in order to increase O_2 supply [20]. During *in vivo* PDT with mouse breast cancer xenografts, tumor tissue oxygen saturation raised 52% along with the body temperature increase from 37°C to 43°C. Meanwhile, the photosensitization reaction rate of Chlorin e6 (Ce6) was also 20% higher at 43°C than that at 37°C, yielding an impetus to ROS generation in addition to elevated O_2 supply. On the other hand, perfusion with exogenously supplied O_2 is also believed to be able to effectively circumvent hypoxia. It is well recognized that hemoglobin is the essential O_2 carrier in red blood cells. Thanks to its intrinsic nature of reversible binding of oxygen [21], hemoglobin was explored to be incorporated into nanomaterials for oxygen self-sufficient PDT. Wang et al. [22] demonstrated the capability of oxyhemoglobin in oxygen supply and protoporphyrin IX co-loaded red blood cell-derived vesicles (HbO_2&PpIX@RDVs) as a promoter for efficient PDT. In 2016, the attempt toward biomimetic artificial red cells (ARCs) was reported by

Cai's group (Figure 1) [23]. In their report, the typical ARC was composed of biocompatible lipid shell and poly (D, L-lactic-*co*-glycolic acid) (PLGA) core, where hemoglobin was cooperated with photosensitizer indocyanine green (ICG) to form an Hb/ICG complex. Upon light irradiation at 808 nm, ICG-loaded ARCs (I-ARCs) led to 9.5 times higher ROS formation than those deoxy-ICG nanoparticles. The capability of hemoglobin of reversibly combining with oxygen was well maintained in the ARCs. Two days after the initial intratumoral I-ARC injection and NIR exposure, necrotic cellular debris and severe damage to tumor tissue were observed as verified by histological analysis of the tissue cross-sections stained with hematoxylin and eosin (H&E) (Figure 1c). In both reports, a steady release of oxygen has been achieved.

Taking into account that hemoglobin, as a protein, might be vulnerable and susceptible to conformation alteration during the chemical modification procedures, the utility of other alternatives such as solutions/materials with considerable oxygen storage capacity would be a better choice.

As the blood substitute [24], perfluorocarbon (PFC) is marked for its completely fluorinated carbon skeleton, in which the high electronegativity turns out to be able to increase oxygen affinity and facilitate the solubility and diffusivity as well as exhibit longer $^1O_2$ lifetime than water. Learned from radiation therapy (RT), which shares partial similarities to PDT in terms of oxygen dependence [25,26], PFC was accordingly engaged in PDT in several recent studies. In a novel approach of oxygen self-enriched PDT, photosensitizer IR780 was encapsulated in a monolayer of lipid nanosystem while having the O_2-containing perfluorohexane droplet as the core (Figure 2a) [27]. As shown in TUNEL assays, a larger number of apoptotic cells were observed in the photodynamic treated tumors with the PFC-assisted O_2 supply, which was also confirmed by H&E staining. In this system, the sustained oxygen supply enabled a long-lasting PDT with the full achievement of the therapeutic efficacy of IR780. It exhibited a superior inhibition for tumor growth to traditional PDT even with a single-dose intravenous injection, which promisingly minimized the bio-safety concerns in consideration of the low dosage needed in total. In another interesting attempt, Que et al. [28] embedded pentafluorophenyl group and porphyrin into PEG-based amphiphilic copolymers (Figure 2b), which then assembled them into nanomicelles. A higher content of pentafluorophenyl segment led to a high oxygen solubility and diffusivity and consequently promoted the formation of cytotoxic $^1O_2$. Furthermore, a physical process that could trap oxygen in the polymer bubbles and then release it in a thermal-responsive manner was also demonstrated. In the work from Huang et al. [29] on monocyte-mediated therapy, Ce6 and superparamagnetic iron oxide nanoparticle (SPION)-loaded polymersomes were saturated with oxygen through pure oxygen purging during lyophilization and then followed by re-hydration under oxygen atmosphere. Release of O_2 was triggered upon its volumetric expansion in response to the local heat as a result of high frequency magnetic field applied on the SPIONs.

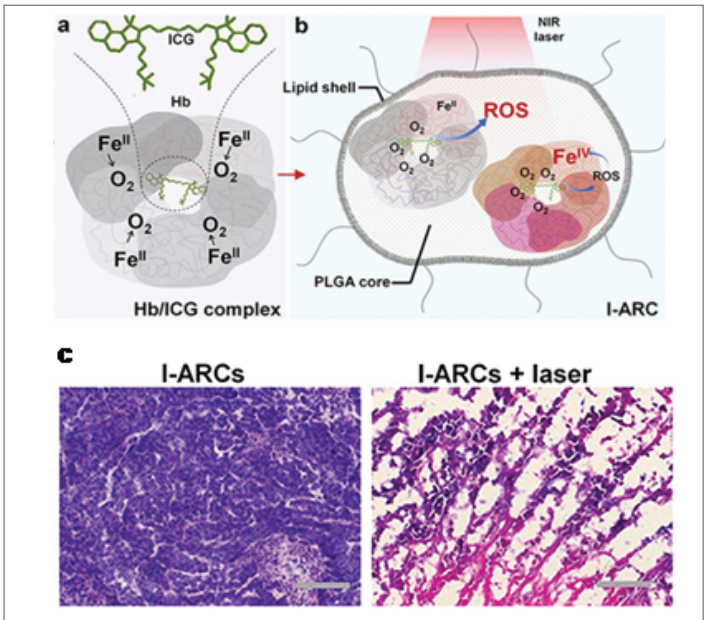

Figure 1. Schematic illustration of (a) Hb/ICG complex and (b) hemoglobin-encapsulated artificial red cell (I-ARC); (c) Optical microscopic images of the cross-sections of tumor tissues without (left) and with (right) laser treatment after staining with hematoxylin and eosin (H&E) [23]. Reproduced with permission.

"Excavation" of local oxygen source

From different perspective, access to the local chemical source of oxygen is another conceivable strategy, mostly focusing on intracellular hydrogen peroxide and water. As a hallmark of malignant cancerous cells, excessive amount of H_2O_2 is often detected [30], which could serve as both oxygen source and the trigger to initiate PDT, according to Chen et al. [31]. When H_2O_2 diffused across the PLGA shell and then into the aqueous core containing catalase, the decomposition mechanism was "switched on". The outbreak of gaseous oxygen was able to rupture the PLGA shell to release the encapsulated photosensitizer, methylene blue (MB), which was subsequently activated upon laser irradiation (Figure 3a). Meanwhile, the oxygen gas in turn provides supplement for the oxygen consumption by PDT. Interestingly, molecular oxygen could be further elevated with the presence of oxygen donating manganese oxide (MnO_2) [32]. Typically, MnO_2, under the neutral pH, simply works as a catalyst, similar to the catalase mentioned above. In the case of an acidic pH within the malignant cancerous cells, besides catalyzing H_2O_2 decomposition MnO_2 itself was reduced to Mn^{2+}, which could yield even greater amount of O_2 with the same amount of H_2O_2 (Figure 3b). Thus, in tumor tissues not only O_2 consumption was compensated but also oxygenated/deoxygenated hemoglobin ratio and vascular saturated O_2 were increased when compared to the saline-treated control groups.

In recognition of its abundance in the living body, water could be used as an endless source for oxygen. Inspired by the solar-enabled water splitting in the exploratory efforts for clean and sustainable energy, 2D nanomaterial of carbon nitride (C_3N_4) with exceptional electronic properties and high biocompatibility has been introduced into the PDT nanosystems [33]. In this endeavor, C_3N_4 nanosheets were decorated with carbon dots for sufficient red light absorption (at 630 nm) in order to split the intracellular water (Figure 3c). Indeed, enhanced oxygen and down-regulated hypoxia-associated protein levels including hypoxia-inducible factor-α (HIF-α) and carbonic anhydrase 9 (CA 9)were observed. The extra O_2 produced by water splitting was converted into cytotoxic singlet oxygen ($^1O_2$). As a consequence, distinctively improved prognosis was achieved. Compared to control groups, inhibited tumor metastasis in liver and lung were observed with oxygen self-sufficient groups, based on both H&E staining and immunofluorescence analyses.

Conclusion and Future Prospects

In this mini-review, we have summarized several possible strategies to overcome the hypoxia hindrance confronted in cancer PDT. As illustrated, ecdemic molecular oxygen could be trapped *via* biological, biomimetic or physical mechanisms, and then delivered into solid tumor with the assistance of nanostructures. On the other hand, intracellularly catalyzed decomposition or oxidation of H_2O_2 as well as the water splitting could supply the PDT with the continuous local source of oxygen. Either strategy has demonstrated its promise and potentials in elevating the oxygen levels for enhanced PDT.

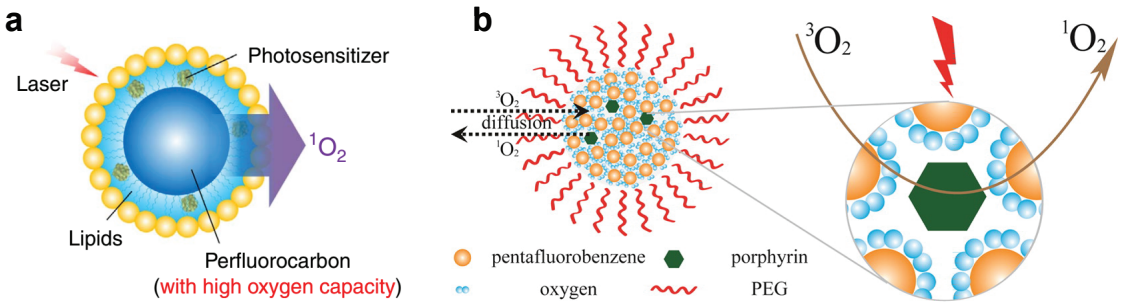

Figure 2. Schematic illustration of mechanisms for (a) O_2 delivery *via* PFC-lipid core/shell nanostructure and (b) enhancement of PDT efficacy by fluorinated domains. Reproduced with permission [27-28].

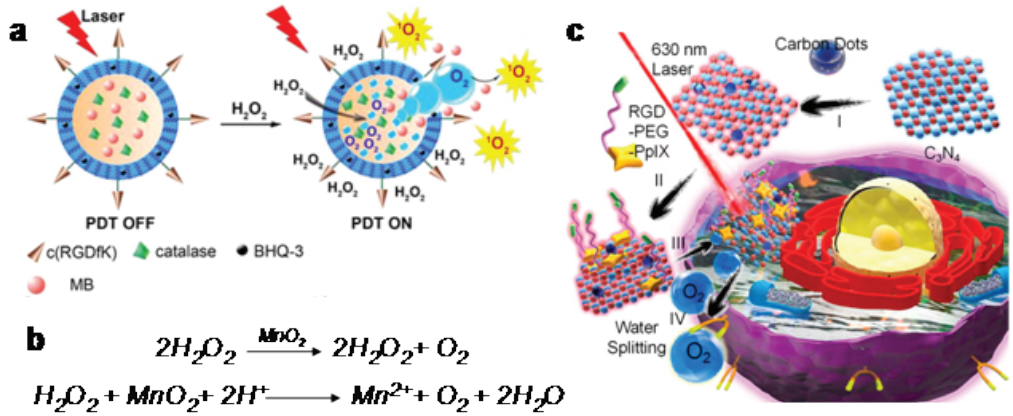

Figure 3. Schematic illustration on (a) the mechanism of H_2O_2-controllable release of photosensitizer and O_2 for improved PDT, (b) balanced chemical equations for H_2O_2 decomposition with the presence of MnO_2 in neutral (pH 7.4) and acidic (pH 5.5) solutions, and (c) light-driven water splitting by carbon dot-doped C_3N_4. Reproduced with permission [31-33].

Despite the exciting progress, additional issues need the attention in better application of above strategies for future PDT. The most important concern is from the excessive oxygen supply. Unlike cancerous cells, healthy cells are more susceptible to excessive oxygen without over-expressed the antioxidants. Hence, for ecdemic oxygen supply, the possible leakage of oxygen during transportation should be cautiously prevented, particularly for those *via* the intravenous injection. On the other hand, the rate for intracellular release of oxygen should be precisely controlled to avoid the massive burst, which may drive excessive oxygen to the neighboring healthy tissues. In terms of local oxygen source excavation, promoted motion of nanomotors is presumable to make the best of native H_2O_2 or H_2O in tumor tissue. Meanwhile, it may also expedite the diffusion of generated $^1O_2$. In the water splitting strategy, photonic energy is partially used for the production of O_2. As a result, less energy is available for photosensitizer activation, which is, leading to less $^1O_2$ generation. The energy shortage could become pronounced in tumors located in the deep tissues. In this regard, an on-site laser source (*e.g.* rechargeable persistent phosphors) might be a good solution [34].

To better address the oxygen limitation, tactics that could extricate PDT from oxygen-dependence would be more appealing for future photochemistry-based cancer therapy. Type-I PDT is believed to generate cytotoxic radicals while less relying on the tissue oxygen [35]. It offers a better choice when featured sensitizers for photo-induced electron transfer and hydrogen abstraction are well designed. Although $^1O_2$-donating endoperoxide therapy [36] is technically not the same as PDT, it may be considered as one of preferable or eventual alternatives for next-generation of PDT.

During cancer therapy, however, the phenotypic heterogeneity among individuals and even within the same neoplastic mass [37], recently termed as molecular pathological epidemiology (MPE), could lead to a significant disparity in treatment efficiency as a result to varying responses to $^1O_2$. In this regard, the establishment of 3D tumor models with patient's own cells would serve as an effective prescreening platform [38], enabling the provision of personalized protocol to individuals for treatment precision. Clearly, significant efforts are still required for PDT in achieving the optimal treatment efficiency and specificity.

References

1. Moan J, Peng Q (2003) An Outline of the Hundred-Year History of PDT. Anticancer Res 23: 3591-3600.
2. Jori G, Spikes JD (1990) Photothermal sensitizers: Possible use in tumor therapy. J Photochem Photobiol B 6: 93-101.
3. Ciocca DR, Calderwood SK (2005) Heat shock proteins in cancer: diagnostic, prognostic, predictive, and treatment implications. Cell Stress Chaperones 10: 86-103.
4. Lepock JR (2003) Cellular effects of hyperthermia: relevance to the minimum dose for thermal damage. Int J Hyperthermia 19: 252-266.
5. Dolmans DEJGJ, Fukumura D, Jain RK (2003) Photodynamic Therapy for Cancer. Nat Rev Cancer 3: 380-387.
6. Agostinis P, Berg K, Cengel KA, Foster TH, Girotti AW, et al. (2011) Photodynamic Therapy of Cancer: An Update. CA Cancer J Clin 61: 250-281.

7. Lovell JF, Liu TW, Chen J, Zheng G (2010) Activatable Photosensitizers for Imaging and Therapy. Chem Rev 110: 2839-2857.

8. Lin LW, Xiong L, Wen Y, Lei SL, Deng XF, et al. (2015) Active Targeting of Nano-Photosensitizer Delivery Systems for Photodynamic Therapy of Cancer Stem Cells. J Biomed Nanotechnol 11: 531-554.

9. Hu Y, Yang YM, Wang HJ, Du H (2015) Synergistic Integration of Layer-by-Layer Assembly of Photosensitizer and Gold Nanorings for Enhanced Photodynamic Therapy in the Near Infrared. ACS Nano 9: 8744-8754.

10. Yang YM, Hu Y, Du H, Wang HJ (2014) Intracellular Gold Nanoparticle Aggregation and Their Potential Applications in Photodynamic Therapy. Chem Commun 50: 7287-7290.

11. Moan J, Berg K (1991) The Photodegradation of Porphyrins in Cells Can Be Used to Estimate the Lifetime of Singlet Oxygen. Photochem Photobiol 53: 549-553.

12. Feng GX, Qin W, Hu QL, Tang BZ, Liu B (2015) Cellular and Mitochondrial Dual-Targeted Organic Dots with Aggregation-Induced Emission Characteristics for Image-Guided Photodynamic Therapy. Adv Healthc Mater 4: 2667-2676.

13. Yang YM, Gao N, Hu Y, Jia C, Chou TM, et al. (2015) Gold Nanoparticle-Enhanced Photodynamic Therapy: Effects of Surface Charge and Mitochondrial Targeting. Ther Deliv 6: 307-321.

14. Ju EG, Dong K, Chen ZW, Liu Z, Liu CQ, et al. (2016) Copper(II)-Graphitic Carbon Nitride Triggered Synergy: Improved ROS Generation and Reduced Glutathione Levels for Enhanced Photodynamic Therapy. Angew Chem Int Ed Engl 55: 11467-11471.

15. Kiyose K, Hanaoka K, Oushiki D, Nakamura T, Kajimura M, et al. (2010) Hypoxia-Sensitive Fluorescent Probes for in Vivo Real-Time Fluorescence Imaging of Acute Ischemia. J Am Chem Soc 132: 15846-15848.

16. Wang W, Moriyama LT, Bagnato VS (2013) Photodynamic Therapy Induced Vascular Damage: an Overview of Experimental PDT. Laser Phys Lett 10: 023001.

17. Tong X, Srivatsan A, Jacobson O, Wang Y, Wang ZT, et al. (2016) Monitoring Tumor Hypoxia Using ^{18}F-FMISO PET and Pharmacokinetics Modeling after Photodynamic Therapy. Sci Rep 6: 31551.

18. Xiao ZW, Halls S, Dickey D, Tulip J, Moore RB (2007) Fractionated Versus Standard Continuous Light Delivery In interstitial Photodynamic Therapy of Dunning Prostate Carcinomas. Clin Cancer Res 13: 7496-7505.

19. Jirsa M, Poučková P, Doležal J, Pospíšil J, Jirsa M (1991) Hyperbaric Oxygen and Photodynamic Therapy in Tumour-bearing Nude Mice. Eur J Cancer 27: 109.

20. Hu DH, Sheng ZH, Gao GH, Siu FM, Liu CB, et al. (2016) Activatable Albumin-Photosensitizer Nanoassemblies for Triple-Modal Imaging and Thermal-Modulated Photodynamic Therapy of Cancer. Biomaterials 93: 10-19.

21. Li TH, Jing XB, Huang YB (2011) Polymer/Hemoglobin Assemblies: Biodegradable Oxygen Carriers for Artificial Red Blood Cells. Macromol Biosci 11: 865-875.

22. Wang LY, Shi XY, Yang CS, Huang DM (2013) Versatile RBC-Derived Vesicles as Nanoparticle Vector of Photosensitizers for Photodynamic Therapy. Nanoscale 5: 416-421.

23. Luo ZY, Zheng MB, Zhao PF, Chen Z, Siu FM, et al. (2016) Self-Monitoring Artificial Red Cells with Sufficient Oxygen Supply for Enhanced Photodynamic Therapy. Sci Rep 6: 23393.

24. Habler OP, Messmer KF (2000) Tissue Perfusion and Oxygenation with Blood Substitutes. Adv Drug Deliv Rev 40: 171-184.

25. Song GS, Liang C, Yi X, Zhao Q, Cheng L, et al. (2016) Perfluorocarbon-Loaded Hollow Bi_2Se_3 Nanoparticles for Timely Supply of Oxygen under Near-Infrared Light to Enhance the Radiotherapy of Cancer. Adv Mater 28: 2716-2723.

26. Teicher BA, Herman TS, Jones SM (1989) Optimization of Perfluorochemical Levels with Radiation Therapy in Mice. Cancer Research 49: 2693.

27. Cheng YH, Cheng H, Jiang CX, Qiu XF, Wang KK, et al. (2015) Perfluorocarbon Nanoparticles Enhance Reactive Oxygen Levels and Tumour Growth Inhibition in Photodynamic Therapy. Nat Commun 6: 8785.

28. Que YR, Liu YJ, Tan W, Feng C, Shi P, et al. (2016) Enhancing Photodynamic Therapy Efficacy by Using Fluorinated Nanoplatform. ACS Macro Lett 5: 168-173.

29. Huang WC, Shen MY, Chen HH, Lin SC, Chiang WH, et al. (2015) Monocytic Delivery of Therapeutic Oxygen Bubbles for Dual-modality Treatment of Tumor Hypoxia. J Control Release 220: 738-750.

30. Szatrowski TP, Nathan CF (1991) Production of Large Amounts of Hydrogen Peroxide by Human Tumor Cells. Cancer Res 51: 794-798.

31. Chen HC, Tian JW, He WJ, Guo ZJ (2015) H_2O_2-Activatable and O_2-Evolving Nanoparticles for Highly Efficient and Selective Photodynamic Therapy against Hypoxic Tumor Cells. J Am Chem Soc 137: 1539-1547.

32. Fan WP, Bu WB, Shen B, He QJ, Cui ZW, et al. (2015) Intelligent MnO_2 Nanosheets Anchored with Upconversion Nanoprobes for Concurrent pH-/H_2O_2-Responsive UCL Imaging and Oxygen-Elevated Synergetic Therapy. Adv Mater 27: 4155-4161.

33. Zheng DW, Li B, Li CX, Fan JX, Lei Q, et al. (2016) Carbon-Dot-Decorated Carbon Nitride Nanoparticles for Enhanced Photodynamic Therapy against Hypoxic Tumor via Water Splitting. ACS Nano 10: 8715-8722.

34. Li ZJ, Zhang YW, Wu X, Wu XQ, Maudgal R, et al. (2015) In Vivo Repeatedly Charging Near-Infrared-Emitting Mesoporous SiO_2/$ZnGa_2O_4$:Cr^{3+} Persistent Luminescence Nanocomposites. Adv Sci (Weinh) 2: 1-6.

35. Zhuang XX, Ma XW, Xue XD, Jiang Q, Song LL, et al. (2016) A Photosensitizer-Loaded DNA Origami Nanosystem for Photodynamic Therapy. ACS Nano 10: 3486-3495.

36. Kolemen S, Ozdemir T, Lee D, Kim GM, Karatas T, et al. (2016) Remote-Controlled Release of Singlet Oxygen by the Plasmonic Heating of Endoperoxide-Modified Gold Nanorods: Towards a Paradigm Change in Photodynamic Therapy. Angew Chem Int Ed Engl 55: 3606-3610.

37. Ogino S, Galon J, Fuchs CS, Dranoff G (2011) Cancer Immunology - Analysis of Host and Tumor Factors for Personalized Medicine. Nat Rev Clin Oncol 8: 711-719.

38. Yang Y, Yang X, Zou J, Jia C, Hu Y, et al. (2015) Evaluation of Photodynamic Therapy Efficiency Using an in vitro Three-dimensional Microfluidic Breast Cancer Tissue Model. Lab Chip 15: 735-44.