



# The Novel Applications of PLGA Nanoparticles for Photodynamic Therapy Technique

Mohammadreza Saboktakin\*

Department of Nanomedicine, NanoBMat Company, Germany

## Abstract

Indocyanine green (ICG) has been exploited as a photosensitizer for use in cancerous phototherapy including breast, brain, and skin tumors. Although ICG is of particular advantage for use in cancer phototherapy, it adversely tends to disintegrate in aqueous medium and such degradation can be markedly accelerated by light irradiation (photodegradation) and/or heating (thermal degradation). Furthermore, ICG after administered intravenously will be readily bound with blood proteins and hence leads to only  $2 \pm 4$  min of plasmatic half-life. Among various pharmaceutical polymers, poly (lactic-co-glycolic acid) (PLGA) is the copolymer of poly (lactic acid) and poly (glycolic acid) and is one of the best defined biomaterials with FDA approval for drug encapsulation due to its biocompatibility, biodegradability, and controllability for drug release. This review shows that novel applications of PLGA polymers as nanocarrier for ICG to improve of physicochemical properties of ICG such as Half-life.

**Keywords:** Poly (lactic-co-glycolic acid) (PLGA); Indocyanine green (ICG); Photodynamic therapy (PDT); Cancer treatment

## Introduction

Among various approaches of breast cancer treatment, near-infrared (NIR)- mediated phototherapy is one of the most promising strategies for serving as a supplement to traditional cancer therapies since it can provide 1) enhanced tissue penetration efficacy as compared with that operated by visible light and 2) moderate toxicity to normal cells/tissues through use of targeted photosensitive agents and/or spatially controlled light irradiation [1]. Generally speaking, phototherapy is carried out by hyperthermia and/or reactive oxygen species (ROS) generated from the photosensitizers under light illumination in the presence of oxygen that the former may cause thermal ablation of cancer cells (i.e., photothermal therapy; PTT), while the latter may seriously interfere cellular metabolism and thus trigger programmed cell death (i.e., photodynamic therapy; PDT) [2,3]. No matter which mechanism is utilized, the photosensitizer plays a key role in the effectiveness of phototherapy. Indocyanine green (ICG) is an U.S. Food and Drug Administration (FDA)-approved tricyanocyanine dye which enables to absorb and fluoresce in the region of  $650 \pm 850$ nm. Currently, in addition to serving as a fluorophoric agent for use in diagnostic purposes such as NIR image-guided oncologic surgery [4], fluorescence angiography [5], and lymph node detection of cancer [6], ICG has been exploited as a photosensitizer for use in cancerous

phototherapy including breast, brain, and skin tumors [7-9] since it enables to produce heat and ROS (i.e., singlet oxygen) upon NIR irradiation. Although ICG is of particular advantage for use in cancer phototherapy, it adversely tends to disintegrate in aqueous medium and such degradation can be markedly accelerated by light irradiation (photodegradation) and/or heating (thermal degradation) [10]. Furthermore, ICG after administered intravenously will be readily bound with blood proteins and hence leads to only  $2 \pm 4$  min of plasmatic half-life [11,12]. These circumstances seriously hinder the applicability of ICG in the clinic and thus a strategy that enables to enhance the aqueous stability and target efficiency of ICG is certainly needed for ICG-mediated therapy. Nanomedicine may offer a feasible means for usage of ICG without aforementioned defects since it may provide merits of enhanced bioavailability, improved stability, and security for the payload [13]. In terms of the materials used for making drug carrier, polymer is often considered as the preferred candidate since it can be manipulated to tailor the properties and/or functionalities required by the product [14]. Among various pharmaceutical polymers, poly (lactic-co-glycolic acid) (PLGA) is the copolymer of poly(lactic acid) and poly(glycolic acid) and is one of the best defined biomaterials with FDA approval for drug encapsulation due to its biocompatibility, biodegradability, and controllability for drug release [15]. Polyethylene glycol (PEG), another FDA-approved polymer with characteristics of nontoxicity and less immunogenicity, is frequently used for surface modification of drug carrier since the retention time of the PEG-coated particle in the blood circulation can be markedly increased [16]. Taken all together, we aim to develop an anti-HER2 ICG-encapsulated PEG-coated PLGA nanoparticles (HIPPNNs) for targeted phototherapy of HER2-expressing breast cancer cells. The use of ICG by implantation of HIPPNNs instead of naked molecules is advantageous because the polymeric carrier (i.e., HIPPNNP) may 1) potentially protect the entrapped ICG from degradation caused by external stimuli such as light, heat, and/or extreme pH [17]; 2) precisely localize the therapeutic region to reduce off-target toxicity, and 3) provide accurate estimation for the efficacy of ICG-mediated phototherapy. There are many of reports that ICG

**Submitted:** 13 May 2019 | **Accepted:** 05 June 2019 | **Published:** 07 June 2019

\***Corresponding author:** Mohammadreza Saboktakin, Department of Nanomedicine, NanoBMat Company, Hamburg, Germany; Email: saboktakin123@gmail.com

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**Citation:** Saboktakin M (2019) The Novel Applications of PLGA Nanoparticles for Photodynamic Therapy Technique. JSMC Nanotechnol Nanomed 3: 7.



encapsulators, such as (poly (lactic-co-glycolic acid) (PLGA) nanoparticles (diameter  $\sim 360\text{nm}$ ) and silica-polymer composite microcapsules (diameter  $\sim 0.6$  to  $2\mu\text{m}$ ) improve the molecular instability of ICG and prolong its plasma half-life [18,19]. However, both of these nanoparticles are limited in size for *in vivo* tumor imaging depending on their EPR effects. Recently, several publications have reported promising results using smaller nanoparticles to encapsulate ICG for *in vivo* imaging. For example, Zheng et al. [20], developed ICG encapsulated PLGA-lipid nanoparticles conjugated with folic acid (FA) and demonstrated their use as NIR contrast agents for tumor diagnosis and targeted imaging. Altinoglu et al., also synthesized biodegradable calcium phosphosilicate nanoparticles (CPNPs) and demonstrated that small size ( $16\text{nm}$ ) ICG- encapsulating CPNPs have significantly better contrast agent optical properties than free fluorophores for tumor imaging [21]. Other inorganic delivery systems using silica nanoparticles have been developed to encapsulate ICG, and the ICG-SiO<sub>2</sub> nanoparticles have the potential to be used as contrast agents for optical NIR imaging as well [22]. Among these nanocarriers, micelles are one of the successful types of drug delivery systems for *in vivo* applications due to their small size (approximately  $10\text{-}100\text{nm}$ ), which reduce clearance by the reticuloendothelial system (RES) and allow for an enhanced EPR effect [23,24]. Therefore, the encapsulation and stabilization of ICG dye as a contrast agent in micellar systems is of particular interest. For example, Pluronic F-127 (PF-127) polymeric micelles are approved by the FDA and have been successfully demonstrated to encapsulate and stabilize ICG as an NIR contrast agent for optical imaging [25,26]. Encapsulation of ICG within various micellar systems was also investigated by Kirchherr and co-workers, and they found many micellar systems improved the optical properties and stability of the ICG [27]. More interestingly, Zheng et al. have recently reported a dual-functional ICG-PL-PEG agent with several unique features for optical imaging and photo-therapy [28]. This may emerge as a new strategy for combining tumor treatment and diagnosis together, using nanovectors with ICG. In summary, this editorial discussed recent developments in nanocarrier ICG contrast agents for NIR optical imaging. Here just some of the areas are collected in terms of subjects and interests but it is hoped that every reader will find something of interest to them. Manchanda et al. [29], have recently reported the fabrication of a novel polymer nanoparticle delivery system with simultaneously entrapped indocyanine green (ICG) and doxorubicin (DOX). This system has potential applications for combined chemotherapy and hyperthermia. Research in our group showed that simultaneous use of ICG and DOX with localized hyperthermia can produce the same effect as that achieved by larger doses of chemotherapy alone. The potential of dual- agent PLGA nanoparticles (ICG-DOXPLGANPs) has explored to overcome multidrug resistance (MDR) mechanisms in cancer cells by increasing intracellular drug concentrations via nanoparticle uptake. ICG-DOX-PLGANPs were prepared by the O/W emulsion solvent evaporation method. The dominant processing parameters that control particle size and drug entrapment efficiencies of ICG and DOX were PLGA concentration, PVA concentration and initial drug content. The previous formulation

optimized based on those parameters. Entrapment efficiency of the optimized ICG-DOX-PLGANPs was measured by fluorescence measurements using the DMSO burst release procedure. The internalization of ICG-DOX- PLGANPs by three cancer cell lines was visualized by confocal laser microscopy and fluorescence microscopy. Cytotoxicity was assessed using the SRB assay. The nanoparticles produced by optimal formulation had sizes of  $135 \pm 2 \text{ nm}$ , ( $n=3$ ) with a low poly-dispersity index ( $0.149 \pm 0.014$ ,  $n=3$ ) and a zeta potential of  $-11.67 \pm 1.8 \text{ mV}$ . Drug loading was approximately 3% w/w for ICG and 4% w/w for DOX ( $n=3$ ). Cellular uptake of ICG and DOX from ICG-DOX-PLGANPs in DOX-resistant MESSA/Dx5 cancer cells was higher compared to free ICG and free DOX treatment. However, the same phenomenon was not observed in MES- SA and SKOV-3 cancer cell lines. The SRB cytotoxicity results show that ICG- DOX-PLGANPs are more toxic than free DOX in DOX-resistant cell lines. In the development of drugs for intra-articular administration, sustained-release formulations are desirable because it is difficult to maintain the effect of conventional injections due to immediate drug leakage from the joint cavity. In this study, a sustained-release poly (lactic-co-glycolic acid) (PLGA) microsphere formulation for intra-articular administration containing indocyanine green (ICG) as a model drug was prepared to follow its fate after intra-articular administration in rats with a real-time *in-vivo* imaging system. ICG administered as an aqueous solution leaked from the joint cavity in a short time and was excreted outside the body within 1-3 d. However, ICG in the sustained-release formulation was retained in the joint cavity and released for 2 weeks. Next, a sustained-release formulation containing PLGA microspheres in a hyaluronic acid (HA) gel formulation was prepared [30] (Figure 1).

Ronak et al. [31], have been developed and characterized multifunctional biodegradable and biocompatible poly lactic-co-glycolic acid (PLGA) nanoparticles loaded with indocyanine green (ICG) as an optical-imaging contrast agent for cancer imaging and as a photothermal therapy agent for cancer treatment. PLGA-ICG nanoparticles (PIN) were synthesized with a particle diameter of  $246 \pm 11\text{nm}$ , a polydispersity index of  $0.10 \pm 0.03$ , and ICG loading efficiency of  $48.75 \pm 5.48\%$ . PIN were optically characterized with peak excitation and emission

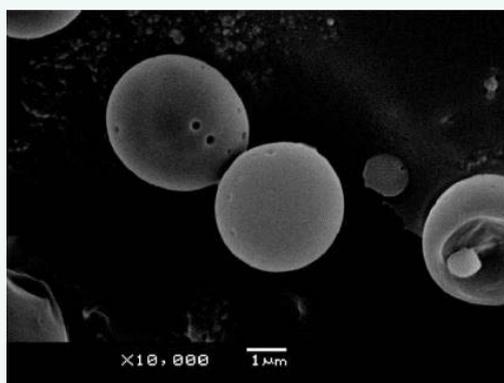
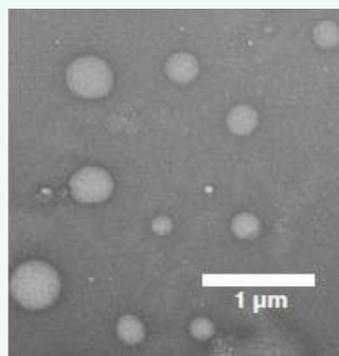


Figure 1 Observation of PGLA microspheres by SEM.

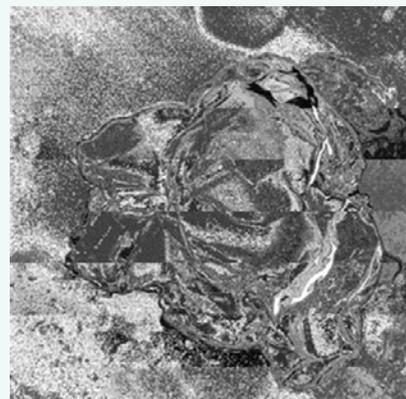
at 765 and 810 ± 5 nm, a fluorescence lifetime of 0.30 ± 0.01 ns, and peak absorbance at 780 nm. The cytocompatibility study of PIN showed 85% cell viability till 1mg/ml concentration of PIN. Successful cellular uptake of ligand conjugated PIN by prostate cancer cells (PC3) was also obtained. Both phantom- based and *in vitro* cell culture results demonstrated that PIN (1) have the great potential to induce local hyperthermia (i.e., temperature increase of 8 to 10°C) in tissue within 5mm both in radius and in depth; (2) result in improved optical stability, excellent biocompatibility with healthy cells, and a great targeting capability; (3) have the ability to serve as an image contrast agent for deep-tissue imaging in diffuse optical tomography (Figure 2).

Nowadays, a new technique such as photodynamic therapy (PDT) is used to achieve effective root canal disinfection and eliminate *Enterococcus faecalis* as the most prevalent species associated with secondary endodontic infections and treatment failures. Employment of an optimized nontoxic photosensitizer (PS) such as indocyanine green (ICG) is a crucial part of this technique; the current study aimed at improving ICG photodynamic properties through conjugation of ICG into nanographene oxide (nGO) as a new PS, to evaluate the antimicrobial effects of nGO/ICG against *E. faecalis*. The PDT based on ICG, at the concentration loaded in nGO, showed a significant reduction in the number of *E. faecalis* at a lower concentration of ICG. In conclusion, the application of nGO as a new drug delivery system, in addition to the anti-bacterial property, offers other benefits such as cost beneficial outcomes due to using the lower dye concentration (less toxicity), and less tooth discoloration. The nGO/ICG-PDT could be proposed as a new approach to treat endodontic infections, alone or in combination with conventional root canal treatments [32] (Figure 3).

Zheng et al. [33], had successfully constructed the fluorescence image guided photothermal therapy reagents based on (WO+ICG)@PLGA nanoparticles. In our design, to improve their tumor targeting, the macrophages as cell-based biocarriers were employed for delivery the (WO+ICG)@PLGA nanoparticles. The macrophages carried these nanoparticles still had phagocytosis to tumor cells and could also secrete plenty of anti-tumor cytokines for immunotherapy of carcinoma. They also further elucidated the superior solid tumor suppression efficiency of the (WO+ICG)@PLGA nanoparticles loaded



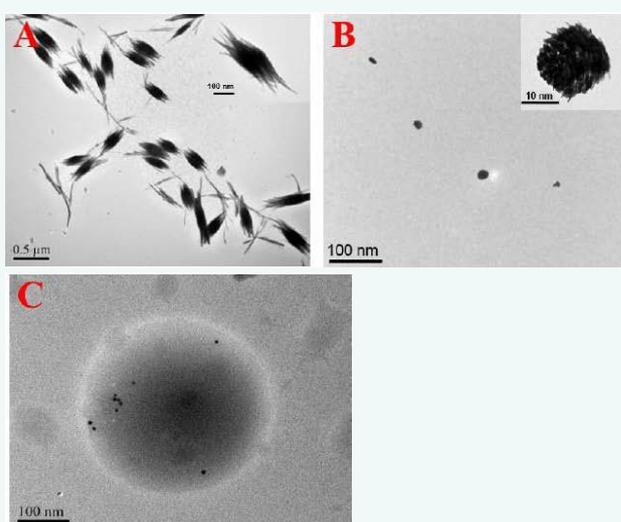
**Figure 2** TEM image of presenting of morphology of PIN.



**Figure 3** The SEM image of the nGO.

macrophages targeting biocarriers delivery system *in vivo*. The system achieved a significant antitumor effect by activating immunotherapy and photothermal therapy *in vivo*. Hence, such kind of (WO+ICG)@PLGA nanoparticles loaded macrophages delivery system has great potential applications as targeting biocarriers loading drugs and imaging agents for visual-guided synergistic therapy *in vivo* (Figure 4).

The photothermal heating and release properties of biocompatible organic nanoparticles, doped with a near infrared croconaine (Croc) dye, were compared with analogous nanoparticles doped with the common near-infrared dyes ICG and IR780. Separate formulations of lipid-polymer hybrid nanoparticles and liposomes, each containing Croc dye, absorbed strongly at 808nm and generated clean laser-induced heating (no production of <sup>1</sup>O<sub>2</sub> and no photobleaching of the dye). In contrast, laser-induced heating of nanoparticles containing ICG or IR780 produced reactive <sup>1</sup>O<sub>2</sub>, leading to bleaching of the dye and also decomposition of coencapsulated payload such as the drug doxorubicin. Croc dye was especially useful as a photothermal



**Figure 4** The TEM images of (A) Nanorod-Bundled WO, (B) Granulated.

agent for laser-controlled release of chemically sensitive payload from nanoparticles. Solution state experiments demonstrated repetitive fractional release of water-soluble fluorescent dye from the interior of thermosensitive liposomes. Additional experiments used a focused laser beam to control leakage from immobilized liposomes with very high spatial and temporal precision. The results indicate that fractional photothermal leakage from nanoparticles doped with Croc dye is a promising method for a range of controlled release applications [34] (Figure 5).

Near-infrared (NIR) laser-induced photothermal therapy (PTT) uses a photothermal agent to convert optical energy into thermal energy and has great potential as an effective local, minimally invasive treatment modality for killing cancer cells. To improve the efficacy of PTT, Chengcheng Niu et al. [35], developed poly (lactide co-glycolide) (PLGA) nanoparticles (NPs) encapsulating super paramagnetic iron oxide ( $\text{Fe}_3\text{O}_4$ ), indocyanine green (ICG), and perfluoropentane (PFP) as synergistic agents for NIR laser-induced PTT. They fabricated a novel type of phase-shifting fluorescent magnetic NPs,  $\text{Fe}_3\text{O}_4$ /ICG@PLGA/PFP NPs that effectively produce heat in response to NIR laser irradiation for an enhanced thermal ablation effect and a phase-shift thermoelastic expansion effect, and thus, can be used as a photothermal agent (Figure 6).

After *in vitro* treatment of MCF-7 breast cancer cells with  $\text{Fe}_3\text{O}_4$ /ICG@PLGA/PFP NPs and NIR laser irradiation, histology and electron microscopy confirmed severe damage to the cells and the formation of many microbubbles with iron particles at the edge or outside of the microbubbles. *In vivo* experiments in mice with MCF-7 tumors demonstrated that  $\text{Fe}_3\text{O}_4$ /ICG@PLGA/PFP NPs could achieve tumor ablation upon NIR laser irradiation with minimal toxicity to non-irradiated tissues. Together, their results indicate that  $\text{Fe}_3\text{O}_4$ /ICG@PLGA/PFP NPs can be used as effective nanotheranostic agents for tumor ablation. Hrebesh M. Subhash, et al. [36], have been described a functional imaging paradigm that uses photothermal optical coherence tomography (PT-OCT) to detect indocyanine green (ICG)-encapsulated biocompatible poly(lactic-co-glycolic) acid (PLGA) nanoparticles embedded in highly scattering tissue phantoms with high resolution and sensitivity. The ICG- loaded PLGA nanoparticles were fabricated using a modified emulsification solvent diffusion method. With

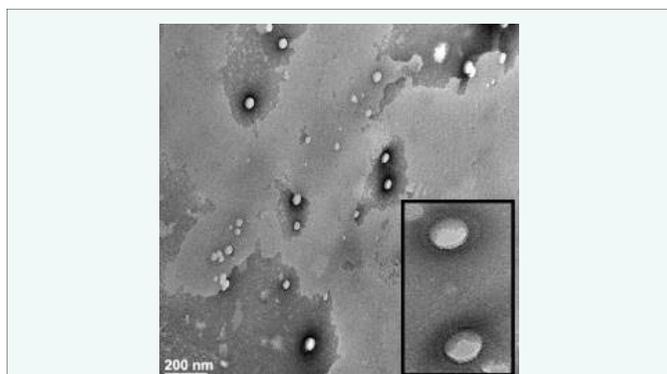


Figure 5 TEM image of Croc/LP-hybrid-NP.

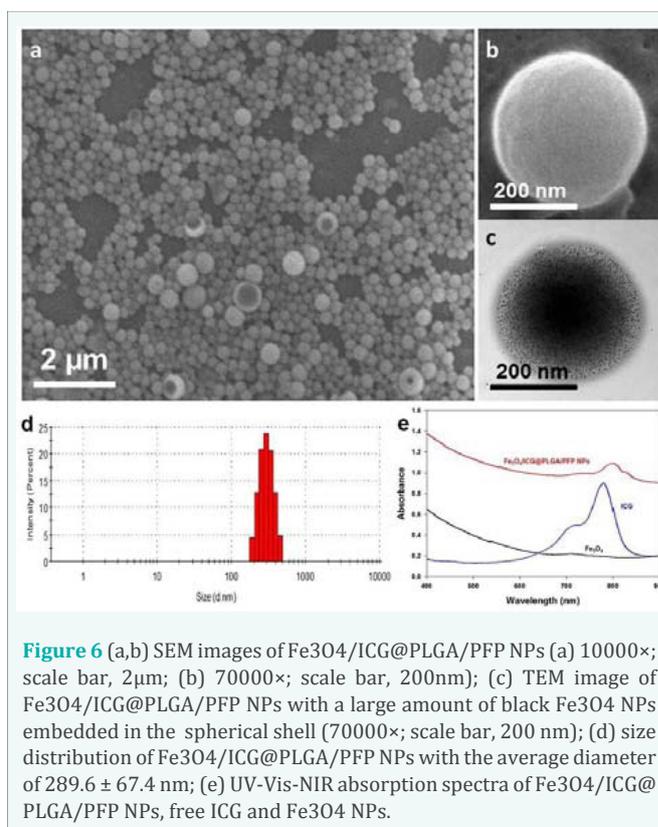


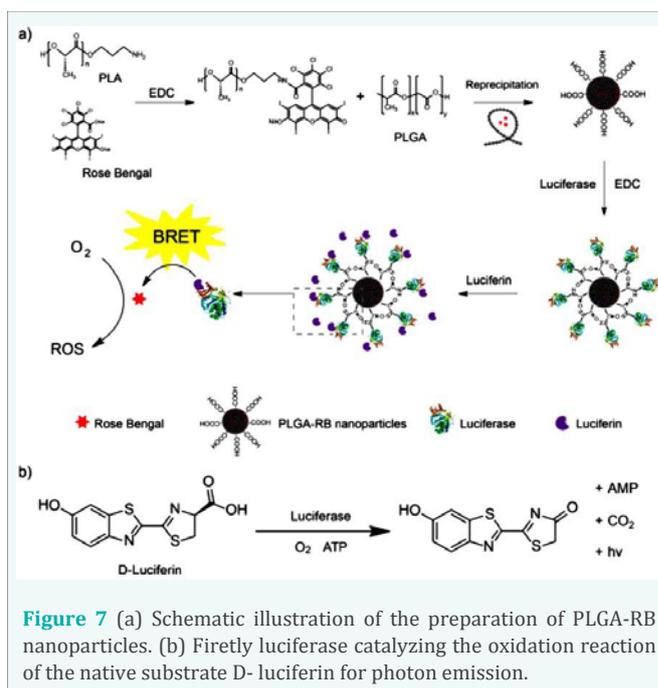
Figure 6 (a,b) SEM images of  $\text{Fe}_3\text{O}_4$ /ICG@PLGA/PFP NPs (a) 10000 $\times$ ; scale bar, 2  $\mu\text{m}$ ; (b) 70000 $\times$ ; scale bar, 200nm); (c) TEM image of  $\text{Fe}_3\text{O}_4$ /ICG@PLGA/PFP NPs with a large amount of black  $\text{Fe}_3\text{O}_4$  NPs embedded in the spherical shell (70000 $\times$ ; scale bar, 200 nm); (d) size distribution of  $\text{Fe}_3\text{O}_4$ /ICG@PLGA/PFP NPs with the average diameter of  $289.6 \pm 67.4$  nm; (e) UV-Vis-NIR absorption spectra of  $\text{Fe}_3\text{O}_4$ /ICG@PLGA/PFP NPs, free ICG and  $\text{Fe}_3\text{O}_4$  NPs.

a 20 kHz axial scan rate, PT-OCT based on spectral-domain interferometric configuration at 1310nm was used to detect phase changes induced by a 808nm photothermal excitation of ICG-encapsulated PLGA nanoparticles. An algorithm based on Fourier transform analysis of differential phase of the spectral interferogram was developed for detecting the depth resolved localized photothermal signal. Excellent contrast difference was observed with PT-OCT between phantoms containing different concentrations of ICG-encapsulated PLGA nanoparticles. This technique has the potential to provide simultaneous structural and molecular-targeted imaging with excellent signal-to-noise for various clinical applications. Photoacoustic imaging (PAI) is an emerging biomedical imaging technique that is now coming to the clinic. It has a penetration depth of a few centimeters and generates useful endogenous contrast, particularly from melanin and oxy-/deoxyhemoglobin. Indocyanine green (ICG) is a Food and Drug Administration-approved contrast agents for human applications, which can be also used in PAI. It is a small molecule dye with limited applications due to its fast clearance, rapid protein binding, and bleaching effect. Edyta Swider et al. [37], showed that they can label primary human dendritic cells with the nanoparticles and image them *in vitro* and *in vivo*, in a multimodal manner. This work demonstrates the potential of combining PAI and  $^{19}\text{F}$  MRI for cell imaging and lymph node detection using nanoparticles that are currently produced at GMP- grade for clinical use. Photodynamic therapy (PDT) is emerging as a noninvasive modality for a variety of cancer treatments [38,39]. In typical PDT, a photosensitizer is activated by external light to produce reactive oxygen species (ROS), which

can damage cancer cells [40-42]. For deep-seated tumors, the efficiency of PDT is decreased due to the limited penetration depth of external light in biological tissue. This problem has hindered further development of PDT in widespread clinical applications. In addition, skin photosensitivity and photothermal injury are also common concerns from the patients receiving PDT treatment [43-45]. For the light penetration issue to be overcome, considerable research has focused on the development of photosensitizers in the near infrared (NIR) range [46]. Up-conversion nanoparticles combined with photosensitizers have been explored because they can absorb NIR photons and emit visible light to activate the photosensitizer for PDT [47,48]. Researchers have explored new approaches, for example, using Cerenkov radiation to activate a photosensitizer for effective PDT [49,50]. Alternatively, X-ray is currently widely used in clinical treatment, and X-ray-activated photodynamic therapy is another way to overcome the light penetration limitation in deep-seated tumors [51-53]. The use of an internal light source is an intriguing solution for the light-penetration problem. For example, implanting fiber-optic light sources and emitting diodes could be a viable approach, but it still requires invasive operation [54-56]. Alternatively, bioluminescence offers an attractive strategy because of the minimally invasive delivery of enzymes and substrates. Bioluminescence is a natural phenomenon that occurs in various organisms, such as marine organisms and some insects, in which visible light is produced via chemical reactions *in vivo* [57,58]. Bioluminescence has been widely used in biological detection and optical imaging [59-61]. Recently, researchers have recognized the therapeutic potential of bioluminescence. Bioluminescence is endogenous fluorescence that can be used to activate the photosensitizer inside the tumors. This process is not affected by the light penetration depth of tissue. Wang et al., reported that luminol has anticancer and antifungal activities through bioluminescence resonance energy transfer (BRET) [62]. Moreover, quantum dots have also been combined with the BRET system for *in vivo* imaging and PDT in recent reports [63-65]. Despite these progresses, the BRET-activated ROS generation and photodynamic effect is largely unexplored. They show effective photodynamic therapy mediated by the firefly luciferase bioluminescence system. Biodegradable poly (lactic-co-glycolic acid) (PLGA) nanoparticles were doped with the photosensitizer Rose Bengal (RB). The PLGA-RB nanoparticles were then conjugated with luciferase, which produced a fluorescent signal in the presence of the luciferin substrate. The endogenous bioluminescence served as a light source to activate the photosensitizer for ROS generation (Figure 7). They evaluated cell toxicity, cellular fluorescence imaging, and therapeutic effect in cellular assays, which indicated that cancer cells were destroyed effectively. The antitumor effect of BRET-PDT was further investigated in tumor-bearing ICR mice, which showed that tumor growth was significantly inhibited. This study provides a promising approach for phototherapy of deep-seated tumors in the absence of external excitation.

## Conclusions

Multifunctional biodegradable and biocompatible poly lactic-co-glycolic acid (PLGA) nanoparticles loaded with indocyanine



**Figure 7** (a) Schematic illustration of the preparation of PLGA-RB nanoparticles. (b) Firefly luciferase catalyzing the oxidation reaction of the native substrate D-luciferin for photon emission.

green (ICG) as an optical-imaging contrast agent for cancer imaging and as a photothermal therapy agent for cancer treatment. To improve the efficacy of PTT, poly (lactide co-glycolide) (PLGA) nanoparticles (NPs) encapsulating superparamagnetic iron oxide (Fe<sub>3</sub>O<sub>4</sub>), indocyanine green (ICG), and perfluoropentane (PFP) as synergistic agents for NIR laser-induced PTT. ICG after administered intravenously will be readily bound with blood proteins and hence leads to only  $2 \pm 4$  min of plasmatic half-life. Among various pharmaceutical polymers, poly (lactic-co-glycolic acid) (PLGA) is the copolymer of poly (lactic acid) and poly (glycolic acid) and is one of the best defined biomaterials with FDA approval for drug encapsulation due to its biocompatibility, biodegradability, and controllability for drug release.

## References

- Cheng L, Wang C, Feng LZ, Yang K, Liu Z. Functional nanomaterials for phototherapies of cancer. *Chem Rev.* 2014; 114: 10869-10939.
- Dolmans DE, Fukumura D, Jain RK. Photodynamic therapy for cancer. *Nat Rev Cancer.* 2003; 3: 380-387.
- Circu ML, AW TY. Reactive oxygen species, cellular redox systems, and apoptosis. *Free Radic Biol Med.* 2010; 48: 749-762.
- Schaafsma BE, Mieog JS, Hutteman M, van der Vorst JR, Kuppen PJ, Loëwik CW, et al. The clinical use of indocyanine green as a near-infrared fluorescent contrast agent for image-guided oncologic surgery. *J Surg Oncol.* 2011; 104: 323-332.
- Mastropasqua R, Di Antonio L, Di Staso S, Agnifili L, Di Gregorio A, Ciancaglini M, et al. Optical Coherence Tomography Angiography in Retinal Vascular Diseases and Choroidal Neovascularization. *J Ophthalmol.* 2015; 2015: 343515.
- Zelken JA, Tufaro AP. Current Trends and Emerging Future of Indocyanine Green Usage in Surgery and Oncology: An Update. *Ann Surg Oncol.* 2015; Suppl 3: 1271-1283.
- Shemesh CS, Moshkelani D, Zhang H. Thermosensitive liposome



- formulated indocyanine green for near-infrared triggered photodynamic therapy: *in vivo* evaluation for triple-negative breast cancer. *Pharm Res.* 2015; 32: 1604-1614.
8. Bernardi RJ, Lowery AR, Thompson PA, Blaney SM, West JL. Immunonanosystems for targeted photothermal ablation in medulloblastoma and glioma: an *in vitro* evaluation using human cell lines. *J Neurooncol.* 2008; 86: 165-172.
  9. Mundra V, Peng Y, Rana S, Natarajan A, Mahato RI. Micellar formulation of indocyanine green for phototherapy of melanoma. *J Control Release.* 2015; 220: 130-140.
  10. Saxena V, Sadoqi M, Shao J. Degradation kinetics of indocyanine green in aqueous solution. *J Pharm Sci.* 2003; 92: 2090-2097.
  11. Mordon S, Devoisselle JM, Soulie-Begu S, Desmettre T. Indocyanine green: physicochemical factors affecting its fluorescence *in vivo*. *Microvasc Res.* 1998; 55: 146-152.
  12. Desmettre T, Devoisselle JM, Mordon S. Fluorescence properties and metabolic features of indocyanine green (ICG) as related to angiography. *Surv Ophthalmol.* 2000; 45: 15-27.
  13. Jain KK. Nanomedicine: application of nanobiotechnology in medical practice. *Med Princ Pract.* 2008; 17: 89-101.
  14. Nair LS, Laurencin CT. Biodegradable polymers as biomaterials. *Prog Polym Sci.* 2007; 32: 762-798.
  15. Makadia HK, Siegel SJ. Poly lactic-co-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier. *Polymers.* 2011; 3: 1377-1397.
  16. Fishburn CS. The pharmacology of PEGylation: Balancing PD with PK to generate novel therapeutics. *J Pharm Sci.* 2008; 97: 4167-4183.
  17. BjoÈrnsson OG, Murphy R, Chadwick VS, BjoÈrnsson S. Physicochemical studies on indocyanine green: molar lineic absorbance, pH tolerance, activation energy and rate of decay in various solvents. *J Clin Chem Clin Biochem.* 1983; 21: 453-458.
  18. Saxena V, Sadoqi M, Shao J. Enhanced photo-stability, thermal-stability and aqueous-stability of indocyanine green in polymeric nanoparticulate systems. *J Photochem Photobiol B.* 2004; 74: 29-38.
  19. Yaseen MA, Yu J, Wong MS, Anvari Bn. Stability assessment of indocyanine green within dextran-coated mesocapsules by absorbance spectroscopy. *J Biomed Opt.* 2007; 12: 064031.
  20. Zheng CF, Zheng MB, Gong P, Jia AG, Zhang PF, et al. Indocyanine green-loaded biodegradable tumor targeting nanoprobe for *in vitro* and *in vivo* imaging. *Biomaterials.* 2012; 33: 5603-5609.
  21. Altinoglu EI, Russin TJ, Kaiser JM, Barth BM, Eklund PC, et al. Near- Infrared Emitting Fluorophore-Doped Calcium Phosphate Nanoparticles for *In Vivo* Imaging of Human Breast Cancer. *ACS Nano.* 2008; 2: 2075-2084.
  22. Liu H, Farrell S, Uhrich K. Drug release characteristics of unimolecular polymeric micelles. *J Control Release.* 2000; 68: 167-174.
  23. Lavasanifar A, Samuel J, Kwon GS. Poly (ethylene oxide)-block-poly (L-amino acid) micelles for drug delivery. *Adv Drug Deliv Rev.* 2002; 54: 169-190.
  24. Chen YP, Li XD. Near-Infrared Fluorescent Nanocapsules with Reversible Response to Thermal/pH Modulation for Optical Imaging. *Biomacromolecules.* 2011; 12: 4367-4372.
  25. Kim TH, Chen Y, Mount CW, Gombotz WR, Li XD, et al. Evaluation of Temperature-Sensitive, Indocyanine Green-Encapsulating Micelles for Noninvasive Near-Infrared Tumor Imaging. *Pharm Res.* 2010; 27: 1900-1913.
  26. Kirchherr AK, Briel A, Mader K. Stabilization of indocyanine green by encapsulation within micellar systems. *Mol Pharm.* 2009; 6: 480-491.
  27. Zheng XH, Xing D, Zhou FF, Wu BY, Chen. Indocyanine Green-Containing Nanostructure as Near Infrared Dual-Functional Targeting Probes for Optical Imaging and Photothermal Therapy. *Mol Pharm.* 2011; 8: 447-456.
  28. Zheng XH, Zhou FF, Wu BY, Chen WR, Xing D. Enhanced Tumor Treatment Using Biofunctional Indocyanine Green-Containing Nanostructure by Intratumoral or Intravenous Injection. *Mol Pharm.* 2011; 9: 514-522.
  29. Romila Manchanda, Tingjun Lei, Yuan Tang, Alicia Fernandez-Fernandez, and Anthony J. McGoron, "Cellular Uptake and Cytotoxicity of a Novel ICG-DOX-PLGA Dual Agent Polymer Nanoparticle Delivery System "K.E. Herold, W.E. Bentley, and J. Vossoughi (Eds.): SBEC 2010, IFMBE Proceedings. 2010; 32: 228-231.
  30. Noda T, Okuda T, Mizuno R, Ozeki T, Okamoto H. Two-Step Sustained-Release PLGA/Hyaluronic Acid Gel Formulation for Intra-articular Administration. *Biol Pharm Bull.* 2018; 41: 937-943.
  31. Patel RH, Wadajkar AS, Patel NL, Kavuri VC, Nguyen KT, Liu H. Multifunctionality of indocyanine green-loaded biodegradable nanoparticles for enhanced optical imaging and hyperthermia intervention of cancer", *Journal of Biomedical Optics.* 2012; 17: 046003.
  32. Tayebeh Akbari, Maryam Pourhajibagher, Nasim Chiniforush, Sima Shahabi, Farzaneh Hosseini, Abbas Bahador. Improve ICG Based Photodynamic Properties through Conjugation of ICG into Nano-Graphene Oxide against *Enterococcus faecalis*", *Avicenna J Clin Microb Infe.* 2018; 5: e64624.
  33. Bin Zheng, Yang Bai, Hongbin Chen, Huizhuo Pan, Wanying Ji, Xiaoqun Gong, et al. Targeted delivery of tungsten oxide nanoparticles for multifunctional anti-tumor therapy *via* macrophages", *Electronic Supplementary Material (ESI) for Biomaterials Science.* 2018.
  34. Guha S, Shaw SK, Spence GT, Roland FM, Smith BD. Clean Photothermal Heating and Controlled Release from Near-Infrared Dye Doped Nanoparticles without Oxygen Photosensitization. *Langmuir.* 2015; 31: 7826-7834.
  35. Chengcheng Niu, Yan Xu, Senbo An, Ming Zhang, Yihe Hu, Long Wang, et al. Near-infrared induced phaseshifted ICG/Fe<sub>3</sub>O<sub>4</sub> loaded PLGA nanoparticles for photothermal tumor ablation. *Sci Rep.* 2017; 7: 5490.
  36. Subhash HM1, Xie H, Smith JW, McCarty OJ. Optical detection of indocyanine green encapsulated biocompatible poly (lactic-co-glycolic) acid nanoparticles with photothermal optical coherence tomography. *Opt Lett.* 2012; 37: 5.
  37. Swider E, Daoudi K, Staal AHJ, Koshkina O, van Riessen NK, van Dinther E. Clinically-Applicable Perfluorocarbon-Loaded Nanoparticles For *In vivo* Photoacoustic, 19F Magnetic Resonance And Fluorescent Imaging. *Nanotheranostics.* 2018; 2: 258-268.
  38. Dolmans DE, Fukumura D, Jain RK. Photodynamic therapy for cancer. *Nat Rev Cancer.* 2003; 3: 380-387.
  39. Moore CM, Pendse D, Emberton M. Photodynamic therapy for prostate cancer a review of current status and future promise. *Nat Clin Pract Urol.* 2009; 6: 18-30.
  40. Lucky SS, Soo KC, Zhang Y. Nanoparticles in photodynamic therapy. *Chem Rev.* 2015; 115: 1990-2042.
  41. Castano AP1, Mroz P, Hamblin MR. Photodynamic therapy and anti-tumour immunity. *Nat Rev Cancer.* 2006; 6: 535-545.



42. Ge J, Lan M, Zhou B, Liu W, Guo L, Wang HA. graphene quantum dot photodynamic therapy agent with high singlet oxygen generation. *Nat Commun.* 2014; 5: 4596.
43. Macdonald IJ, Dougherty TJ. Basic principles of photodynamic therapy. *J. Porphyrins Phthalocyanines.* 2001; 5: 105- 129.
44. Guan KW, Jiang YQ, Sun CS, Yu H. A two-layer model of laser interaction with skin A photothermal effect analysis. *Opt Laser Technol.* 2011; 43: 425-429.
45. Brown S. Photodynamic Therapy - Two photons are better than one. *Nat Photonics.* 2008; 2: 394-395.
46. Mitsunaga M, Ogawa M, Kosaka N, Rosenblum LT, Choyke PL, Kobayashi H. Cancer cell-selective *in vivo* near infrared photoimmunotherapy targeting specific membrane molecules. *Nat. Med.* 2011; 17: 1685-1691.
47. Chen G, Qiu H, Prasad PN, Chen X. Upconversion Nanoparticles: Design, Nanochemistry, and Applications in Theranostics. *Chem Rev.* 2014; 114: 5161-5214.
48. Liang LE, Care A, Zhang R, Lu YQ, Packer NH, Sunna A, et al. Facile Assembly of Functional Upconversion Nanoparticles for Targeted Cancer Imaging and Photodynamic Therapy. *ACS Appl Mater Interfaces.* 2016; 8: 11945-11953.
49. Kamkaew A, Cheng L1, Goel S, Valdovinos HF, Barnhart TE, Liu Z, et al. Cerenkov Radiation Induced Photodynamic Therapy Using Chlorin e6-Loaded Hollow Mesoporous Silica Nanoparticles. *ACS Appl Mater Interfaces.* 2016; 8: 26630-26637.
50. Tang Y, Hu J, Elmenoufy AH, Yang X. Highly Efficient FRET System Capable of Deep Photodynamic Therapy Established on X-ray Excited Mesoporous LaF<sub>3</sub>:Tb Scintillating Nanoparticles. *ACS Appl Mater Interfaces.* 2015; 7: 12261-12269.
51. Chen W, Zhang J. Using nanoparticles to enable simultaneous radiation and photodynamic therapies for cancer treatment. *J Nanosci Nanotechnol.* 2006; 6: 1159-1166.
52. Hu J, Tang Y, Elmenoufy AH, Xu H, Cheng Z, Yang X. Nanocomposite-Based Photodynamic Therapy Strategies for Deep Tumor Treatment. *Small.* 2015; 11: 5860-5887.
53. Elmenoufy AH, Tang Y, Hu J, Xu H, Yang X. A novel deep photodynamic therapy modality combined with CT imaging established via X-ray stimulated silica-modified lanthanide scintillating nanoparticles. *Chem Commun.* 2015; 51: 12247-12250.
54. Choi M, Choi J, Kim S, Nizamoglu S, Hahn SK, Yun SH. Light- guiding hydrogels for cell-based sensing and optogenetic synthesis *in vivo*. *Nat. Photonics.* 2013; 7: 987-994.
55. Kim TI, McCall JG, Jung YH, Huang X, Siuda ER, Li Y, et al. Injectable, Cellular-Scale Optoelectronics with Applications for Wireless Optogenetics. *Science.* 2013; 340: 211-216.
56. Bagley AF, Hill S, Rogers GS, Bhatia SN. Plasmonic Photothermal Heating of Intraperitoneal Tumors through the Use of an Implanted Near-Infrared Source. *ACS Nano.* 2013; 7: 8089-8097.
57. Widder EA. Bioluminescence in the ocean: origins of biological, chemical, and ecological diversity. *Science.* 2010; 328: 704- 708.
58. Herring PJ. Bioluminescence of marine organisms. *Nature.* 1977; 267: 788-793.
59. Li J, Chen L, Du L, Li M. Cage the firefly luciferin!—a strategy for developing bioluminescent probes. *Chem Soc Rev.* 2013; 42: 662-676.
60. Ando Y. Development of a quantitative bio/chemiluminescence spectrometer determining quantum yields: Reexamination of the aqueous luminol chemiluminescence standard. *Photochem Photobiol.* 2007; 83: 1205-1210.
61. El-Dakdouki MH, Xia J, Zhu DC, Kavunja H, Grieshaber J, O'Reilly S. Assessing the *in Vivo* Efficacy of Doxorubicin Loaded Hyaluronan Nanoparticles. *ACS Appl Mater Interfaces.* 2014; 6: 697-705.
62. Yuan H, Chong H, Wang B, Zhu C, Liu L, Yang Q. Chemical molecule-induced light-activated system for anticancer and antifungal activities. *J Am Chem Soc.* 2012; 134: 13184-13187.
63. Xiong L, Shuhendler AJ, Rao J. Self-luminescing BRET-FRET near-infrared dots for *in vivo* lymph-node mapping and tumour imaging. *Nat Commun.* 2012; 3: 1193.
64. Hsu CY, Chen CW, Yu HP, Lin YF, Lai PS. Bioluminescence resonance energy transfer using luciferase-immobilized quantum dots for self-illuminated photodynamic therapy. *Biomaterials.* 2013; 34: 1204-1212.
65. Kim YR, Kim S, Choi JW, Choi SY, Lee SH, Kim H, et al. Bioluminescence-Activated Deep- Tissue Photodynamic Therapy of Cancer. *Theranostics.* 2015; 5: 805- 817.