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Indocyanine Green-Loaded Nanocarriers as Contrast Agents for NIR Fluorescent Optical Imaging

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Optical imaging approaches offer the potential for non-invasive diagnosis and real-time, high-resolution, *in vivo* disease monitoring. Usually using UV to near-infrared (NIR) light, optical imaging uses wavelength-dependent interactions (scattering, absorption and fluorescence) in tissues to yield unique contrasts. 650-900 nm wavelength NIR optical fluorescence imaging has become a particularly attractive technology for disease diagnosis, treatment monitoring, and drug screening due to its low absorption, and significant autofluorescence imaging depth *in vivo* [1-3]. However, the lack of significant endogenous fluorescence contrast limits the diagnosis ability of this technology. Therefore to increase the signal-to-noise ratio and improve imaging resolution, the development of exogenous NIR optical contrast agents is a necessity [4-6].

Currently the only NIR fluorescent contrast agent approved by the United States Food and Drug Administration (FDA) for direct administration in medical diagnostics is Indocyanine Green (ICG) [7,8]. ICG is a water-soluble, amphiphilic tricarbocyanine dye with the adsorption and emission maxima around 780 and 810 nm, respectively [9]. Due to its low toxicity (LD_{50} of 50-80 mg/kg for animal subjects) [10] and capacity to absorb and emit in the NIR spectral range, ICG is used clinically as a contrast agent for visualizing blood and clearance, studying liver function, and guiding biopsies [11-13]. Despite its many advantages, ICG is still limited by several drawbacks: i) it aggregates easily into amphiphilic molecules in aqueous solutions to induce self quenching and low quantum yields [14]; ii) when administered in molecular form, ICG is rapidly cleared from the body with a short half-life about 2-4 min [15-17]; iii) it often binds to proteins leading to rapid agglomeration [11]; iv) it undergoes oxidation and dimerization, resulting in decreased absorption/emission and variability in the maximum absorption wavelength [18,19]; v) it is instable in aqueous solutions and prone to photobleaching under light exposure [16,20]; vi) ICG lacks target moieties for molecular imaging. To address these intrinsic drawbacks of ICG for *in vivo* imaging, a potential approach is to encapsulate ICG into nanocarriers that provide increased stability, protection from nonspecific plasma protein binding, prolonged circulation times and potential targeting. This editorial will focus on some of recent advances in the design of NIR contrast agents based on nanovector encapsulation of ICG.

There are many of reports that ICG encapsulators, such as (poly (lactic-coglycolic acid)(PLGA) nanoparticles (diameter ~360 nm) and silica-polymer composite microcapsules (diameter ~0.6 to 2 μm) improve the molecular instability of ICG and prolong its plasma half-life [21,22]. 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. [23] developed ICG encapsulated PLGA-lipid nanoparticles conjugated with folic acid (FA) and demonsstrated their use as NIR contrast agents for tumor diagnosis and targeted imaging [23]. Altinoglu et al. also synthesized biodegradable calcium phosphosilicate nanoparticles (CPNPs) and demonstrated that small size (16 nm) ICG-encapsulating CPNPs have significantly better contrast agent optical properties than free fluorophores for tumor imaging [24]. Other inorganic delivery systems using silica nanoparticles have been developed to encapsulate ICG, and the ICG–SiO_2 nanoparticles have the potential to be used as contrast agents for optical NIR imaging as well [25].

Among these nanocarriers, micelles are one of the successful types of drug delivery systems for *in vivo* applications due to their small size (approximately 10-100 nm), which reduce clearance by the reticuloendothelial system (RES) and allow for an enhanced EPR effect [26,27]. 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 [28,29]. 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 [30]. More interestingly, Zheng et al. [23] have recently reported a dual-functional ICG-PL-PEG agent with several unique features for optical imaging and photo-therapy [31]. 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.

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