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High-Performance Red/Near-IR Carbon Dots as Fluorescence Probes for Tumor Imaging *In Vivo*

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Carbon dots (CDots) are brightly fluorescent, especially in the same green spectral region overlapping that of the green fluorescent protein, and also benign and nontoxic. For imaging *in vivo,* however, red/near-IR probes are required for the high optical transmittance through tissues and the contrast against interference from autofluorescence background. Herein, high-performance red/near-IR CDots are designed and prepared by modifying the core carbon nanoparticles in CDots with the incorporation of selected dye species into the nanoparticle structure. The representative modified CDots thus obtained are used as fluorescence probes in the *in vivo* imaging of normal and tumor-bearing nude mice via various exposure pathways. The results suggest that these red/near-IR CDots are indeed excellent probes for fluorescence imaging *in vivo,* especially with their enhanced tumor uptake. The potentially far-reaching implications of being able to design and synthesize the modified CDots of strong optical absorptions and bright fluorescence emissions in the red/near-IR are discussed in terms of their broad applicability to *in vivo* imaging and theranostics.

Introduction

Optical bioimaging with fluorescent nanomaterials as imaging agents has attracted much interest in research fields including both nanomaterials development and *in vitro* and *in vivo* imaging applications. Among the widely pursued have been semiconductor quantum dots (QDs), such as CdSe/ZnS nanoparticles as a more popular representative, for their high optical performance and other advantageous properties over those of conventional organic dyes.[1–3] Because of the heavy metal content in most of the high-performance semiconductor QDs and the associated toxicity concerns,[4,5] there have been many studies on the development of other fluorescent nanomaterials as alternatives to the semiconductor QDs, including carbon "quantum" dots or carbon dots (CDots).[6,7]

CDots are generally defined as small carbon nanoparticles with various surface passivation schemes (Figure 1).[6–9] Ever since their original finding,[6] CDots have attracted much attention for their interesting optical properties including especially the bright and colorful fluorescence emissions, and their other unique and/or advantageous characteristics.[8–15] The optical absorptions of CDots are dictated by the electronic transitions of the core carbon nanoparticles in the dots. The emission mechanism is such that following photoexcitation there is rapid charge separation, and the electrons and holes thus formed are trapped at various defect sites of the carbon nanoparticles, which are stabilized by the particle surface passivation. The radiative recombinations of the electrons and holes are responsible for the observed fluorescence emissions.[8,13] The fluorescence and photoinduced redox properties of CDots have been widely exploited for technological applications,[8–15] such as in bioimaging, optoelectronic devices, optical coding for anti-fake uses, and photocatalysis and energy comversions.[16–20] In fact, CDots now represent a rapidly advancing and expanding research field, as reflected by the large and ever increasing number of recent publications in the literature.

As bioimaging probes, CDots are known to be biocompatible without any significant toxicity *in vitro* and *in vivo*.[10,14,21–23]

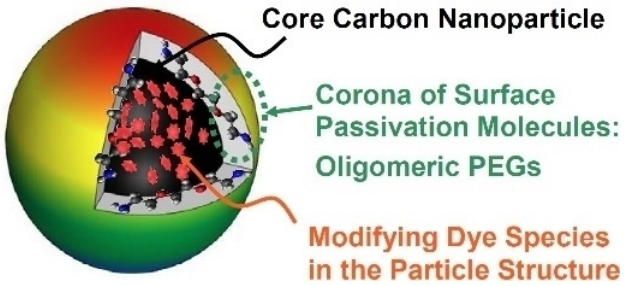

Figure 1. A cartoon illustration on the general configuration of a CDot and the modification of core carbon nanoparticle structure by red/near-IR absorptive and emissive species.

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Their optical performance is also high, with observed fluorescence quantum yields approaching unity in the spectral region overlapping that of green fluorescent protein (GFP).[24,25] The combination of high performance and non-/low-toxicity has stimulated broad interests in using CDots for cell and *in vivo* imaging applications.[22,23,26–31] For example, Yang, *et al.* demonstrated in the *in vivo* imaging experiments that bright green fluorescence of CDots could be observed in mice post-injection in different routes.[23] In a direct comparison with the established CdSe/ZnS QDs for *in vivo* imaging, Cao, *et al.* concluded that the CDots were performance-wise competitive, especially in the green spectral region.[26] More recently, Ding, *et al.* prepared CDots of brighter red emissions for the observation of fluorescence from the back of a mouse following subcutaneous injection.[30] Li, *et al.* used CDots emissive around 680 nm for the imaging of tumor in mice following the intratumoral injection.[31] These and other studies represent the general pursuit of CDots with stronger optical absorptions and brighter fluorescence emissions in the red/near-IR spectral region to take full advantage of the nontoxic nature of CDots for bioimaging *in vivo*. However, since the electronic transitions are dictated by the core carbon nanoparticles in CDots, the targeted substantial performance enhancements in the red/near-IR would require modifications of the carbon nanoparticles beyond the particle surface passivation. As reported recently,[32,33] the core carbon nanoparticles could be modified by red/near-IR organic dyes in the synthesis of the dots via thermal carbonization processing, yielding modified CDots of the desired strong absorptions and emissions in the longer wavelength spectral region, thus particularly useful to *in vivo* imaging applications.

In the work reported here, we used CDots with the core carbon nanoparticles modified by cresyl violet (CV) in the dot synthesis (denoted as CV@CDots with "@" signifying the modification, **Figure 1**) as high-performance red/near-IR fluorescence probes for the imaging in normal and tumor-bearing nude mice. Injections for different exposure pathways were evaluated, and an enhanced tumor uptake of the probes was observed. The results have validated the concept and practice on the highly versatile and effective platform of CDots with a dye-modified or incorporated carbon nanoparticle core to serve as red/near-IR fluorescence probes, which are high performance in terms of strong optical absorptions and bright fluorescence emissions yet benign and nontoxic, particularly valuable to *in vivo* imaging and theranostics in general.

Results and Discussion

CDots in which the core carbon nanoparticles are modified by the fluorescent dye CV in the dot synthesis was prepared by microwave-assisted thermal carbonization processing of a precursor mixture containing oligomeric polyethylene glycol (PEG, molecular weight ~1,000) and CV.[32] The PEG molecules in large excess were designed to be the carbon source for the core carbon nanoparticles, modified by CV-derived species, and those PEG moieties only partially carbonized in the processing would become surface passivation agents in the final CDots, denoted as PEG-CV@CDots (**Figure 1**). In the processing with microwave irradiation, the degree of carbonization was assessed and controlled by monitoring the relative absorbances at 400 nm and 520 nm, which are predominantly contributed by the intrinsic absorption of the nanoscale carbon and the modifying CV species, respectively.[32] Post-processing, the reaction mixture was cleaned and separated on an aqueous Sephadex G-100 gel column.[34] Results from the transmission electron microscopy (TEM) characterization suggest an average dot size of about 5 nm in diameter, with a size distribution standard deviation of about 1.5 nm (**Figure 2**).

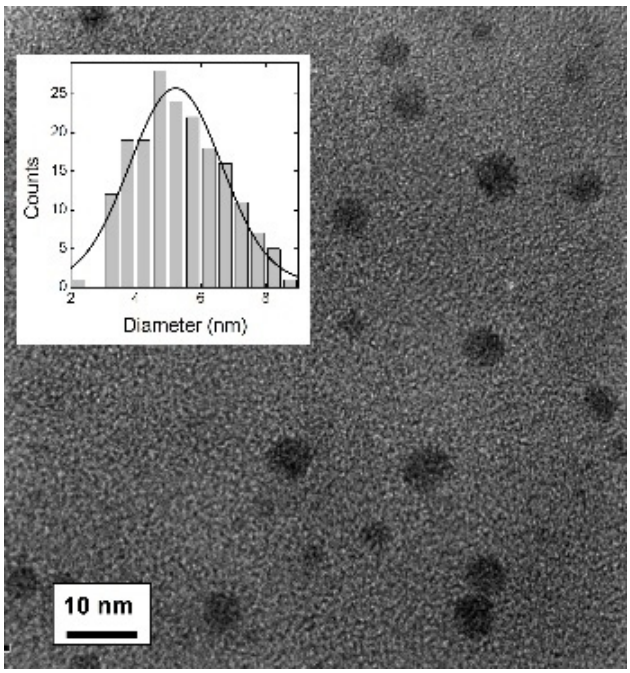

Figure 2. Representative TEM images of the PEG-CV@CDots. Inset: A statistical size analysis based on multiple image sets.

The optical absorption spectrum of the PEG-CV@CDots is compared with that of the PEG-CDots (the corresponding neat CDots without the CV modification) in **Figure 3**. The former is obviously much more absorptive in the longer wavelength spectral region, into which the excitation (at 550 nm, for example) resulted in bright red/near-IR fluorescence emissions (Figure 3), with an observed quantum yield of 33% in reference to the known fluorescence quantum yields of rhodamine 6G (95% in ethanol)[35,36] and an estimated average fluorescence lifetime of about 5 ns. The PEG-CV@CDots of much enhanced absorption and fluorescence emissions in the red/near-IR are ideally suited as probes for fluorescence imaging *in vivo*.

Normal nude mice were used for the imaging evaluation *in vivo* after subcutaneous injection. Upon the anesthesia by isoflurane, each nude mouse was subcutaneously injected with the PEG-CV@CDots (20 μL of a 38 μM solution) and placed in the imaging facility equipped with a subject table at 37 °C. As shown in **Figure 4**, there was bright red fluorescence on the

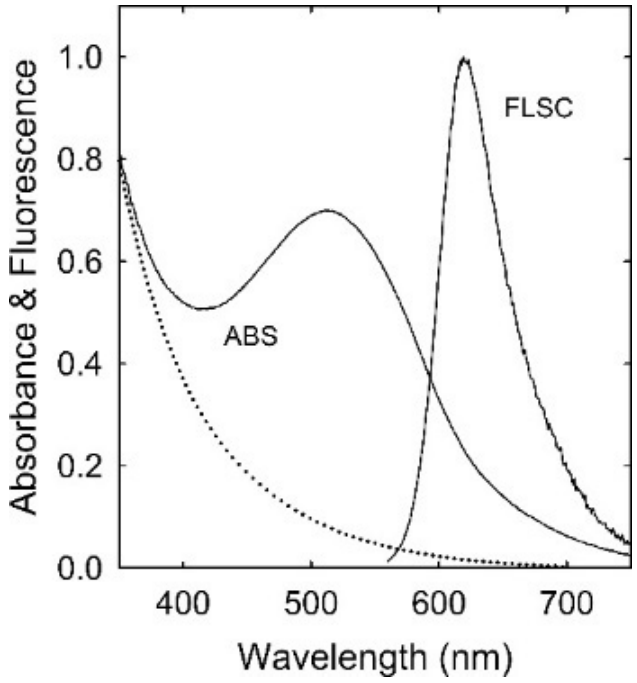

Figure 3. Absorption (ABS) and fluorescence (FLSC, 550 nm excitation) spectra of the PEG-CV@CDots in aqueous solution, with ABS of the PEG-CDots (doted line) shown for comparison.

back of the nude mouse. The efficient spectral un-mixing could distinguish the signal of the PEG-CV@CDots from that of autofluorescence (tinted as green, **Figure 4**). Based on the color-coded image (the radiant efficiency range 1.2×10^{8} - 1.2×10^{9}), the contrast between the PEG-CV@CDots and the background was high, suggesting that the PEG-CV@CDots could indeed serve as excellent probes for fluorescence imaging *in vivo*. The probe diffusion was very slow, and the fluorescence fainted after 24 h. As shown in Figure 4(f), the injection area (indicated by the red arrow) exhibited no meaningful fluorescence signals (the radiant efficiency range 1.2×10^{7} - 1.2×10^{8}).

Intratumor injection as a widely adopted injection method in assessing the imaging and therapy effect of nanomaterials was applied to the evaluation of the PEG-CV@CDots as fluorescence probes. Nude mice bearing tumor (papillary thyroid carcinoma cell line TPC-1) were used for intratumor injection and the imaging evaluation *in vivo*. Upon the anesthesia, each nude mouse was intratumorally injected with the PEG-CV@CDots (20 μL of a 38 μM solution). Strong red fluorescence emissions were observed from the tumor site immediately after the injection (**Figure 5**). The probe did not diffuse to the nearby tissue significantly, and the red emissions were associated with the tumor only. The signal decayed slowly over time, with the emission intensity at the tumor site decreased to about one-third of the initial intensity after 9 h (**Figure 5**). However, no meaningful signal was found in other tissues around the tumor, which could be due to the probe diffusion being too slow to reach sufficient accumulation in the surrounding tissues. At 48 h post-injection, the signal intensity at the tumor site became similar to the background intensities of hind leg and cheek, but still higher than those in the nearby area (**Figure 5**).

The nude mice bearing tumor were also intravenously injected with the PEG-CV@CDots (200 μL of a 38 μM solution) for *in vivo* imaging. After circulation for 30 min, there were red fluorescence emissions from the probes in the abdomen area.

The most intense signal was from the bladder (**Figure 6**), similar to what was found in the previous study on *in vivo* imaging of CDots without the dye modification.[23] The obvious bladder accumulation of the dots must be due to their small sizes, as generally known in the literature that small particles on the order of 5 nm or less in diameter would be excreted primarily through the renal pathway.[23]

Beyond the bladder, there was also significant signal from the small intestine (**Figure 6**), suggesting that the PEG-CV@CDots could enter the gastrointestinal tract. Typically, molecules of suitable hydrophobicity would be excreted into bile and enter the gastrointestinal tract. The surface of the PEG-CV@CDots is covered by PEG species, which could facilitate the excretion through both urine and bile. Similar phenomenon was observed with the PEG-coated Ag_2Se quantum dots, where meaningful Ag and Se elements were detected in both urine and feces.[37] In the previous *in vivo* imaging study of the similarly PEG-functionalized CDots without the dye modification,[23] which were strongly fluorescent only in the green (around 500–520 nm), there was no clear signal from the gastrointestinal tract probably because it was masked due to the strong optical absorption by tissue in the green spectral region. Here, the red/near-IR emissive PEG-CV@CDots as probes could apparently enable optical penetration through tissues for the detection of fluorescence signals from the gastrointestinal tract (**Figure 6**).

Of particular interest was the observation of significantly stronger signals from the tumor (**Figure 6**). The tumor tissue was much more fluorescent than the nearby skin tissue, even though the total fluorescence intensity of tumor was still lower than that of bladder. As one might expect, the abundant blood vessels in tumor would facilitate the accumulation of the fluorescence probe, thus the significant imaging contrast over the surrounding tissue. With respect to possible effect of the enhanced permeability and retention (EPR).[38] However, the probe PEG-CV@CDots is probably too small in size for the EPR to be significant. Thus, the conjugation of the probe with targeting moieties might be necessary for even higher tumor uptake in theranostics applications. The relatively significant fluorescence signals from the ear, paws, and the tail (**Figure 6**) could be attributed to the thinner skin in those areas.

At 6 h after the intravenous injection, the mice were sacrificed to collect the organs for *ex vivo* imaging (**Figure 7**). The strongest fluorescence was found in the gallbladder (total radiant efficiency of 6.4×10^{9}) and small intestine (total radiant efficiency of 3.0×10^{10}), while weaker signals in liver (total radiant efficiency of 2.0×10^{9}), stomach (total radiant efficiency of 3.2×10^{9}), and large intestine (total radiant efficiency of 1.2×10^{9}). The bright gallbladder indicated that the probe PEG-CV@CDots could be secreted into bile, consequently into the

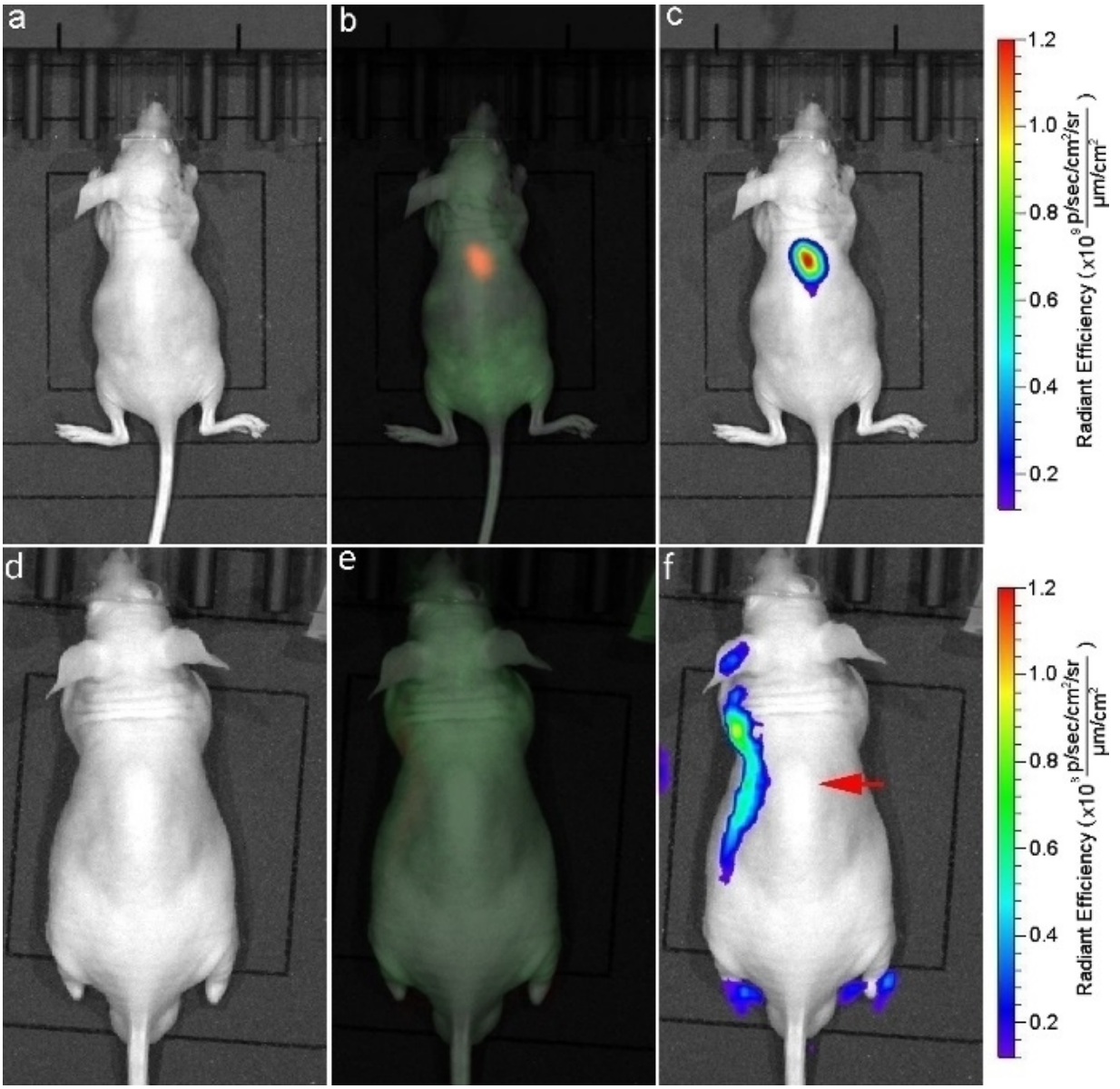

Figure 4. Images with subcutaneous injection of the PEG-CV@CDots at 10 min post injection: (a) bright field; (b) fluorescence (excitation/emission pair 520 nm/620 nm); (c) color-coded image; and at 24 h post injection: (d) bright field; (e) fluorescence; (f) color-coded image (the injection area indicated by the arrow).

small intestine, and then eliminated as feces. The bladder was nearly non-fluorescent after the urine was excreted, suggesting that the probe existed in the urine rather than the bladder tissue. Similarly, when the gastrointestinal tract was cut to separate the inside contents, the majority of fluorescence was found in the inside contents (**Figure 8**). The fluorescence in dissected tumor was weak, because after 6 h excretion, the PEG-CV@CDots were largely cleared from body and found in the excreta. The fast and nearly complete excretion of the dots may imply a lack of long-term toxicity. As related, there was also no visible abnormal behavior by the mice throughout the imaging experiments.

The results presented and discussed above clearly demonstrate that the PEG-CV@CDots are excellent fluorescence probes for bioimaging *in vivo,* with the strong absorption and bright emissions in the red/near-IR enhancing optical transmission through tissues and overcoming background fluorescence interference. Mechanistically on the probes, fluorescence emissions in CDots are widely considered as being due to radiative recombinations of electrons and holes that are generated by ultrafast charge separation in the core carbon nanoparticles following the photoexcitation and stabilized by the surface passivation schemes.[8,13] There are apparently significant effects in several respects associated with the incorporation of dye molecules such as CV into the carbon nanoparticles, with their relationships likely being much beyond a simple guest and host arrangement. Even strictly on the basis of such an arrangement, the dye species in the carbon

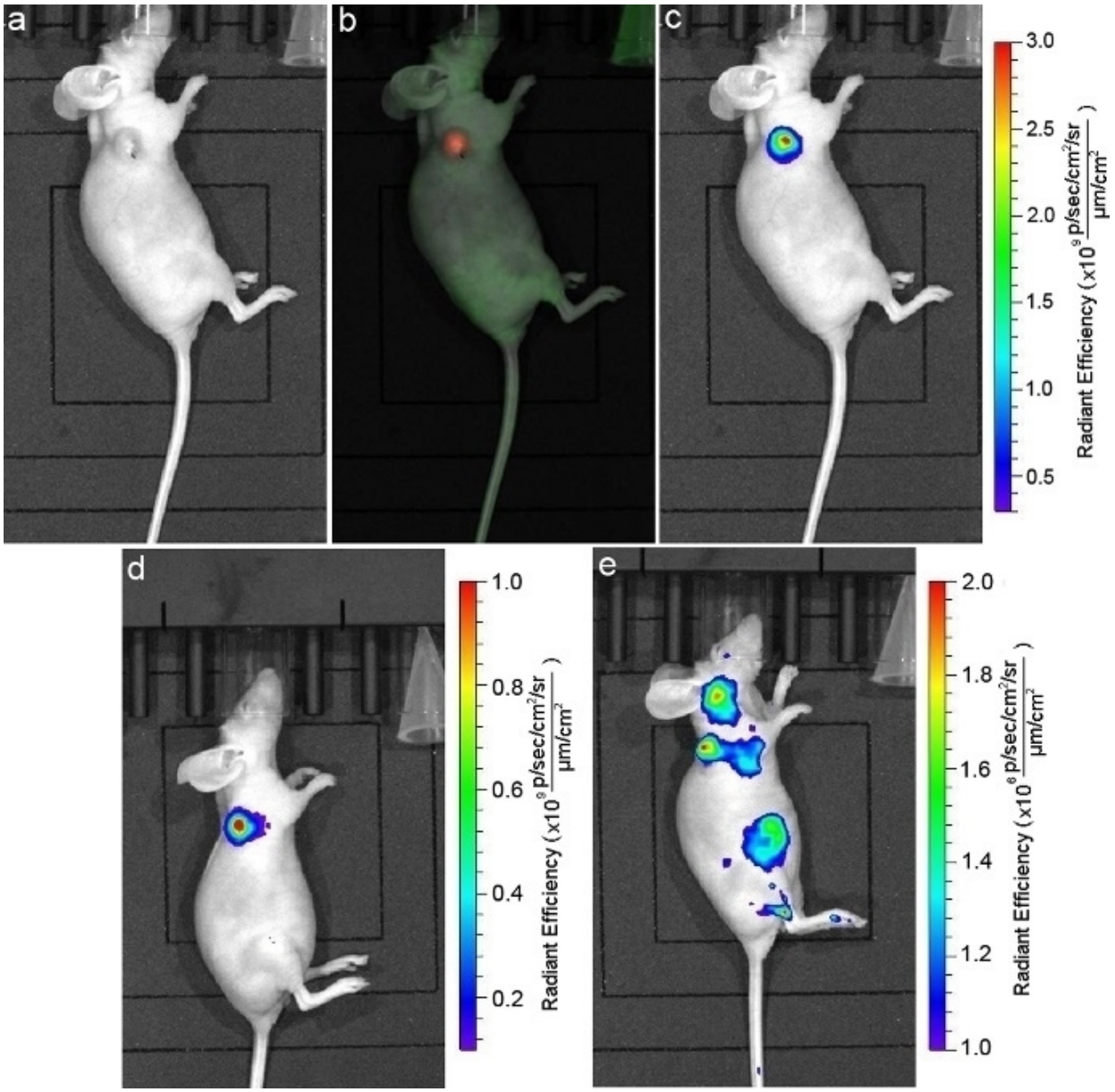

Figure 5. Images with intratumor injection of the PEG-CV@CDots. At 10 min post-injection: (a) bright field; (b) fluorescence; and (c) color-coded. (d) and (e) are color-coded images at 9 h and 48 h post-injection, respectively.

nanoparticle structure would benefit from the confined and more hydrophobic environment to result in brighter fluorescence emissions. Beyond that, there has been substantial experimental evidence suggesting likely a sharing of the excited state energies or potentially an integration of the electronic structures between the carbon nanoparticles and the incorporated dye species. For example, when the PEG-CV@CDots were excited into the blue/green spectral region for the population of primarily the excited states of the carbon nanoparticles (**Figure 3**), the corresponding green fluorescence emissions were not quenched by the incorporated dye species as one would expect, namely that there were no meaningful excited state energy transfers to the dye species. In contrast, for the dye-CDot combination in a different configuration with the dye species tethered to the dot surface, there are generally substantial fluorescence resonance energy transfers (FRET), as known in the literature.[27,28] The potential integration of electronic structures in the dye-modified CDots, the PEG-CV@CDots and the like, will have far-reaching implications beyond their serving as high-performance bioimaging probes, deserving further investigations.

Dye-modified CDots of the kind used in this study apparently retain the nontoxic nature of neat CDots without the modification, exhibiting no meaningful toxicity to cells.[33] Results from this study suggest that they are likely also nontoxic *in vivo,* which may be further confirmed in a

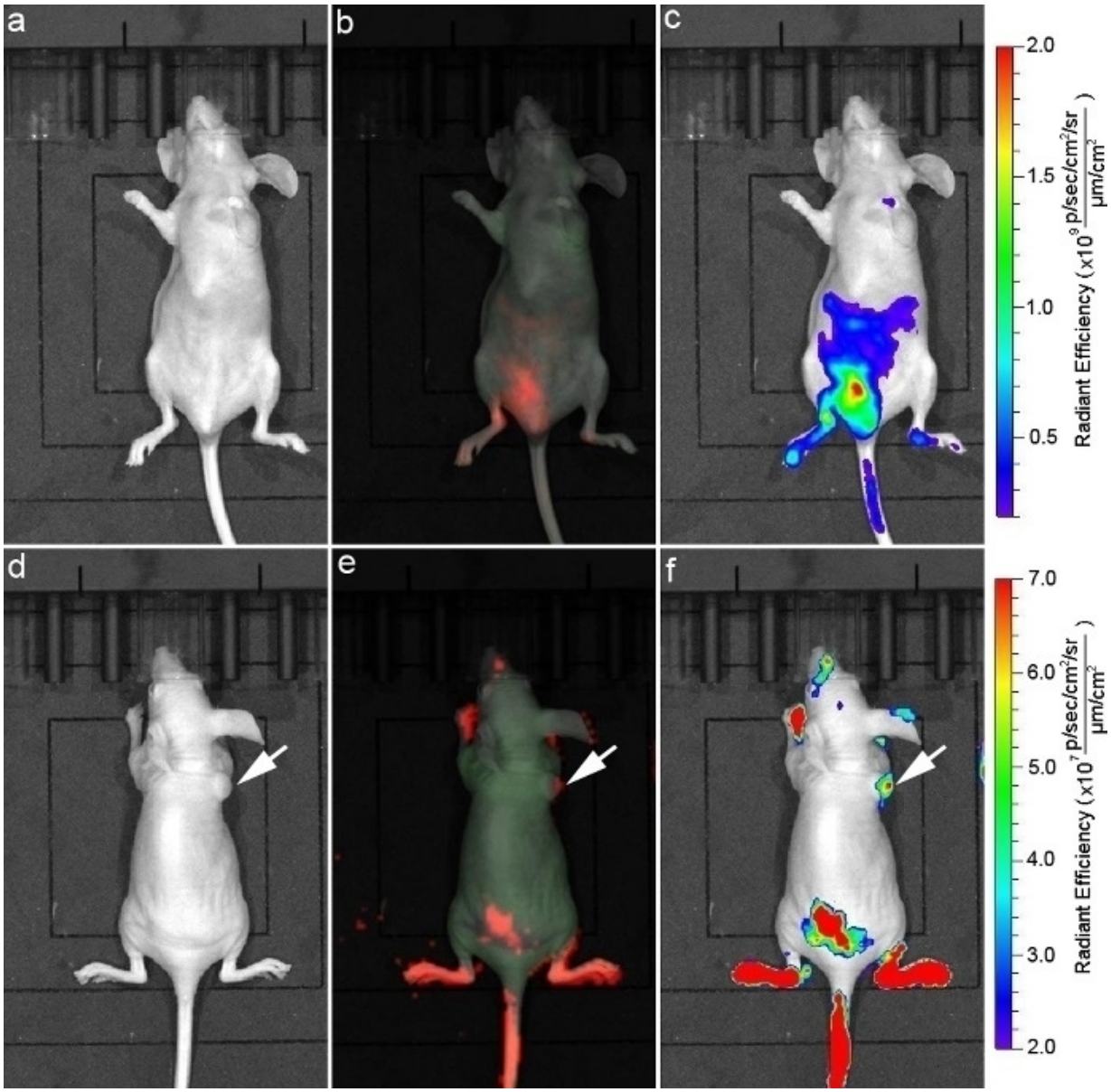

Figure 6. Images with intravenous injection of the PEG-CV@CDots at 30 min post-injection. Face up: (a) bright field; (b) fluorescence; and (c) color-coded. Face down: (d) bright field; (e) fluorescence; and (f) color-coded. The tumor was indicated by the white arrows.

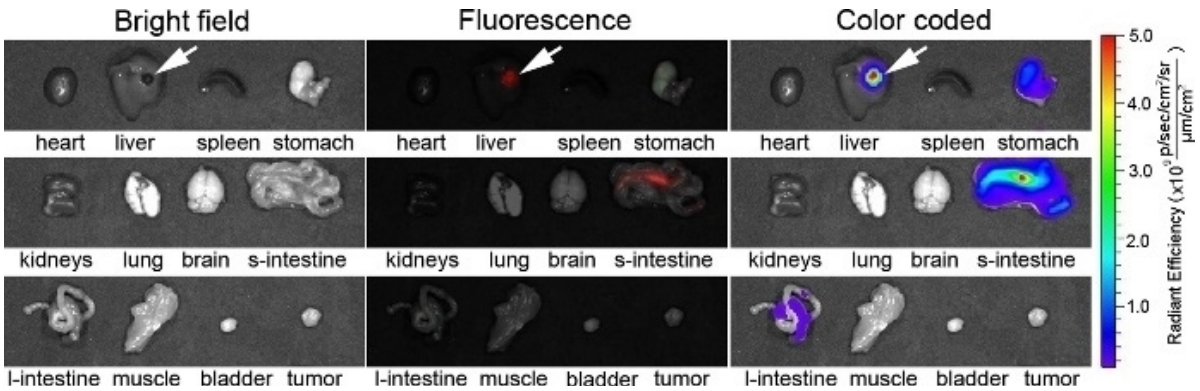

Figure 7. Dissected organs of the mouse intravenously injected with the PEG-CV@CDots. The gallbladder was indicated by the white arrows.

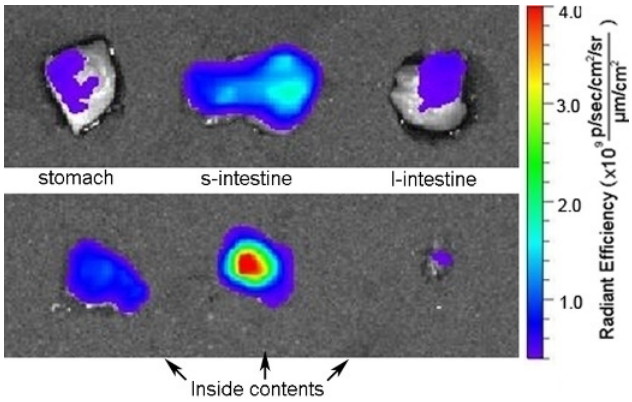

Figure 8. Color-coded images of gastrointestinal tract tissues (upper) and their inside contents (lower).

dedicated investigation on more systematic evaluations of *in vivo* toxicity and biodistribution, as planned. Also interesting and valuable will be the conjugation with specific targeting species by taking advantage of the surface functional groups on the dot surface for fluorescence probes of much enhanced *in vivo* imaging capabilities.

Conclusions

The modification of core carbon nanoparticles in CDots via the incorporation of selected dye species into the nanoparticle structure represents a highly versatile and effective approach in the design and preparation of high-performance red/near-IR CDots while preserving their benign and nontoxic characteristics. As a representative in such a new dot platform, the PEG-CV@CDots were evaluated in the *in vivo* imaging of normal and tumor-bearing nude mice following their exposure to the dots via different injection routes. The results suggest that these red/near-IR CDots are indeed excellent fluorescence probes for bioimaging *in vivo,* including also their apparently enhanced tumor uptake. With their further development and validation, broad applications of these high-performance and nontoxic probes in bioimaging and theranostics in general may be envisaged.

Supporting Information Summary

The supporting information includes the experimental procedures.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: carbon · fluorescence · imaging agents · tumor · red/near-IR emission

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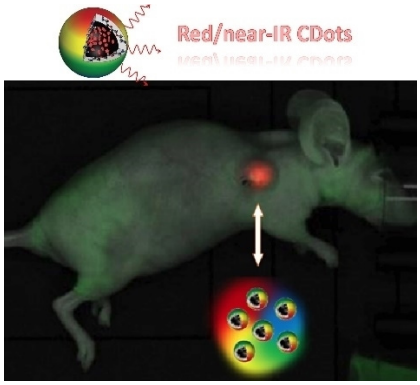

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High-Performance Red/Near-IR Carbon Dots as Fluorescence Probes for Tumor Imaging *In Vivo*