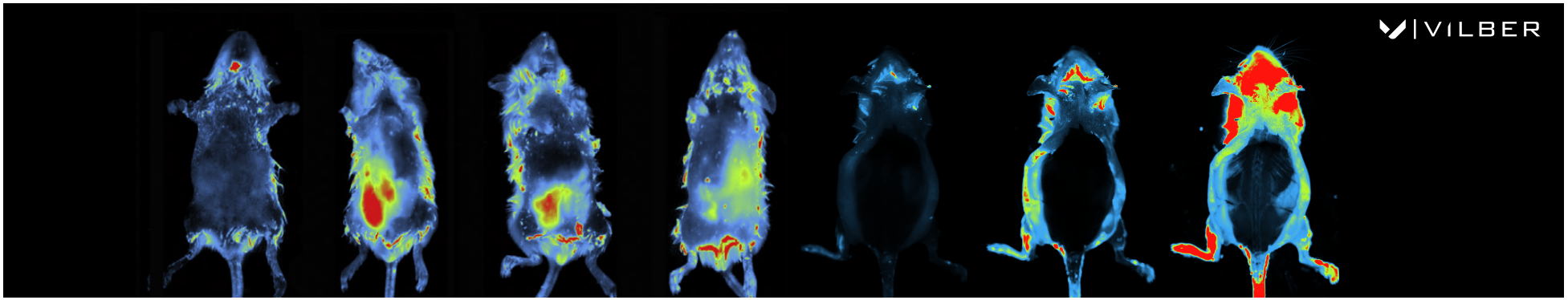

STIMULI RESPONSIVE PEGYLATED BISMUTH SELENIDE HOLLOW NANOCAPSULES FOR FLUORESCENCE/CT IMAGING AND LIGHT-DRIVEN MULTIMODAL TUMOR THERAPY

AUTHORS

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INTRODUCTION

Nanoparticles (NPs) have emerged as attractive drug carriers for intracellular delivery in the field of nanomedicine. To achieve an optimum antitumor efficacy, NPs have been developed to enhance the intracellular delivery of therapeutic molecules. As an example, bismuth chalcogenides nanomaterials, bismuth selenide (Bi_2Se_3) NPs possess high photoelectric absorption coefficient of Bi and an antitumor activity of Se element. However, solid Bi_2Se_3 NPs present a considerable low drug loading efficiency due to their limited surface area. Alternatively, researchers reported a highly porous Bi_2Se_3 sponge with expanded surface area for encapsulating chemotherapeutic drugs to achieve synergistic thermo-chemotherapy. Moreover, to be effective, Bi_2Se_3 NPs has to be coupled with other functional modalities for cancer theranostics such as Chlorin e6 (Ce6). Ce6 is a photodynamic therapy (PDT) agent with near infrared (NIR) fluorescence emission. Since free Ce6 molecules are incapable of effective tumor targeting, resulting in a rapid degradation and blood clearance during long-term circulation, it can be coupled with Bi_2Se_3. This combination gives way to photodynamic therapy (PDT) which is a noninvasive therapeutic strategy for adjuvant treatment of cancer or other diseases.

OBJECTIVE

In this study, we developed a multifunctional nanoagent platform on the basis of hollow mesoporous Bi_2Se_3 nanocapsules (NCs) for fluorescence/CT bimodal imaging and chem/photothermal/photodynamic combination therapy of cancer.

The integration of Ce6 and PEG endows Bi_2Se_3 NCs with unique advantages for achieving an improved performance both in tumor diagnosis and therapy, as well as long term stability in blood circulation, which are regarded as substantial progress on the basis of primary studies.

MATERIAL & METHODS

Female BALB/c mice (4-6 weeks of age, 22~25 g each) were subcutaneously inoculated with 4T1 cells (1×10^6 in saline) on dorsal side. Then, all the mice were raised and housed in an animal house for ~10 days till the tumor volume reached 150~200 mm^3.

Preparation of hollow mesoporous Bi2Se3@PEG NCs.

A multifunctional nanocomplex (Bi2Se3@PEG/DOX/Ce6 nanocapsules, or BPDC NCs in brief) has been developped that was constructed by loading chlorin e6 (Ce6) and doxorubicin (DOX) into PEGylated hollow bismuth sulfide nanocapsules. After the surface modification with PEG, antitumor drug of DOX and photosensitizer Ce6 were loaded into hollow Bi_2Se_3 NCs via hydrophobic action and electrostatic adsorption.

Fluorescence imaging.

For fluorescence imaging *in vivo*, BALB/c mice bearing 4T1 tumors were intravenously injected with BPDC NCs (equivalent DOX concentration : 4 mg·kg-1) or Ce6. At predesigned time points, infrared fluorescence images of mice were acquired using the fluorescence imaging system (Fusion FX7 Spectra, VILBER, France). The mice were sacrificed at 24h post-injection, and tumors as well as major organs were excised for *ex vivo* imaging.

RESULTS

Figure 1. Fluorescence images of BALB/c mice bearing 4T1 tumors before (BF) and after (FF) intravenous injection of BPDC NCs.

Infrared fluorescence images of mice, showing accumulation of BPDC NCs, were acquired using the Fusion FX7 Spectra, VILBER, France, at different time points. Major organs and tumors were excised at 24h post-injection and effective accumulation and enrichment of BPDC NCs was found in solid tumor region, as evidenced by the strong local fluorescence emission.

Figure 2. Fluorescence images of BALB/c mice bearing 4T1 tumors before (BF) and after (FF) intravenous injection of Ce6.

Infrared fluorescence images of mice, showing accumulation of Ce6, were acquired using the Fusion FX7 Spectra, VILBER, France, at different time points. Major organs and tumors were excised at 24h post-injection and effective accumulation and enrichment of Ce6 was found in the liver, as evidenced by the strong local fluorescence emission.

CONCLUSION

Nanoparticles (NPs) have emerged as attractive drug carriers for intracellular delivery in the field of nanomedicine. This study has successfully designed and synthesized a multifunctional theranostic agent (BPDC NCs) by loading DOX and Ce6 into PEG-SH decorated hollow mesoporous Bi_2Se_3 NCs, which can be specifically delivered into the tumorous tissue through the enhanced permeability and retention effect as evidenced by the fluorescence imaging system Fusion FX7 (Vilber Lourmat, France). As expected, BPDC NCs demonstrated a remarkable anti-tumor effect *in vivo*, resulted from not only the rapid tumor-specific accumulation but also the combined PTT/PDT/chemotherapy effect. The ex-vivo imaging of tumors and major organs further confirmed higher tumor uptake and retention of BPDC NCs because of their prolonged blood circulation compared to free Ce6 (Figure 1. & Figure 2.).

Figure 1.

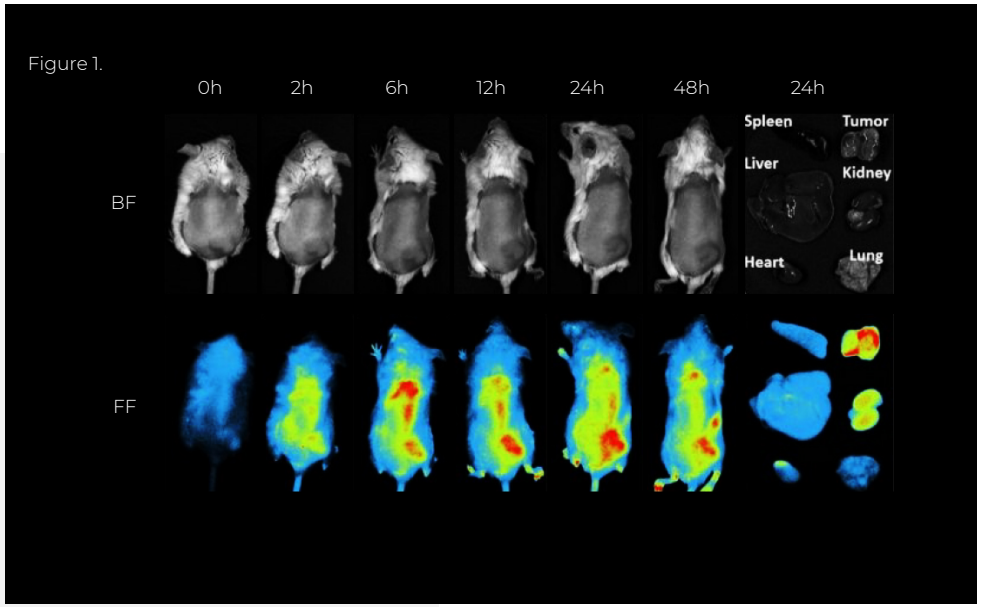

Figure 2.