Editorial

Light-Mediated Deep-Tissue Theranostics

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Abstract

This theme issue provides an overview on recent developments of light-mediated imaging and therapy approaches, with an emphasis on those that transcend the shallow tissue penetration dogma.

Key words: tissue penetration, theranostics, nanoparticles, photodynamic therapy, photothermal therapy

Light-mediated imaging and therapy has been widely investigated in pre-clinical studies, especially for cancer related applications. However, the clinical utility of the techniques has been rather limited. While the causes may be multifold, a common impediment is the shallow penetration of light. When light hits body tissues, a majority of the photons are scattered or absorbed. This restricts the penetration of light to one centimeter or less, limiting the applications of light-mediated approaches to superficial positions. Due to this reason, many imaging and therapy procedures, while perfectly demonstrated in small animals, are regarded as of limited clinical relevance.

Recent advances in materials science, nanotechnology, engineering, and light delivery has led to breakthroughs that may transcend the limitation. For instance, scientists have developed novel optimal nanomaterials, which, unlike conventional fluorophores, emit in the second near-infrared window (1100-1400 nm), where tissue absorbance and scattering is at the minimum. Progress has also been made in developing energy-converting phototherapies that allow X-ray, Cherenkov radiation, ultrasound, or microwaves to indirectly activate a photodynamic therapy (PDT) or photothermal therapy (PTT) procedure, again with the objective of breaking the shallow penetration dogma. Moreover, new imaging methodologies, such as photoacoustic imaging (PAI), persistent luminescence imaging, chemiluminescence resonance energy transfer imaging, Cherenkov luminescence imaging, and X-ray-induced optical luminescence imaging, have been developed and investigated. Furthermore, there have also been efforts of bringing together advances from more than one front to achieve combination therapy or theranostics, often in the form of novel multiple nanoplatforms.

In this special issue, we invite experts worldwide to share with us cutting-edge developments in light-mediated imaging and therapy. These include techniques that are developed to improve the efficiency or accuracy of light-mediated therapy at a deep tissue position. For instance, Xie *et al.* demonstrated that with MC540-SrAl$_2$O$_4$:Eu@SiO$_2$ nanoparticles, PDT can be activated from beneath thick tissues with X-ray irradiation [1]. This methodology, referred to as X-ray induced photodynamic therapy (X-PDT), breaks the shallow tissue penetration dogma of conventional PDT and may find wide applications in modern oncology. The authors also showed that X-PDT is more than just a PDT derivative but rather a PDT and RT combination, which explains the excellent treatment efficacy observed with the new modality. Kohane *et al.* developed a theranostic nanoplatform consisting of a gold nanostar (AuNS) core, and a shell of

coordination polymer (CP) tethered with gadolinium and gemcitabine monophosphate [2]. These AuNS@CP nanoparticles afforded high T_1 contrast, strong two-photon photoluminescence (TPL), good gemcitabine loading capacity, and excellent photothermal effect. Impressively, their migration *in vivo* not only can be monitored by MRI, but also by intravital TPL at the microscopic level, allowing for precise photothermal- and chemo- combination therapy. Mohs *et al.* synthesized a panel of hyaluronic acid (HA) based nanoparticles that were either physically entrapped with indocyanine green (ICG) or covalently conjugated with Cy7.5 [3]. These formulations were evaluated as intraoperative optical imaging agents for accurate tumor removal.

We also want to highlight several studies that attempt to develop smart nanoplatforms responsible for light-based cues. For instance, Lovell *et al.* reported a novel porphyrin–phospholipid (PoP) liposome that can encapsulate anti-cancer agents and release them under near-infrared (NIR) irradiation in a controlled manner [4]. The authors were able to monitor the drug release *in vivo* by intravital microscopy (IVM) and they confirmed the great treatment efficacy of the approach in MIA Paca-2 tumor bearing mice. Zheng *et al.* prepared a smart DOX/IR-780-co-loaded temperature-sensitive-liposome (DITSL), in which IR-780 was incorporated into the temperature-sensitive lipid bilayer and doxorubicin (DOX) into the hydrophilic core [5]. Under 808 nm irradiation, DITSL showed controlled drug release, enabling combination photothermal- and chemo-therapy against cancer. Cui *et al.* introduced a mitochondria-targeting drug delivery system, ZnPc/CPT-TPPNPs [6]. These nanoparticles can preferentially accumulate in mitochondrion of a cell and, under photo-irradiation, produce reactive oxygen species (ROS) to damage the organelle. Meanwhile, the yielded ROS also facilitated the release of camptothecin, which is a topoisomerase I inhibitor targeting nucleus DNA. Jon *et al.* reported a new nanomedicine designated as SP³NPs, which can simultaneously mediate PDT and PTT [7]. *In vivo* experiments showed that SP³NPs can preferentially accumulate in tumors after systemic injection, mediating imaging-guided combination PDT/PTT for efficient tumor eradication.

The special issue also includes several timely review articles. For instance, Hasan *et al.* overviewed recent advances and new strategies that aim at increasing the 'damage zone' of PDT beyond the reach of light in the body [8]. Richard *et al.* reviewed developments on nanoprobes with persistent luminescence properties [9]. Unlike conventional fluorophores, these persistent luminescence nanoprobes can emit photons at the absence of excitation light, linking to small background interference and deeper imaging depth. Han *et al.* reviewed recent progress on synthesizing calcium fluoride based upconversion nanoparticles and their use as novel nanoagents in cancer imaging and therapy [10]. Huang *et al.* summarized developments in PAI, which affords good contrast, high resolution, and deep tissue penetration [11]. Meanwhile, Chu *et al.* reviewed progress on developing genetically encoded probes for PAI, with an emphasis on BphP1-based tags [12]. Compared with molecule or nanoparticle based PAT probes, genetically encoded ones afford advantages including facile labeling of cells and protein targets and good *in vivo* stability. Wang wrote a nice overview on IVM, with a focus on its applications in nanomedicine developments [13]. IVM is an emerging imaging tool that can be used to study living subjects under physiological conditions at high spatial and temporal resolutions. Finally, Xing *et al.* summarized light-triggered theranostic strategies, including those based on Cerenkov radiation, and discussed current challenges and future perspectives [14].

In summary, light-mediated imaging and therapy has made tremendous progress in the past decade but the clinical translation of the approaches had been hampered by the relatively shallow penetration of light. With emerging nanomaterials, engineering techniques, and novel strategies that address the issue, it is expected that many of the light-mediated approaches will be brought forward and eventually make an impact in the clinic.

Competing Interests

The authors have declared that no competing interest exists.

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