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Cover Story

3D mesoscopic fluorescence tomography for photoimmunotherapy monitoring *in vivo*

Enhancing drug delivery to cancer is expected to significantly improve the effectiveness of therapy [1]. Targeted cancer therapies offer the promise of more effective tumor control with fewer side effects than conventional cancer therapies. An emerging cancer therapy with minimal side effect is photoimmunotherapy (PIT) based on a targeted monoclonal antibody (mAb)-photo absorber conjugate (APC), e.g., mAb conjugated with a near-infrared (NIR) phthalocyanine dye (IR700). Upon exposure to intense levels of NIR light, the conjugate becomes lethal, but only to those cells to which it is bound [2]. PIT induced highly selective cancer cell death, while leaving most of the tumor blood vessels unharmed, resulting in a significantly improved effectiveness of anticancer drugs [3]. The current macroscopic fluorescence reflectance imaging for monitoring fluorescence of APCs does not have the resolution and depth information on the 3D mAb-IR700 distribution *in situ* [3]. Real-time monitoring of 3D theranostic agent distribution within the tumor micro-environment will be critical for further understanding of the PIT mechanism and optimizing the effectiveness of treatment [4].

The paper by the team led by Professor Yu Chen and Dr. Hisataka Kobayashi in this issue applied a multi-modal optical imaging approach including high-resolution optical coherence tomography (OCT) and high-sensitivity fluorescence laminar optical tomography (FLOT), to provide 3D tumor micro-structure and micro-distribution of mAb-IR700 in the tumor simultaneously during PIT *in situ* and *in vivo* [4]. The multi-wavelength FLOT can also provide the blood vessels morphology of the tumor. Thus, the 3D FLOT reconstructed images allow us to evaluate the IR700 fluorescence distribution change with respect to the blood vessels and at different tumor locations/depths, thereby enabling evaluation of the therapeutic effects *in vivo* and optimization of treatment regimens accordingly. The proposed FLOT/OCT system enables evaluation of the 3D micro-distribution of mAb-IR700 at different depths with a minimally invasive manner by removing the skin over the tumor. Due to the low penetration depth, this new multi-modal imaging technology is applicable predominantly for applications in which tissues of interest are superficial, such as the exposed mouse brain, skin, and preclinical research at current stage. While, the two imaging modalities could be integrated into a functional endoscopy system in the future for more studies on different disease models and potentially clinical applications [4].

In this same issue, Sulheim et al. evaluate how tumor heterogeneity affects nanoparticle accumulation by applying different imaging modalities. The Sulheim team used micro-computed tomography, contrast-enhanced ultrasound, and diffusion-weighted and dynamic contrast-enhanced magnetic resonance imaging for *in vivo* tumor characterization as well as fluorescence microscopy and histology for *ex-vivo* tumor characterization [5]. They suggest that the number of vessels and vessel morphology and function can help to predict nanoparticle accumulation in the tumor.

The papers by the two teams are important, as their studies highlight that efficiency of targeted drug delivery to tumors depends on individuals, as each has a different number of vessels and vessel morphology heterogeneity. This basically means that there is no universal mechanism that any nanomedicine may enjoy over other drug delivery systems. This, in part, explains why nanomedicine formulations have not been effective in clinical trials. The imaging methods are applicable for other cancer treatment methods, such as monitoring the 3D distribution of theranostic agents *in vivo* in real time, although they may not be completely non-invasive. The work by the two groups is expected to contribute significantly to the understanding of the mechanisms of tumor-targeted drug delivery and theranosis. After three decades of research in nanomedicine, it is time to produce clinically useful formulations through mechanistic understanding of how drug delivery systems reach and distribute themselves around the target tumors.

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