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Editorial

Development of Nanoprobes for Non-Invasive Mapping of Sentinel Lymph Node

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It has been widely accepted, from clinical point of view, that the sentinel lymph node (SLN) plays an important role in draining metastatic cancer cells from primary tumor [1]. In the clinical cases of breast cancer and melanomas [2,3], identification (mapping) of SLN is now an indispensable procedure for subsequent SLN biopsy and choices of rational therapy protocols. Although traditional SLN tracers such as blue dyes and radioactive colloids are being used in clinic for SLN mapping, the patients indeed suffer from unfavorable side effects and complications. For example, isosulfan blue dye was found to induce an allergic reaction in patients [4]. Besides, radioactive agents could lead to tissue damage of patients and adversely influence the healthy of operator under long-term radiation exposure. Current clinical context suggests that an effective and safe probe for accurate SLN imaging is highly required in clinic.

An ideal SLN mapping probe principally should possess the following features: 1) adequate retention ability in SLN for subsequent mapping and harvest; 2) non-/low cytotoxicity and good biocompatibility to human body; 3) offering a high resolution for SLN visualization; 4) good photo-stability for repeated imaging; 5) particle size in the range from 10 to 50 nm in diameter. It was found that the size of SLN tracer has an effect on its retention in SLN [5]. For example, the radioactive colloids with the size of ~200 nm move slowly from injection site into SLN. As a result, after injection, the patients have to stay in hospital for a long time prior to SLN mapping. By contrast, the nanoparticles with the size of 10-50 nm can more rapidly travel and keep in SLN within a long period of time. Although small molecular probes such as blue dyes may also quickly move into SLN, they will shortly diffuse from lymphatic nodes to the surrounding tissues, affording poor SLN imaging as a result of enhanced background. Obviously, it is difficult to design small molecular probes which meet all these criteria for an ideal SLN mapping.

Nanotechnology offers an enormous opportunity to generate imaging probes [6]. To date, a few nanoscale nanoparticles have been designed and applied as nanoprobes for SLN mapping. Figure 1 illustrates typical nanoprobes which may be classified into two categories: inorganic and organic nanoprobes [7,8]. Inorganic nanoprobes encompass superparamagnetic iron oxide (SPIO) nanoparticles, quantum dots, gold nanocages silica nanopartilces, and single wall carbon nanotubes (SWNT). Organic nanoprobes comprise nanogels, nano-liposomes, nano-complexes, and nano-micelles. SPIO nanoparticles are one of the most widely used nanoprobes for clinical diagnosis by magnetic resonance (MR) technology. Although two SPIO nanoparticles (Resovist and Feridex) are approved by United States Food and Drug Administration (FDA) for MR imaging of liver, they are not ideal for SLN mapping owing to their large particle size (60 and 120 nm, respectively) [9]. Alternatively, other nanoprobes such as gold nanocages, quantum dots and silica nanopartilces may be readily prepared which have the sizes of 10-50 nm and applicable for SLN reorganization by near-infrared (NIR) fluorescence imaging or photo acoustic imaging (PAI) in a small animal (mouse or rat) [10] or large animal (pig) model [11]. Organic nanoparticles can also be fabricated with the sizes of 10-50 nm. However, they should be further modified with imaging agents. As such, organic nanoparticles for SLN mapping are documented largely focusing on the synthesis of new NIR dyes [12], NIR dye-labeled nanogels and nanomicelles [13].

A critical challenge of SLN nanoprobes for clinical use is the lack of systematic evaluation of bio-safety in animal and human body. For example, clinical translation of inorganic nanoprobes is seriously hampered by their compositions of highly toxic metal ions [14]. Although a lot of *in vitro* data indicate that inorganic SLN nanoprobes are less toxic, it is hard to ensure no leaky of these ions (e.g. Cd, Se) in the body for a long period of time. As to those SLN nanoparticles comprising inert metals (e.g. Au, Ta), their bio-safety in the body must be well established. The most encouraging news on SLN imaging tracer is official approval of technetium ^{99m}Tc Tilmanocept (trade name: Lymphoseek) by FDA in 2013. This agent consists of biocompatible dextran labeled with ^{99m}Tc which can assist doctor for lymph node metastasis detection. The current context indicates that organic nanoprobes based on biocompatible materials hold great promise for potential clinical translation.

Another barrier to SLN nanoprobes for clinical translations is the availability of an effective imaging system which allows physicians to visualize SLN in a convenient and harmless way. Some imaging systems have been developed which can be applied for clinical SLN diagnosis by NIR fluorescence imaging or PAI. NIR fluorescence imaging has several advantages such as high photon penetration, high signal-to-noise ratio, and rapid, safe imaging modality. In order to assist doctors to visualize invisible NIR fluorescence by naked eyes, Susan et al. developed a portable FLARE™ imaging system to "observe" NIR fluorescence images in animal and human surgery [15]. This system comprise a cart, an articulating arm, two independent fluorescence channels, two monitors, an imaging head, a footswitch and a customized software. FLARE™ system is able to provide sensitive, real-time mapping of all lymph nodes in surgical field and accurate SLN identification. Moreover, equipped software can sign SLN and its lymphatic channel in green whereas

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other normal node in red. Clinical trial results showed that, for SLN mapping of 6 women patients of breast cancer, both FLARE™ and lymphoscintigraphy system detected the same amounts of SLNs. Further clinical trials with more cases are however needed. A main shortcoming of FLARE™ imaging system is that a white light instead of routine light must be provided by the system to illuminate surgical field since routine light has strong NIR fluorescence background. Thus, FLARE™ system offers an opportunity for further clinical use of NIR-emitting nanoprobes.

Although NIR fluorescence offers deep penetration ability in living tissue with a low auto-fluorescence background, pure optical imaging system encounters a serious limitation on penetration ability in deeper tissues due to innate light scattering nature. PAI enables deeper imaging modality by detection of photoacoustic wave generated by absorbed diffuse light [16,17]. A few experimental data reveal that PAI depth is in the range of 0.7-30 mm depending on the ultrasonic frequency [18]. This penetration depth is more close to that of SLN in human body, which is normally detected at the depth of 41±19 mm [19]. Traditional PAI systems are equipped with a single-element ultrasound (US) transducer or one-dimensional (1D) array US probe. Besides, 3D PAI systems with 2D matrix array US probes have been developed recently [20-23]. Wang et al. illustrated a 3D imaging system to enable 3D PAI and US imaging without mechanical scanning [24]. In this work, the uptake of MB into the SLN was clearly observed by the imaging system in a rat model 30 min after intradermal injection. This system provides sub-millimeter spatial resolution, fast data acquisition (20-36s), and real-time 3D US imaging. This study manifests potential clinical advancement of PAI for use in SLN mapping [25]. Overall, it can be anticipated that the development of nanoprobes and imaging systems for non-invasive imaging will make great impact on clinical SLN diagnosis in the future.

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