Non-invasive trapping and imaging of circulating tumor cells

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A new type of system can potentially image rare circulating tumor cells with simultaneous non-invasive detection at a flow rate twice that of a human radial artery.

Metastasis, where circulating tumor cells (CTCs) from a primary tumor spread to other organs through the blood or lymphatic system, causes over 90% of cancer deaths. Identifying CTCs remains a big challenge due to their rarity in blood. Although many techniques can separate and identify CTCs, all are applicable in vitro, not in vivo. In addition, they can only sample very limited volumes because repeatedly sampling by blood draws, invasive biopsies, and bone marrow aspirations is unfeasible. In particular, a limited sample volume significantly decreases diagnostic confidence. Furthermore, real-time readout is not possible.

Photoacoustic (PA) imaging, which uses ultrasound transducers to detect short laser-pulse-induced acoustic sources, has been used for many biomedical applications. PA imaging provides high optical contrast in the near IR region and sub-millimeter acoustic resolution of targets up to several centimeters deep within the body. In recent years, many researchers have shown that by coupling well-designed contrast agents to biological objects, such as tumor cells, targets can be differentiated from the background using PA imaging. However, when it is necessary to detect targeted cells in blood, the strong PA background signal from blood can easily mask the signals from the contrast agents, especially for rare cell types such as CTCs.

We have developed a new imaging technique to suppress these strong background signals through the magnetic accumulation and manipulation of cells (i.e., CTCs) targeted with magneto-sensitive contrast agents. This approach, called magnetomotive photoacoustic (mmPA) imaging, uses nanoparticles with combined strong magnetic and optical absorption properties. Specifically, multifunctional nanometer-scale composite contrast agents consisting of a highly optical absorptive gold nanorod coupled with magnetic nanospheres can be chemically linked (i.e., targeted) to diseased cells. With an efficient magnetic trapping system, targeted cells can be accumulated, manipulated, and then differentiated from the non-magnetic background by motion filtering. This non-invasive technique is particularly interesting for clinical applications as it can sample large blood volumes in a short exam time while providing a real-time readout.

We recently presented the results of two initial tests of this technology in the Journal of Biomedical Optics. One of the methods we explored, presented here, examined the trapping, imaging, and manipulation of polystyrene beads (10μm in diameter) targeted with a composite contrast agent. These beads mimic targeted CTCs and were circulated in a 1.6mm stream.
polytetrafluoroethylene tube to simulate CTCs moving in the peripheral vasculature. Figure 1 shows ultrasound/PA fusion images: the process of trapping targeted beads in a right-to-left stream with a flow rate of 12ml/min (twice that in the human radial artery). Ultrasound signals are displayed in grayscale, whereas PA signals are superimposed in ‘hot’ pseudo-color. The top and bottom tube boundaries can be clearly seen in the ultrasound image. Figure 1(b)–(g) illustrates the course of the experiment: after applying the magnetic force (at time=0), beads gradually accumulated at the bottom of the tube owing to the strong trapping force; the PA signal amplitude increased correspondingly. The beads were released in Figure 1(h) by removing the magnets.

We repeated the same experiment replacing the transparent medium with an ink solution, mimicking the optical absorption of blood. Figure 2(a) and (b) shows fusion images with the magnets at different positions (black triangles). The PA signals of the trapped beads appeared at the lateral positions, corresponding to the magnet placement. The strong PA signals on the top wall were induced by the added ink. To detect CTCs in a blood vessel in vivo, another consideration is that background signals can overlap with the PA signals of trapped CTCs, making it difficult to distinguish targeted cells. Figure 2(c) shows how, by applying a simple subtraction filter to produce the mmPA image, bead signals are preserved whereas ink signals are suppressed to overcome this problem.

These results must be followed up with well-designed animal studies before considering clinical translation, and this is something we plan to do. However, our results do suggest that mmPA imaging with magnetic trapping of targeted rare cells might be an exciting tool to identify CTCs circulating in large blood vessels (e.g., the human radial and brachial arteries). By targeting these peripheral vessels, large blood volumes can be sampled in reasonable procedure times, enabling highly sensitive (<1CTC/mL of blood), and potentially highly specific, non-invasive monitoring of CTCs. Such a technology could be an invaluable tool in optimally managing metastatic disease.

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References

Figure 2. (a) and (b) Fusion images (ultrasound imaging in grayscale and photoacoustic imaging in color) of beads in ink solution acquired at two magnet positions. (c) Differential (magnetomotive photoacoustic) image of (a) and (b). Triangles indicate the position of the magnet.

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