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BIOIMAGING Hot nanoparticles light up cancer:

Targeting magnetic nanoparticles to tumours then applying an alternating magnetic field can improve the contrast for infrared thermal imaging

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Like inflamed tissues, malignant tumours have higher temperatures than normal tissues because they have an increased metabolic activity, and this rise in temperature can be detected using infrared imaging. The process of identifying breast cancer by its thermal signature has been studied for many years¹ because it is simple, safe and inexpensive, but it has not proved successful in clinical trials because the temperature differences between cancerous and normal tissues deep within the breast are difficult to measure². Furthermore, the difference in temperature is non-specific in that one cannot easily distinguish tumours from other local inflammation.

Writing in *Nanomedicine*, Israel Gannot and colleagues³ at Tel Aviv University now report an ingenious extension to infrared imaging that increases the temperature in the tumour by selectively heating it using magnetic nanoparticles and an external alternating magnetic field. An algorithm is used to classify the thermal data, predict the location and calculate the depth of the tumour. The method detected artificial tumours up to 14 mm below the surface of the skin.

To identify several possible clinical scenarios, the Israeli team first simulated a wide range of tumour depth, size and emission power by embedding an electrical heat source (which acts as a tumour) in a glass cup containing aqueous gel that mimics healthy tissue. From this experiment, the sensitivity, specificity and accuracy of the set-up were estimated as a function of heat deposition. Threshold values that help to decide whether or not a tumour exists were determined and used in the detection algorithm. In a second experiment, the thermal behaviour of 'real' tissues was simulated by embedding an agar gel containing magnetic nanoparticles into a piece of pig skin. Gannot and co-workers proposed that in an *in vivo* setting, the nanoparticles can be targeted to tumours using antibodies.

The *in vitro* experiments showed that the method could correctly locate the simulated tumours and estimate their position and depth using the infrared images. The classification method in the algorithm used to identify the tumours allows a trade-off between sensitivity and specificity but essentially all the tumours were detected when sufficient heat was deposited. The error in the estimated position was less than two millimetres.

Our body regulates local temperatures by removing excess heat through increasing blood flow, and the mechanisms of this process have been thoroughly explored^{4,5}. The greater potential of the technique proposed by Gannot and co-workers lies in its ability to interrogate the dynamic character of the way in which tissues respond to heat; it allows us to see how much extra blood can be supplied and how swiftly the blood flow can be changed when tissues are heated.

Unlike normal tissues, blood flow in cancer tissues cannot be increased further by heating because the hyperactive metabolism already causes the blood vessels to be fully dilated.

This means that heating leads to much higher temperatures in cancerous tissues than in normal ones because less heat dissipation occurs in the constant blood flow. However, when heat deposition ceases, temperatures in the cancer might also drop faster than in normal tissues because the blood flow in normal tissues starts to decrease, whereas the blood flow in cancerous tissues remains high and can pump heat away faster. The proposed technique allows the rate and magnitude of the response of tissues to heating to be measured and used as diagnostic indicators.

Other imaging techniques, such as dynamic contrast enhanced-magnetic resonance imaging (DCE-MRI), also use the dynamics of blood flow to identify cancer; the rate of uptake and removal of the contrast agent in DCE-MRI allows cancer to be distinguished from normal tissues⁶. The two methods could be complementary because DCE-MRI measures the amount of blood delivered to tissues and the proposed infrared imaging technique might be capable of providing more information on how swiftly the amount of blood delivered can be changed by a heating stimulus.

The present set-up is well suited to preclinical studies using rodent models but there are significant challenges that need to be overcome before it can be implemented in the clinic. For instance, although the present penetration depth of 14 mm is sufficient for preclinical studies, it will not be good enough for human studies because tumours may reside much deeper. Delivery of nanoparticles to cancer is generally easier than to normal tissues because tumours have more porous vessels⁷. Yet, delivery remains a problem in most nanoparticle applications because white blood cells, known as macrophages, rapidly remove them. Better methods that can deliver large numbers of nanoparticles to the tumour need to be realized because many nanoparticles will be required to heat it⁸.

The proposed technique is clever and should enable temperature regulation and blood flow to be used as markers for cancer detection and characterization, thereby expanding the thermal signature of cancer from just being hot to how it responds to extra heating.

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Figure 1.

Improving the contrast in infrared thermal imaging. (1) A normal blood vessel (green channel) delivering antibody-targeted nanoparticles (blue shapes) into cancer tissues (cancer cells shown in orange). (2) Cancer has a greater number of blood vessels, which are more porous than in normal tissues. (3) Antibodies on the nanoparticles bind to the antigens (red shapes) that are specific to the cancer and keep them in place while the unbound nanoparticles are absorbed into the lymph system. (4) Nanoparticles are heated using an external radiofrequency coil that generates an alternating magnetic field in the normal and cancerous tissues. The heated nanoparticles (red circles) raise the temperature of the cancer tissue slightly and this is detected by an infrared camera.