Immunotherapy Is Radiology's Next Frontier

RESEARCHERS at Duke University Medical Center report using mechanical high-intensity focused ultrasound (HIFU) to activate the immune system to recognize and attack malignant tumors, pointing the way toward a whole new field in cancer therapy for radiologists.

The study was detailed in the August 3, 2007, issue of the *Journal of Translational Medicine*.

Similar to radiofrequency ablation, HIFU operates on a much smaller scale and without needles. HIFU essentially shakes the tumor, causing it to fracture and release parts of dead tumor cells in a form that can be recognized by the immune system. This immunogenic approach allows radiologists to treat a primary tumor while achieving a systemic approach to combating metastatic disease.

HIFU got its start as researchers contemplated an immune system apt to overlook cancer cells and suggested that for an effective response to occur, the body might need assistance in recognizing cancer cell surface proteins, as well as other proteins enclosed within cancer cells that send a danger signal.

In their research, the Duke team used a special ultrasound probe to create cavitation within the tumor. Researchers found that antigen-presenting cells recognized cancer specific proteins and responded by creating an immune cell that conferred either immunity or resistance to that particular cancer.

"It's a similar concept to vaccinating a patient for cancer with their own cancer cells," said Bradford Wood, M.D., chief of interventional radiology research and acting director of science and research for the diagnostic radiology department at the National Institutes of Health Clinical Center. "Immunotherapy is an entire discipline within oncology, and image-guided therapies can play a role in immunomodulation," said Dr. Wood.

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>
> **Bradford Wood, M.D.**

Mechanical HIFU Created Immune Response

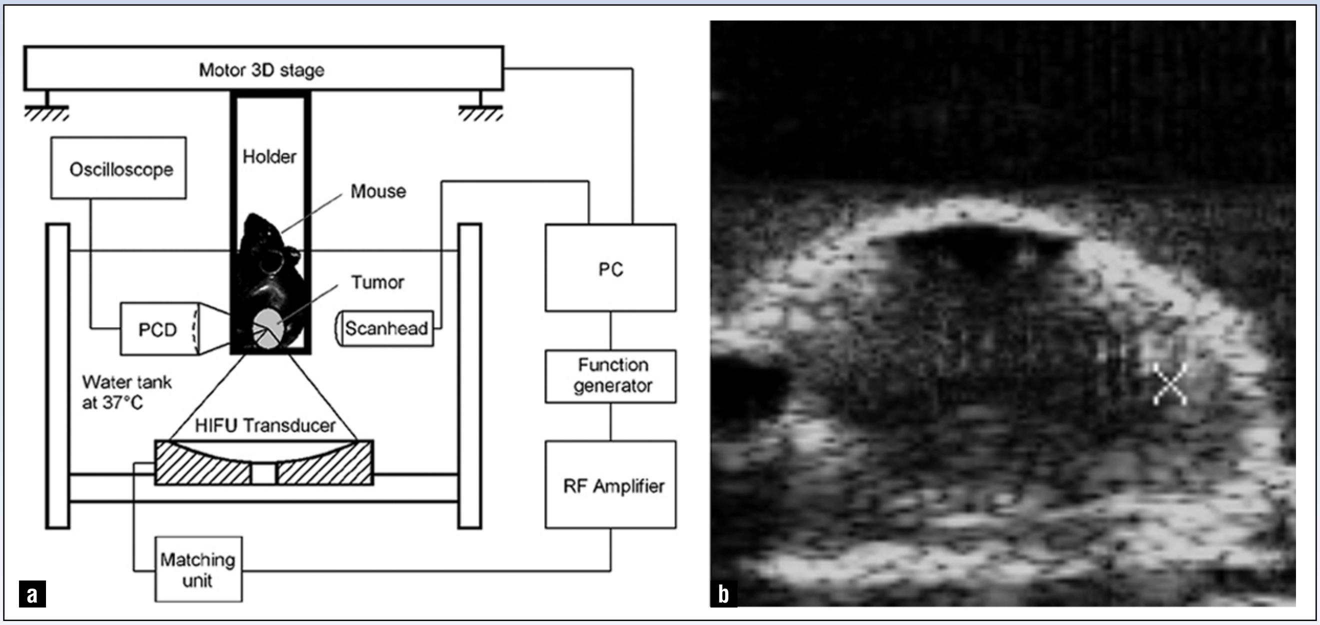
Duke researchers used thermal and mechanical HIFU to treat mice with MC-38 colon adenocarcinoma, observing the effects on immune response. The study was part of a series designed to investigate tumor treatment with HIFU. Researchers evaluated reduction in tumor size, immune system activation and the possibility that increased immune response would have more diffuse activity against other tumors in the body.

Mechanical disruption of the tumor induced a more effective immune response than thermal or no treatment, the study revealed. Co-author Michael A Morse, M.D., associate professor of medicine at Duke University Medical Center, explained: "We looked at this several ways. We measured the T cells in the mice after they were treated with either mechanical HIFU or thermal HIFU. We looked at their ability to respond to tumor cells in the laboratory, and T cells we removed from the mice recognized the tumor. The immune system must have been activated against the tumor and it was more effective with mechanical HIFU than thermal HIFU."

Michael A Morse, M.D.
Duke University

Researchers also studied the tumor and found primary tumor size was smaller with thermal HIFU than with mechanical HIFU or no HIFU application. While heating a tumor during treatment may have proven a bit more effective than the mechanical HIFU, Dr. Morse said, researchers still favor mechanical HIFU since the resulting immune response may be of benefit in the prevention and treatment of metastatic disease.

HIFU and radiofrequency, already widely used in clinical radiology, stimulate the body's immune response. The mechanistic bioeffects and roles of HIFU are not yet completely understood, but the Duke study shows



HIFU exposure system and B-mode guidance.
(a) Diagram of the in vivo HIFU exposure setup. *(b)* Alignment of the mouse tumor with the focus of the HIFU transducer was aided by B-mode ultrasound imaging.
Hu, et. al. "Investigation of HIFU-induced anti-tumor immunity in a murine tumor model." *Journal of Translational Medicine* 2007;5:34.

the potential for harnessing such a response, said Dr. Wood.

Dr. Morse said that when studies move from the mouse model to humans, researchers hope to activate an immune response that can prevent or treat metastatic disease, not just the primary tumor.

Research Spotlights Interdisciplinary Strengths

NIH researchers have studied mechanical HIFU to enhance drug delivery or efficacy, said Dr. Wood, but the work of the Duke team differs from standard thermally ablative HIFU or other experimental mechanical types of HIFU. Depending upon how it is used, HIFU can cause cavitation or shear stresses.

"Mechanical sheer stress may be induced by a pulsed, focused ultrasound," said Dr. Wood. The HIFU in the study is not purely mechanical—it is likely that some cavitation plus thermal and sheer stress effects occur, the latter of which can actually move tissue on a very small scale."

Previous HIFU research has focused on enhancing thermal ablation efficiency. HIFU is FDA-approved for fibroid ablation and is being investigated for drug delivery, pain control, thrombolysis, seizures and deep brain stimulation.

"The most fertile grounds for novel work are in the Neverlands between disciplines that take advantage of each others strengths," Dr. Wood said. "This is a scenario that can image to define, then partly kill and stimulate a tumor all in the same setting, with image-guided energy deposition and a little booster to the oncologist's approach of immunotherapy.

"HIFU is in its infancy," Dr. Wood continued. "There is still much work to be done in this area and I am glad there are radiologists and radiologic scientists who are interested. It could open up a whole new field of cancer therapy for radiologists. The road is long, but noninvasive tissue destruction or image-guided drug deposition will be the surgery of the future." □

Learn More

- The abstract for "Investigation of HIFU-induced anti-tumor immunity in a murine tumor model" is available at *www.translational-medicine.com/content/5/1/34.*