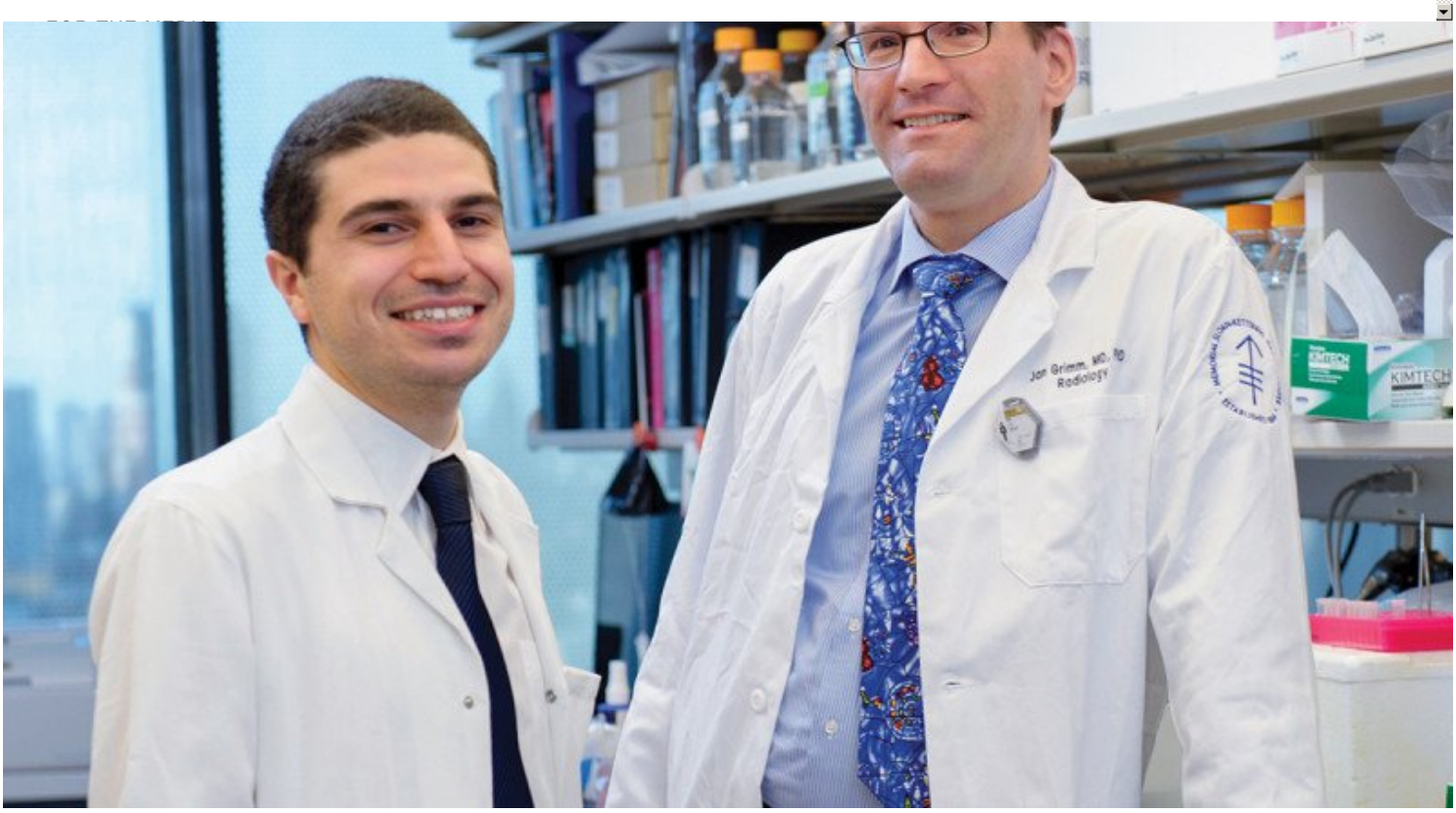

Radiologist and molecular imaging specialist Jan Grimm (right) and laboratory member Daniel Thorek

Summary

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A new imaging approach being investigated by Memorial Sloan Kettering researchers could provide better information about a tumor's molecular activity,

allowing for a more accurate diagnosis based on the tumor's specific disease signature.

The technique makes use of Cerenkov light, a faint glow created when charged particles (electrons or positrons) travel through a medium, such as water or tissue, faster than light can travel through that same medium. A kind of "sonic boom" for light, Cerenkov light is given off naturally by many of the radioactive tracers that are already commonly used in medical imaging techniques such as positron emission tomography (PET). Although discovered more than 100 years ago, Cerenkov light has only recently been considered for biomedical imaging purposes.

Now researchers in the laboratory of Memorial Sloan Kettering radiologist and molecular imaging specialist Jan Grimm are investigating whether the Cerenkov light given off by these tracers could be harnessed to provide information about precise biological processes within a tumor - such as the activity of a protein known to promote cancer spread.

"In this era of personalized medicine, there is an urgent need for a way to sensitively detect and quantify molecular activity," Dr. Grimm says. "We wanted to explore whether Cerenkov light could be engaged to provide more specific information about the tumor's biological properties."

An Extra Layer of Information

Conventional methods of cancer imaging are effective primarily in showing a tumor's location and dimensions rather than specific protein activity. For example, PET scans track a radioactive tracer coupled with a molecule that accumulates in certain tissues. The most common tracer, fluorodeoxyglucose (FDG), shows the location of a tumor based on increased glucose intake, a hallmark of cancer cells.

Dr. Grimm and three members of his laboratory aimed to find out whether Cerenkov light emitted by radiotracers could be used to activate additional imaging agents that add information about specific disease processes. For example, certain agents glow brightly when excited by Cerenkov light — some only after being activated by encountering certain proteins.

In a September 8 online publication in the journal *Nature Medicine*, they describe experiments in which they created a molecular probe that interacts specifically with a protein called MMP-2, which is known to be overactive in aggressive breast tumors. MMP-2 converts the probe into a form that will become fluorescent when excited by the Cerenkov light. By measuring this Cerenkov-induced fluorescence, the researchers are then able to calculate and quantify the protein's activity.

"This technique allows us to receive and analyze two signals at the same time," says Daniel Thorek, the study's first author. "The Cerenkov light is coming from the tracer we use for PET scans, which is already well-validated as an indicator of cancer. And secondly, we're able to use the Cerenkov-induced fluorescence to detect and measure the activity of MMP-2, which can provide information about the tumor's aggressiveness."

The researchers demonstrated this technique, called secondary Cerenkov-induced fluorescence imaging (SCIFI), in mice that had been implanted with human breast cancer tumors expressing varying levels of the MMP-2 protein. While conventional PET imaging showed no significant difference between the tumors, SCIFI detected a signal only from tumors with high levels of MMP-2 – therefore clearly marking these tumors as more aggressive, which would not have been possible using PET alone.

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A Clearer Signal

Dr. Grimm explains that the method is very sensitive because the Cerenkov light that activates the imaging probe comes from within the tumor rather than from an external light source. "If you activate the probe with excitation light from an external source, that external light is reflected partly back and scattered, creating a lot of background noise and making it harder to measure the actual signal. Using Cerenkov light, which is internal, gives you a much better excitation source."

He adds that SCIFI testing is still in an early stage, but because the method uses probes that are already common in medical imaging it should be easy to transition the new technique into human trials. Because Cerenkov light is very low, it requires use of a sensitive camera to detect the fluorescent signal. Dr. Grimm speculates that the first SCIFI applications in humans may be in laparoscopic procedures, in which instruments are inserted through small incisions in the skin.

The researchers emphasize that SCIFI would not replace but complement PET scans. "PET is a really phenomenal technology and we're just adding more sophisticated probes to extract additional information," Dr. Thorek says. "This approach leverages the advantages of nanoparticles, radiotracers, and optical imaging and brings these fields together very nicely."

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