Science Translational Medicine Podcast

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Host – Megan Frisk
Hello, I'm Megan Frisk, and welcome to the *Science Translational Medicine* Podcast for June 11th, 2014. Today I'll be speaking with Dr. John Kuo, associate professor of Neurological Surgery and Human Oncology at the University of Wisconsin in Madison, Wisconsin. He'll be talking about a new class of imaging agents that his team has discovered: agents that are not only able to image tumors but may also have therapeutic benefit.

In a perfect world, we would be able to see tumors clearly without any background "noise" from surrounding, healthy tissue. We'd also be able to treat tumors without damaging the surrounding, healthy tissue. Such specificity, however, often comes at a price. Adding layers of complexity to an imaging agent to make it so specific may render the agent unable to translate to the clinic. Additionally, the specific agent may end up too narrow, working for only one or two different types of cancer. Conversely, a nonspecific, broadly applied molecule often finds itself in healthy cells, obscuring images and limiting treatment options. Now, John Kuo and his colleagues have discovered a new class of imaging agents that is the best of both worlds. These small molecules are taken up only by cancer cells—or, preferentially by cancer cells—but still have broad applicability in, as the authors have demonstrated, over 50 different types of cancer. They tested these agents—called alkylphosphocholine analogs, or APC analogs—in both rodent models of human cancer and in patients with brain tumors.

Dr. Kuo is here with me now on the line to tell us more.

Interviewer – Megan Frisk
Welcome, Dr. Kuo, and thanks for joining me today.

Interviewee – John Kuo
Thank you. It's a pleasure.

Interviewer – Megan Frisk
So, this is a new class of small-molecule, cancer-imaging agents. Can you tell us how you discovered these APC analogs? Was it by chance or did you specifically seek out molecules that fit a certain description or mechanism?

Interviewee – John Kuo
This has actually been a long time coming. My colleague and friend, Dr. Jamey Weichert, was working with Dr. Ray Counsell at the University of Michigan and noted that Fred

Snyder and colleagues published a series of papers showing abundance and accumulation of phospholipid ethers, a certain class of organic molecules in cancers versus normal cells. And so they went forward and synthesized a large number of classes using structure-activity analysis of phospholipid ethers—specifically these APC, or alkylphosphocholine, analogs. And they were able to show selective tumor retention across many different cancers because they seemed to mimic these phospholipid ethers. So when I arrived here at the University of Wisconsin Carbone Cancer Center, Jamey approached me and wanted to test this in our cancer models, specifically cancer stem cell models derived from brain cancer. And we were able to—despite my initial skepticism—show these exciting results that the APC analogs appeared to be very broadly targeted against cancer possibly through a phospholipid membrane lipid raft mechanism of uptake and be potentially useful for cancer imaging as well as therapy.

Interviewer – Megan Frisk
You mentioned cancer stem cells a couple of times. Why might one want to image cancer stem cells?

Interviewee – John Kuo
Well, it's important to remember that recent work has shown that there's a subset of cells in many different cancers, including brain cancer, breast cancer, that may have stem-like properties and appear to be therapeutically resistant to current therapies. And a hallmark feature of these cancer stem-like cells is the ability to reinitiate and regrow the entire tumor, suggesting that they may underlie much of the incurable nature of the cancers that we see. So that was what was exciting about these APC analogs. Not only do they image and are selectively retained in the cancer cell lines that have been studied throughout the world for different cancers over the decades, we're able to show—at least with brain cancer—that the brain cancer stem cells are also not excluded.

Interviewer – Megan Frisk
What's really interesting about your paper is that you have this class of molecules—these APC analogs—and you're able to both fluorescently label them and radiolabel them so you can work with different imaging modalities. What would be the benefit of using one imaging agent versus the other?

Interviewee – John Kuo
Well, you have touched on something that is very important about this base analog, the APC analog. It is essentially a cancer-homing agent to which we can attach many different payloads. Imaging payloads, such as iodine-124, iodine-125, or even therapeutic payloads like iodine-131 could be attached to a cancer-homing agent across many different cancers. A very exciting set of analogs that we have created and are working with are the optically fluorescent ones. As a surgeon, I would love to be able to see tumors intraoperatively and especially in the brain to know what is resectable, what is going into functional brain, and then to follow up with postoperative imaging to see what else needs to be treated with adjuvant therapies. What's exciting is that the APC analog backbone is essentially the same and therefore across all of these different functional groups—both iodine for imaging or therapy and optically fluorescence for

visualization—these can all be used and expected to target the exact same cells whether it is preop or postoperative residual or even potentially clinical recurrence that is detected later.

Interviewer – Megan Frisk
So you're a surgeon; you're doing this, you're seeing tumors every day. How do these analogs compare to what's already out there? What would be your routine imaging agent, and how are these APC analogs better?

Interviewee – John Kuo
Routinely we are using, for example, CT scans with contrast agents or MRI scans with gadolinium contrast agents, which are not targeting cancer; they're targeting areas of anatomical disruption, especially in the brain, such as blood-barrier or tumor-brain barrier disruptions. So those imaging contrasts rely on leakage across blood vessels that are abnormal in areas of let's say cancer, but may also leak across and show enhancement in areas of postoperative scar, in areas of infection or inflammation. Moreover, PET imaging has been used as a supplement but relies usually on hypermetabolism. And that, for me, is very much not useful in the brain because the brain is very hypermetabolic in itself so any PET-positive signal due to tumor will be lost within the normal brain background that's very high in PET imaging. These APC analogs are cancer cell–directed and also cancer stem cell–directed. So they're direct cancer labeling and uptake agents. And when I-124 or I-125 is used as an imaging add-on for the APC analog, we have seen very exciting results in early human trials that it is able to detect tumor throughout the body. In both animals and humans, we're able to detect what were initially unknown or asymptomatic metastases of cancer to other sites in a body, including the brain. And in even patients in early clinical trials who have asymptomatic brain mets that were detected, this actually was verified by standard imaging and changed their clinical management.

Interviewer – Megan Frisk
So you mentioned you got to patients, but first you had to go through animal models. So you looked at human tumors growing in mice, and you looked at everything from brain to breast to prostate, and you see that this works. But were there any tumors that didn't work, and do you know why?

Interviewee – John Kuo
One class of cancers were not successfully imaged, and these are the liver cancer lines that were tested both in vitro as well as in animal models. This may relate back to the original observations by Fred Snyder that liver cells and liver cancer lines appear to express a higher level of the enzymes than other cancers to metabolize APC analogs or related phospholipid ethers.

Interviewer – Megan Frisk
Another interesting point that you already touched on but we should come back to is that these agents are not only able to image the tumors, but they have an inherent therapeutic

benefit. So can you explain how they're acting as these "double agents" to kill cancer cells?

Interviewee – John Kuo
Sure. The tagging with iodine-131—which is a high-energy emitter that goes half a millimeter to 2 millimeters into surrounding tissue—to these APC analogs will allow a specific localized radiotherapy to the cancer cells directly. And we have initial animal model data across many different cancers, including brain cancer, triple-negative breast cancer, pancreatic cancer, that show even without an optimized dose selective survival benefit. And this is now in early clinical trials for humans, as well.

Interviewer – Megan Frisk
It's very exciting that you have this broadly applicable to all cancers, it's highly specific, you've already tested it in dozens of cancers in animals and now you're in patients. So, what's next? When are these ready for all cancer patients?

Interviewee – John Kuo
Well, even though we have made a lot of progress in the animal models, I think, as you know, many scientists have been able to treat or cure cancer in animals. We need to prove this in humans for all the different cancer types. And while I may be saying that this is a cancer stem cell– and all-cancer–targeting agent, we need to prove it for every single cancer type to be sure of that since our work has primarily focused on the cancer stem cells from brain cancer, given that it could certainly be a very important complement to the very exciting age we live in of precision medicine with the targeted agents that are now also approved or in clinical trials.

Interviewer – Megan Frisk
Dr. Kuo, thank you so much for joining me today, and congratulations on a really exciting paper.

Interviewee – John Kuo
Thank you very much to you and the listeners, from my colleagues and myself.

Host – Megan Frisk
That was Dr. John Kuo, associate professor of Neurological Surgery and Human Oncology at the University of Wisconsin–Madison. Check out his paper in the June 11th issue of *Science Translational Medicine* by going to our Web site at stm.sciencemag.org.

I'm Megan Frisk, and thank you for listening!

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