New route for old cancer agents

By Tracey Baas, Senior Editor

Researchers at the **University of Wisconsin–Madison** and **Cellectar Biosciences Inc.** have exploited differences in lipid architecture between cancer and normal cells to create compounds that deliver radiolabels selectively to different types of malignant cells while sparing healthy ones.[1]

The group has started multiple clinical trials of its agents for imaging, radiotherapy and intraoperative tumor margin detection.

Cancer cells were first shown to differ in lipid uptake from normal cells over four decades ago through studies on phospholipid ethers.[2–4] About 20 years later, researchers at the **University of Michigan** looked for imaging uses of the findings by investigating how chemical alterations of aryl phospholipid ethers and alkylphosphocholines affected the compounds' uptake and retention in tumors.[5–7]

Those studies were led by Raymond Counsell and his graduate students, including Jamey Weichert. In 2006, the duo developed the tumor imaging agent 18-(p-iodophenyl)octadecyl phosphocholine (CLR1404),[8] which selectively accumulated in tumors and showed low toxicity in rats.

Now, a team co-led by Weichert and John Kuo at the University of Wisconsin–Madison found that linking the cancer homing properties of CLR1404 with radioiodine or fluorescent or near-infrared labels did not diminish its selective uptake and retention in tumors. They also showed CLR1404 uptake and retention in therapeutically resistant cancer stem cells. Indeed, the results suggested that CLR1404 could deliver radioisotopes or other chemical groups to cancer and cancer stem cells in many different malignancies and could serve as a scaffold for generating diagnostic or therapeutic agents.

Weichert is now an associate professor of radiology, medical physics and pharmaceutics at UW-Madison and founder and CSO of cancer company Cellectar. Kuo is an associate professor of neurological surgery and human oncology and director of the Comprehensive Brain Tumor Program at the **University of Wisconsin School of Medicine and Public Health**.

Incubation of fluorescently labeled or radioiodinated CLR1404 showed three- to ninefold greater uptake in multiple human cancer cell lines than in matched human normal cell lines. In patient-derived cell lines, fluorescently labeled CLR1404 showed higher uptake in human glioblastoma stem-like cell lines than in normal fetal neural stem cells.

Conversely, pretreatment with filipin III, an agent that disrupts lipid rafts and sequesters cholesterol, reduced uptake by about 40%. The team concluded that CLR1404 uses lipid rafts as a major portal into cancer cells.

Next, the team explored the imaging and therapeutic potential of the CLR1404 scaffold using two different iodine radioisotopes in mouse models of 57 different types of cancer.

In genetic tumor or xenograft mouse models, PET imaging detected ^{124}I-CLR1404 in primary or metastatic tumors but not in benign or premalignant tumors or in inflammatory or premalignant lesions.

Because ^{131}I is a well-established cytotoxic radioisotope, the team tested the therapeutic potential of ^{131}I-CLR1404.

In xenograft mouse models of cancer, a single dose of 100–145 microcuries of ^{131}I-CLR1404 decreased tumor growth and increased survival compared with a dose of unlabeled CLR1404. In radioresistant uterine sarcoma and glioma mouse models, two doses achieved similar effects.

Finally, the researchers started multiple Phase I/Ib PET imaging trials and reported examples of radiolabeled CLR1404 imaging from the first three patients.

In a patient with non–small cell lung cancer (NSCLC) and a patient with glioma, PET imaging of ^{124}I-CLR1404 clearly visualized tumors throughout the brain and body. In the third patient, who had colorectal cancer, single-photon emission computed tomography using ^{131}I-CLR1404 showed uptake and retention of the compound in the tumor and in metastases. Successful imaging agent detection of brain metastases suggested that the compounds can cross the blood brain barrier.

Results were published in *Science Translational Medicine*.

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> ***—Matt Vander Heiden, Massachusetts Institute of Technology***

Kuo told *SciBX* that preliminary follow-up results in patients with end-stage cancer treated with ^{131}I-CLR1404 showed disease stabilization with a low side effect profile.

One size might fit all

The broad-spectrum approach of targeting cancer cells based on their lipid composition could be an effective strategy for developing imaging and therapeutic agents.

"People are starting to remember how useful conventional chemotherapies are to treat a variety of different cancers," said Matt Vander Heiden, an associate professor of biology at the Koch Institute for Integrative Cancer Research at the **Massachusetts Institute of Technology**.

Marcel Verheij, chair of the Department of Radiotherapy at the **Netherlands Cancer Institute** and a professor at the **Free University Amsterdam**, noted that CLR1404 itself could be used to optimize patient selection.

"This broad-spectrum approach is different from the trial-and-error strategy that has been used in the past for conventional chemotherapy," he said. "By first identifying which tumors incorporate the imaging

variant of CLR1404, a preselection of patients with a high chance of responding to the therapeutic variant becomes possible."

He added, "The preselection offers the opportunity to avoid exposing patients with poor uptake to the possible side effects. This strategy could also allow for a better staging of patients by visualizing sites of metastatic disease and for identifying residual disease following surgery or other local treatments."

Julie Novak, VP of research and project management at cancer imaging company **Blaze Bioscience Inc.**, agreed. "Having a companion imaging agent can be helpful in selection of patients if the specificity of both agents proves to be similar in human cancer patients. Positive imaging data may not correlate with therapeutic utility, but negative imaging data might be useful in excluding patients in trials with little chance of benefiting from the therapy," she said.

"We are always looking for a one-size-fits-all therapeutic-diagnostic agent as it limits costs for clinical translation, has a broader applicability and a more well-known pharmacokinetic-pharmacodynamic profile."
—Gooitzen van Dam, University of Groningen

Vander Heiden wanted to see more mechanistic details of the preferential uptake of the analogs into cancer cells over normal cells. "There's a long history of studies that show lipid compounds selectively accumulate in cancer cells, but how that occurs and how lipid rafts contribute to that uptake remains to be determined," he said. He added that these mechanistic studies should include tumor cells, normal cells and rapidly proliferating normal cells that often contribute to toxicity profiles.

According to Novak, one of the key opportunities for the PLE approach may be in imaging during cancer surgery, though little data are provided in the paper for the intraoperative imaging compound.

"The team will ultimately have to show in a clinical setting that the agents improve surgeons' ability to distinguish tumor from nontumor tissues," Novak added. "This boils down to contrast at the time of surgery—the higher the contrast achieved, the more easily the surgeon can make a call."

She said that it would be important to show "consistent uptake in tumor tissue, retention by the tumor, clearance from normal tissues within an acceptable time post-dose and brightness that enables detection by imaging devices within their dynamic range."

In addition, she cautioned that the overlap between cancer pathways and inflammatory or other disease processes can cause some tumor imaging agents to label nontumor tissues, a process that could compromise effectiveness in surgery.

According to Gooitzen van Dam, the dual therapeutic-diagnostic potential is a significant advantage. "We are always looking for a one-size-fits-all therapeutic-diagnostic agent as it limits costs for clinical translation, has a broader applicability and a more well-known pharmacokinetic-pharmacodynamic profile." van Dam is a professor of surgery and head of the Intraoperative Imaging Research Group at the **University of Groningen**.

CLR1404 and radioisotope analogs were first patented in 2001 by the University of Michigan and Cellectar. Cellectar patented the fluorescent analogs in 2012 and has subsequently filed patent applications for diagnostic and therapeutic use of all compounds. The team is open to discussing partnering opportunities.

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