Detecting Ovarian Cancer Earlier

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A novel radiopharmaceutical may help pinpoint early ovarian tumors.

Early detection represents a critical strategy against ovarian cancer, the fifth most common cause of cancer-related death in women in the United States. While most ovarian cancer is diagnosed at an advanced stage at which the 5-year survival rate is less than 30 percent, early detection increases the 5-year survival rate to about 93 percent.

"Ovarian cancer is well-treated if detected early. But it usually isn't," said Lawrence Marnett, Ph.D., dean of basic sciences and professor of biochemistry, chemistry and pharmacology at Vanderbilt University School of Medicine. "Serous ovarian cancer is the most malignant and most common form of ovarian cancer and it spreads through the abdomen early so that it isn't detected until at an advanced stage."

In a recent study reported in ACS Omega, Marnett and colleagues including Md. Jashim Uddin, Ph.D., research associate professor in the Department of Biochemistry at Vanderbilt, designed a cyclooxygenase (COX)-1 targeted imaging agent for early detection of ovarian cancer.

"We were hoping to use molecules that are expressed in ovarian cancer as targets for imaging those tumors as they develop," Marnett said.

Cyclooxygenases: Markers of Early Lesions

The new radiopharmaceutical developed by the team, referred to as [18F]FDF, is a COX-1 inhibitor labeled with fluorine-18, a radioisotope necessary for PET imaging. "It was a major accomplishment and used a lot of chemistry to do was looks pretty simple on a piece of paper," Marnett said.

To start, an established COX-2 inhibitor, Vioxx, was redesigned to selectively bind COX-1 instead of COX-2.

"We knew from a lot of work that had been done in the literature, and work in our own laboratory, that if you take the methylsulfonyl substituent off Vioxx and replace it with other functional groups, it actually selectively binds to COX-1," Marnett said.

Incorporation of the fluorine radioisotope was trickier.

"This is tough chemistry," Uddin said. "The precursor is not stable under the conditions that you have to use to introduce fluorine-18." Uddin attached a substituent to stabilize the chemical scaffold and developed a novel Lewis-acid catalyzed chemistry scheme to incorporate fluorine-18.

Validating the Compound

Uptake of [18F]FDF was fivefold higher in tumors than in normal muscle tissue, indicating that signal intensity from [18F]FDF can distinguish a COX-1 expressing tumor from the background noise of COX-1 expression in the peritoneal cavity. The compound also exhibits other key requirements for use as a PET imaging agent: minimal defluorination, minimal off-target organ uptake, and a plasma half-life of 1.2 hours.
Two preclinical mouse models of ovarian cancer were used to evaluate \(^{18}\text{F}\)FDG in the recent study. Maximal uptake of \(^{18}\text{F}\)FDG occurred one hour post-injection in a subcutaneous xenograft model, and in less than five minutes in a more physiologically relevant peritoneal tumor model.

“The point here,” Uddin explained, “is that when it is physiologically relevant, and you have vascular connections with the tumor, then you can deliver material pretty easily and quickly to the tumor.”

Future studies are in the pipeline to validate \(^{18}\text{F}\)FDG for diagnostic targeting of ovarian cancer, including metabolism and toxicology studies.

**BIO(S)**

**Lawrence Marnett, Ph.D.**

Lawrence Marnett, Ph.D., is Mary Geddes Stahlman Professor of Cancer Research, dean of basic sciences, and professor of biochemistry, chemistry and pharmacology at Vanderbilt University School of Medicine. He is director of the A.B. Hancock, Jr. Memorial Laboratory for cancer research and the Vanderbilt Institute of Chemical Biology. His research focuses on the role of cyclooxygenase in cancer and inflammation.

**Md. Jashim Uddin, Ph.D.**

Md. Jashim Uddin, Ph.D., is research associate professor of biochemistry at Vanderbilt University School of Medicine. His research is focused on the development of methods and agents for diagnostic and therapeutic targeting of cyclooxygenase isozymes in carcinogenesis.