Researchers define shape of enzyme linked to prostate, breast cancers

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(Medical Xpress) -- A University of Kansas researcher has made a discovery that should lead to improved treatments for prostate and breast cancer.

Emily Scott, an associate professor of medicinal chemistry at KU, has provided the first experimental evidence regarding the shape of cytochrome P450 17A1 – or CYP17A1 – an enzyme that makes hormones that promote the growth of prostate and breast cancer. By defining the shape of this enzyme, Scott's research will enable the design of more effective drugs to stop undesirable hormone production in cancer patients.

"To inhibit an enzyme, a drug needs to bind to it," Scott said. "But without knowing the shape of an enzyme, designing a drug to bind to it is like designing a key without knowing the shape of the lock. By revealing the shape of CYP17A1, our research will enable the design of better 'keys,' or in this case, better drugs."

Scott's findings – co-authored by then-graduate student Natasha DeVore – appear this week in the online edition of *Nature*, the world's most highly cited interdisciplinary science journal. The print edition will be available Feb. 2.

Determining the structure of proteins like CYP17A1 is challenging because they are usually located in cellular membranes and tend to fall apart or stick together when scientists try to study them. Without

structural information, previous research used computational studies to predict that drugs designed to inhibit CYP17A1 would orient in a certain way – specifically, parallel to a part of the enzyme called the heme.

But Scott's research demonstrates that the most promising current treatments bind very differently than previously predicted. Using X-ray crystallography, Scott examined CYP17A1 in the presence of two promising new drugs – abiraterone, which was recently approved by the FDA, and TOK-001, which is in early clinical trials – and found that they bind perpendicularly to the heme, not parallel as previously thought.

"When proteins like CYP17A1 are so difficult to work with, scientists often turn to similar proteins for which more data is available and make a best guess about the protein actually under study," Scott said. "That is what the previous computational experiments did in this case, and it's a good start, but there is no substitute for actually doing the experiment – even if the experiment is difficult or time-consuming or expensive. The taxpayer-funded grant investment in this research was well-spent because the current data changes our concepts about how these drugs for prostate cancer and breast cancer are likely to work at the level of atoms."

In addition to showing how these drugs work, the CYP17A1 structures reveal multiple new opportunities to improve these drugs or design new drugs. Many current drugs, in addition to blocking the enzyme's cancer-causing activity, also block the enzyme's normal activities, which leads to side effects in areas like immune response and blood pressure.

"The new data also immediately told us how to design better prostate cancer and breast cancer drugs by making the drugs more complementary to the shape of the enzyme cavity in which they bind," Scott said.

Scott's work is funded by the National Institutes of Health via an award to the Center of Biomedical Research Excellence in Protein Structure and Function at KU, and by a grant from the National Institute of General Medical Science. Future work will be funded by a pilot project from the KU Cancer Center. Scott has also submitted a proposal to NIH for additional funding.

Breast cancer is the most frequently diagnosed cancer in women and ranks second as a cause of cancer death in women. Prostate cancer is the most frequently diagnosed cancer and the second-leading cause of cancer death in men.

Provided by University of Kansas