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Emily Scott, PhD, keeps a bright yellow kids' shape-sorting cube in her office. It comes in handy when Scott, an associate professor of medicinal chemistry at the University of Kansas, has to explain her work - figuring out the structures of disease-related proteins so drugs can be designed to home in on them - to non-scientists.

Proteins resemble shape sorters in that they have a hole, or active site, where drugs can nestle. "If we know the shape of the hole, we can better fill it with a drug," Scott says. "The more complementary a drug's shape is to the target protein, the more likely it is to be effective."

Scott, also a member of The University of Kansas Cancer Center's Drug Discovery, Development, and Experimental Therapeutics research program, recently uncovered the structure of a protein linked to prostate cancer, the most common cancer and the second leading cause of cancer-related deaths in men. This work, completed with former graduate student Natasha DeVore, was published in the February 2012 issue of the journal *Nature*.

Prostate cancer mainly affects older men and is fueled by the body's production of steroid hormones, including testosterone and other male hormones, collectively called androgens. An established treatment for this disease is to block androgen production in the reproductive tract. Such castration was accomplished in the past by surgery and more recently with drugs. Sometimes, though, prostate cancer morphs into a form that resists castration and can rapidly spread elsewhere. Patients at this stage live for an average of just 18 months.

Over the years, researchers have learned that other tissues in the body, including the adrenal glands and even cancer cells themselves, can also churn out androgens. So scientists, including Scott, are increasingly interested in designing drugs to block the function of a single protein needed to make

androgens in all tissues of the body. This key protein is a member of a large family of proteins called cytochrome P450s, or CYPs (pronounced "sips").

Humans have 57 CYPs, a quarter of which help clear foreign chemicals from the body. "This could be aspirin taken for a headache, pesticide residue on an apple, or carcinogens inhaled while walking behind a diesel bus," Scott explains. Other CYPs work on normal metabolic processes such as converting vitamin D into its active form.

The CYP protein of interest that Scott has been studying is called CYP17A1; it facilitates the metabolic process of converting cholesterol into steroid hormones. CYP17A1 accomplishes two sequential chemical reactions, both of which are required to make androgens. In females, a different CYP protein then turns androgens into estrogens. "Without CYP17A1, you can't make androgens *or* estrogens anywhere in the body," Scott says. "So blocking this protein's function could be an effective therapy for both prostate and some types of breast cancer."

Determining the shape of CYP proteins is no easy task, because they often clump together or even unravel completely when extracted from the cell membranes where they normally reside. Undeterred, Scott and DeVore turned *E. coli* into bacterial "factories" producing large quantities of a form of human CYP17A1 protein. The proteins were then coaxed into forming tiny crystals. "The proteins in these crystals were lined up like rows of soldiers, and we shot X-rays at them," Scott says. "Because they were all facing the same direction, the X-ray beams bounced off in an organized pattern of spots that we used to decipher CYP17A1's shape."

Scott and DeVore used the same technique, X-ray crystallography, to learn how two promising new prostate cancer drugs - abiraterone, recently FDA-approved; and TOK-001, currently in a Phase III clinical trial - interact with CYP17A1. Since CYP17A1's structure had yet to be deduced at the time both drugs were designed, researchers used proteins with known shapes and similar functions as their template. It was, Scott says, "a scientific best guess."

What she and DeVore reported in *Nature* is that abiraterone and TOK-001 bind to CYP17A1 quite differently than predicted. "Think of the cavity inside CYP17A1 as having a flat floor, a ceiling and walls," Scott explains. "Both drugs have a flat side that scientists thought would pack parallel to the floor, but instead the drugs are positioned against one of the walls, which also happens to be flat."

For Scott, being able to visualize CYP17A1 and how it interacts with these new drugs has shed light on "some pretty obvious ways to design drugs that better fill the cavity and bind more selectively," she says. "With abiraterone and TOK-001, there's extra space - against the cavity's other walls and up by its ceiling - that could be filled to improve these drugs. Right now it's like a size-10 person wearing size-14 clothes; the drugs don't fit as well as they could."

There are also other ways to improve these drugs, Scott adds. A variety of CYPs act on cholesterol to

produce chemical byproducts that, in stepwise fashion, get turned into different steroid hormones. CYP17A1 carries out two sequential reactions that are essential in producing androgens. However, the first reaction is also critical in yielding the appropriate amounts of other steroid hormones such as aldosterone, which affects blood pressure, and cortisol, which influences the immune system. Because abiraterone and TOK-001 block both of CYP17A1's reactions, they also substantially disrupt blood pressure and the immune response. These side effects can force some patients to discontinue treatment, or cause the therapy to fail.

"What we really need is a drug that stops only the second of CYP17A1's reactions that produce androgens, leaving other important physiological pathways unaffected," Scott says.

An engineer's perspective - looking at something that's broken to find out how it works - could yield a clue as to how this might be achieved. Some people are born with a disease in which an altered form of CYP17A1 can carry out the first - but not the second - chemical reaction needed to make androgens. This "broken" CYP17A1 helps point researchers to the precise part of the protein's machinery where new drugs should be targeted. As a result, Scott says, it should be possible to design drugs that specifically halt CYP17A1's second reaction and so affect only androgen and, ultimately, estrogen production.

Scott says that none of this research progress would have been possible without a variety of support. She credits DeVore's hard work and enthusiasm for the project; funding from the National Institutes of Health and KU's NIH-funded Center of Biomedical Research Excellence (COBRE) in Protein Structure and Function; and Chunjing Liu, a medicinal chemist working at KU's COBRE in Cancer Experimental Therapeutics, who made abiraterone - which was not commercially available at the time - for her research.

Scott is now collaborating with department colleague Jeffrey Aubé, PhD, to make improved versions of abiraterone based on what she's learned. She recently received pilot funding for this new project from The University of Kansas Cancer Center.

Even with an ideal drug for advanced prostate cancer in hand, researchers will still need to figure out how to best use it in patients. "It's an iterative process that takes time," Scott says, "but scientific progress is a series of getting better and better ideas about how things work and, in our case, then exploiting those ideas to improve human health. What we're learning about CYP17A1 could eventually make a difference in the lives of many men and women."

Right now, abiraterone adds 3.8 months, on average, to the 18-month life expectancy of patients with advanced prostate cancer. "If you've reached month 17, an extra 3.8 months sounds like an eternity," Scott says. "But it's not very much, especially if you're a patient in your 30s or 40s. We have to do better, and so we need better drugs."