SSRL Data Directs Prostate Cancer Drug Design

Prostate cancer is the most common cancer in men[1]. Incidence increases with age such that approximately 65% of U.S. men in their 60's and 80% of those in their 70's have prostate cancer[2]. Although prostate cancer can often be treated at earlier, localized stages, aggressive, high risk prostate forms are responsible for prostate cancer being the No. 2 cause of mortality in U.S. men[1]. Part of the reason for this high mortality is the lack of effective drugs to fight aggressive, metastatic prostate cancer. SSRL is helping investigators change that.

Since prostate cancer proliferates in response to the presence of androgen steroid hormones such as testosterone, blocking synthesis of such hormones is an obvious strategy to treat prostate cancer[3]. Cytochrome P450 17A1 (CYP17A1), a heme-containing monooxygenase, performs two sequential chemical reactions to generate androgens. The first new drug targeting this enzyme was approved in 2011 and has been shown to add an average of 3.9 months to the 10.9-month overall survival without the drug[4]. The active form of this drug, abiraterone, was designed by knowing the structures of the usual steroid hormone substrates of CYP17A1 and empirical medicinal chemistry approaches because of the lack of structural information about the CYP17A1 enzyme. CYP17A1 is partially embedded in membranes and the flexibility and lack of stability when the enzyme is extracted from the membrane has long frustrated attempts to discern the CYP17A1 structure. In the absence of such information, homology modeling had suggested that abiraterone, itself a molecule with a steroidal scaffold, bound in a more-or-less parallel orientation with the planar heme.

Using synchrotron facilities at the Stanford Synchrotron Radiation Lightsource, Dr. Emily Scott and Natasha DeVore from the University of Kansas solved the first structures of CYP17A1. A complex with abiraterone showed that the drug binds more perpendicular to the heme than parallel to it (Figure 1) and identified key spatial and chemical features that provide new opportunities to not only improve current steroidal drugs like abiraterone, but

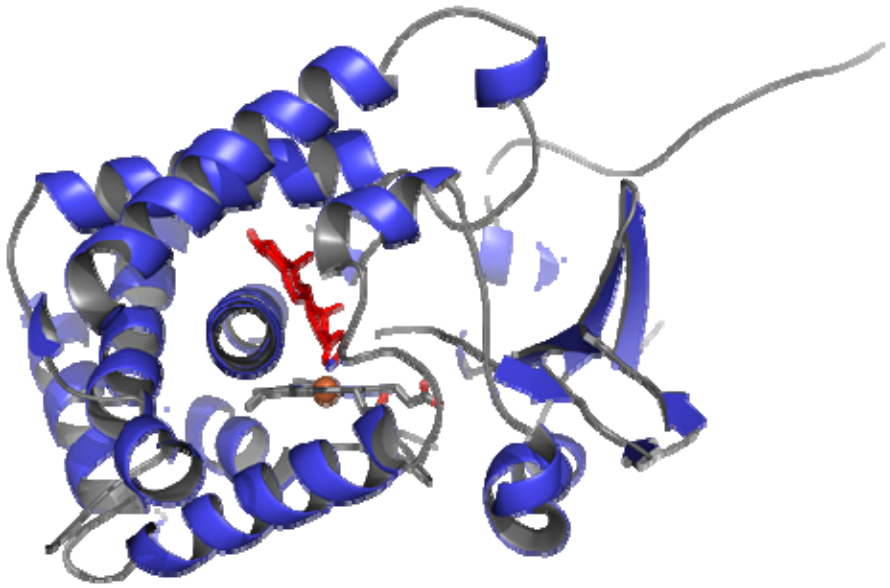

Figure 1: Scientist's first glimpse at the structure of the human cytochrome P450 17A1 (blue ribbons) demonstrated that the FDA-approved drug abiraterone acetate (Zytiga®, shown in red sticks) binds more perpendicular to the heme (grey sticks with red sphere for iron) than the parallel orientation proposed and identified key structural and chemical features that are expected to facilitate drug design efforts.

also to develop new compounds that have fewer side effects. Drugs like abiraterone block both chemical reactions that CYP17A1 accomplishes; the first reaction is a hydroxylation necessary to make not only androgens but also hormones that control blood pressure and inflammation. The second reaction is a lyase step only necessary for androgen synthesis. Thus abiraterone usually requires the co-administration of other drugs to control high blood pressure, edema, and cardiovascular effects. The new structural information provides an important starting point for ongoing studies at the University of Kansas and SSRL to determine how the two different reactions are controlled, which will facilitate the design of new drugs that halt only androgen production and provide new avenues for prostate cancer patients.

Primary Citation

DeVore, N.M. and Scott, E.E. (2012) Cytochrome P450 17A1 structures with prostate cancer drugs abiraterone and TOK-001. *Nature* 482:116-119.

References

1. American Cancer Society. (2012) Cancer Facts & Figures 2012. Atlanta: American Cancer Society.
2. Haas, G.P., Delongchamps, M.D., Brawley, O.W., Wang, C.Y., and de la Roza, G. (2008) The worldwide epidemiology of prostate cancer: Perspectives from Autopsy Studies. Can J Urol 15:3866-3871.
3. Bruno, R.D. and Njar, V.C. (2007) Targeting cytochrome P450 enzymes: a new approach in anti-cancer drug development. Bioorg Med Chem, **15**:5047-5060.
4. de Bono, J.S. et al. (2011) Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 364:1995-2005.

SSRL is primarily supported by the DOE Offices of Basic Energy Sciences and Biological and Environmental Research, with additional support from the National Institutes of Health, National Institute of General Medical Sciences and the National Center for Research Resources.