Developing Novel Therapeutics for Prostate Cancer

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Objective

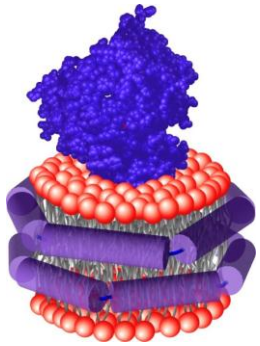
Prostate cancer (PC) is the most commonly diagnosed malignant neoplasm among the American male population and represents the second most common cancer among men worldwide. Recently, CYP17A1 has been identified as a potent target for inhibition in the treatment of advanced prostate cancer. By solubilizing this membrane protein using the Nanodisc system and thus rendering it amenable to interrogation by spectroscopic and surface based analytical platforms, we seek to identify mechanism based inhibitors for this and other steroidogenic P450 enzymes.

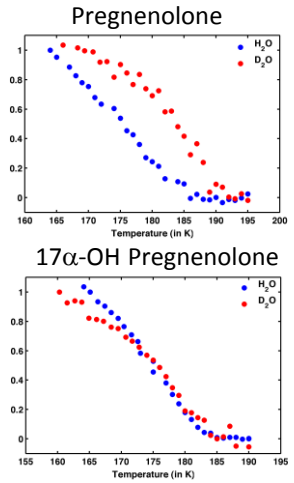
Research Highlights

- A high-pressure instrument has been adapted to interface with BIND biosensors, permitting investigation of protein-protein interactions at up to 3 kbar.
- Detailed resonance Raman investigations have been conducted that have identified the the alcohol on C-17 of hydroxylated substrates forms a hydrogen bond with the oxy-complex of CYP17.
- Cryoradiolysis of the CYP17 oxy-complex has been employed to successfully generate the peroxo-ferric intermediate, and the decay kinetics of this species in H_2O and D_2O buffer systems was found to be isotopically sensitive in the presence of pregnenolone, but not 17α-hydrxoxypregnenolone, suggesting involvement of a novel reaction intermediate in CYP17 catalyzed C-C lyase chemistry.

Future Research

- Future research will focus on further adapting the BIND biosensor to high pressure studies of protein-protein interactions, as well as continuing our commitment to interrogation of the key reaction intermediates that give rise to CYP17's unique C-C lyase activity that represents the first committed step of androgen formation.





The above figures show a kinetic solvent isotope effect during annealing of the peroxo-ferric intermediate in the presence of pregnenolone, but not in the presence of 17a-hydroxypregnenolone (right), and CYP17 incorporated into a Nanodisc (left), a membrane mimetic that enables rigorous biophysical interrogations of membrane bound proteins.