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### Post-doctoral Research Projects

**Molecular basis for anti-malarial drug resistance in the bc<sub>1</sub> complex-** Hydroxyquinones such as atovaquone are used therapeutically to treat *Plasmodium falciparum* malaria and *Pneumocystis jirovecii* pneumonia. These compounds act by binding to the ubiquinol oxidation site at center P in the bc<sub>1</sub> complex. The purpose of this project is to understand how mutations in cytochrome b allow these pathogens to become resistant to hydroxyquinones.

**Proton conduction pathways in the bc<sub>1</sub> complex-** In the Q cycle mechanism protons are carried across the membrane as hydrogen's on the quinol. However, the linkage of proton chemistry to electron transfer during quinol oxidation and quinone reduction requires pathways for moving protons to and from the aqueous phase and the hydrophobic environment in which the quinol and quinone redox reactions occur. The purpose of this project is to identify the amino acids that form these proton conducting channels.

**Structural basis for negative cooperativity in the bc<sub>1</sub> complex-** Anti-cooperative binding of inhibitory structural analogs of ubiquinol and half-of-the-sites reactivity during ubiquinol oxidation imply that binding of ligands in the ubiquinol oxidation pocket at center P in one monomer of the bc<sub>1</sub> dimer causes a conformational change at center P in the other monomer. The purpose of this project is to identify the amino acids that transmit that conformational change.

**Relationship between semiquinone stability and rate of quinone reduction in the bc<sub>1</sub> complex-** In the protonmotive Q cycle mechanism, reduction of ubiquinone at center N involves a semiquinone intermediate that is sufficiently stable to be EPR detectable. It is not known how stable the semiquinone must be in order to be a kinetically competent intermediate. The purpose of this project is to investigate the relationship between semiquinone stability and rate of ubiquinone reduction by investigating rates of cytochrome b<sub>H</sub> oxidation/reduction through center N when semiquinone stability is altered by mutations in cytochrome b.

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Positions are available to work on the post-doctoral research projects described above. These positions provide training in bioenergetics, protein biochemistry, enzyme kinetics, and yeast molecular biology, with particular emphasis on structural biology and molecular modeling. Individuals interested in learning more about these projects may contact me by phone or e-mail, and may learn more about our laboratory by visiting our lab web-site.

Yours truly,

*Bernard L. Trumpower*