Structural Studies of Thioredoxins and Associated Inhibitor Based Complexes

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The thioredoxin redox system is ubiquitous in all living cells and is used as a sophisticated mechanism for maintaining an intracellular reduced state. The redox proteins are also known to be important in a multitude of biological functions, including controlling cell cycle regulation, and studies in various human malignancies and cell lines in *vitro* have shown an up regulation of thioredoxin, demonstrating a definite link between thioredoxin and cancer [1], [2].

There are currently two novel heteroaromatic quinol inhibitors under development at the Cancer Research Laboratories of the University of Nottingham. These inhibitors are thought to have a novel mode of action leading to an irreversible binding of the inhibitor to the active site, thus irreparably inactivating the protein.

The research group has obtained the crystal structures of *Tuberculosis Bacterium* and human thioredoxins. By studying the crystal structure of thioredoxin-inhibitor complex it will be possible to apply structure-activity relationships and thus enable the research group to not only understand how these quinols block the activity of thioredoxin, but also to develop these drugs with the intention of improving their affinity for the binding site.

[1] Arrigo A.P., *Free Radical Biol. and Med.,* 1999, **27 (9/10)** 936. [2] Soini Y., et al., *Clinical Can. Res.,* **7**, 1750.

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