**Structural Studies of Glutathione S-transferase Inhibitors – A Promising Target for Anti-cancer Drug Design**

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Glutathione S-Transferases (GSTs), phase II detoxification enzymes, primarily function to detoxify unwanted toxic compounds in the cell [1]. They are, however, overexpressed in many cancers and shown to be deleterious to cancer chemotherapy's success by reacting with certain anti-cancer drugs. GSTs, therefore, have been identified as an attractive target for inhibitor drug design to increase the efficacy of treatment [2].

Drug resistance remains a limiting factor in cancer chemotherapy and thus understanding the mechanisms of this effect represents an essential step in improving cancer treatment. There are many reports correlating over-expression of GST and reduced sensitivity to chemotherapy in lung, liver, breast, ovarian, and other forms of cancer[1]. GSTs are hypothesized to catalyse conjugation of GSH to anticancer drugs forming inactive conjugates, therefore, decreasing efficacy in treatment. The precise mechanisms responsible for the development of resistance to these commonly used anti-cancer agents is currently unknown. Gaining insight, through structural studies by X-ray crystallography, of this enzyme complexed to these compounds, will aid in the design of effective, and specific, inhibitors.

One of the major aims of this work is to determine the 3D structures of these complexes and subsequently pursue structure-based drug design of human GST pi class enzyme (hGSTP1-1) with the hope of discovering potent specific inhibitors. I have collected over 25 data sets of GST complexed to a range of compounds, several of which have been solved and the structures completed. The structure of the hGSTP1-1 in complex with these compounds will identify critical residues which will aid drug design of novel, therapeutic, GST inhibitors.

[1] Sheehan D., et al., *Biochem. J*., 2001, **360**, 1. [2] Farmer G., *Nature Rev. Drug. Discov.,* 2004, **3**, 547.

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