# Researchers unveil vital key to cancer

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University of Manchester scientists have uncovered the 3-D structure of Mps1 -- a protein that regulates the number of chromosomes during cell division and thus has an essential role in the prevention of cancer -- which will lead to the design of safer and more effective therapies.

Mps1 belongs to the family of proteins called kinases. When subsets of these enzymes become deregulated, cancer can be one of the outcomes – making them a critical target for research by oncologists.

Over 100 of the 500 or so kinases have been shown to be associated with cancer, but so far scientists only know the 3D structure of a handful. Knowing the structure is critical for the design of new kinase inhibitors as therapeutic agents, an area of enormous importance to the pharmaceutical industry. Over 100 kinase inhibitors are currently in clinical trials, and the revolutionary kinase inhibitor Glivec was approved for treating Leukaemia in the UK in 2001.

Mps1 is particularly important as it controls a 'checkpoint' that cells use to encourage accurate chromosome sorting during mitosis. Mps1 therefore prevents aneuploidy, the change in the number of chromosomes that is closely associated with cancer.

Dr Patrick Eyers and his team, including Hong Kong-born PhD student Matthew Chu, used the Diamond Light synchrotron, a "super-microscope" that works by speeding electrons around a huge doughnut-shaped chamber the size of five football pitches until they are travelling so fast they emit high energy particles. The X-rays were "fired" at a pure

sample of the protein, allowing the researchers to "see" the protein's atomic structure for the first time.

Their structure revealed the pocket where Mps1 binds to ATP, the natural substrate from which Mps1 transfers a phosphate group to its cellular target proteins. Further work showed the protein in complex with the ATP-competitive inhibitor SP600125, a well-known but non-specific inhibitor of many kinases, which revealed a secondary pocket not utilised by this compound. If a next-generation drug can be designed to specifically block this secondary pocket, it is hoped that Mps1 will be specifically disabled, killing rapidly dividing cells such as those found in tumours.

The team hopes its work will allow chemists to design an anti-cancer drug with fewer side effects, allowing scientists to assess the relative importance of Mps1 inhibition in different disease indications, including those that are currently hard to treat such as lung and pancreatic cancers.

Dr Eyers, whose findings are published in the Journal of Biological Chemistry (August 2008), said: "The crystallalographic structures of only a few key "mitotic" kinases are currently known so we are very early in the game. The scientific community has high hopes for developing novel "anti-mitotic" cancer therapies using this method of structure-based drug design.

"Mps1 is a rational target because of its critical role in preventing aneuploidy. We wanted to see what this protein looked like at the molecular level and, by revealing the active site "lock", help design a new inhibitory "key" to physically block the ATP-binding site.

His colleague Dr Lydia Tabernero added: "This work presents the first crystallographic structure of human Mps1, an important regulator of chromosomal stability and a potential target in cancer therapy. Our

research has revealed several important structural features and additional binding sites that could be exploited for the development of specific Mps1 inhibitors."

Source: University of Manchester