# Astex Scientists Solve Structure of Cyclin Dependent Kinase 4

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Astex Therapeutics Limited, the leading fragment based drug discovery company, today announced that its scientists have published the first 3-dimensional structure of cyclin-dependent kinase 4 (CDK4) a key enzyme involved in cell cycle control and implicated in the progression of a number of different forms of cancer. The crystal structure of CDK4 in complex with a regulatory D-type cyclin is reported in the leading science journal Proceedings of the National Academy of Sciences (PNAS)†. Although X-ray crystallographic structures have been determined for various cyclin-dependent kinase - cyclin complexes, the cyclinD1-CDK4 complex has remained highly refractory to structure determination and this has severely limited the potential to design selective inhibitors of the enzyme to test as potential new therapies for the treatment of cancer.

“The crystal structure of CDK4 was determined as part of our successful cell cycle drug discovery programme,” said Dr Harren Jhoti, Astex’s Chief Executive Officer. “The insights provided by this new discovery will help us to design a new generation of selective inhibitors of this critical enzyme. By using the 3-dimensional structure of CDK4 to explore how drug compounds bind to and inhibit the action of the enzyme, we will be able to use rational drug design to identify novel therapeutics with potential in the treatment of a number of important diseases.”

† Philip J. Day, Anne Cleasby, Ian J. Tickle, Marc O'Reilly, Joe E. Coyle, Finn P. Holding, Rachel L. McMenamin, Jeff Yon, Rajiv Chopra, Christoph Lengauer, Harren Jhoti, Crystal structure of human CDK4 in complex with a D-type cyclin. PNAS 23 Feb 2009 (doi:10.1073/pnas.0809674106)

Editor's Notes

Astex Therapeutics

Astex is a UK-based biotechnology company that discovers and develops novel small molecule therapeutics. Using its pioneering fragment-based drug discovery platform Pyramid™, Astex has built a pipeline of five molecularly targeted oncology drugs, of which three are currently being tested in clinical trials and two are in pre-clinical development.

In addition to its proprietary research programmes, Astex’s productivity in lead discovery has been endorsed through numerous partnerships with major pharmaceutical companies, including AstraZeneca, Bayer-Schering, Boehringer Ingelheim, Novartis and Johnson and Johnson.

For further information on Astex please visit the Company’s website at www.astex-therapeutics.com

About CDK4

Cyclin-dependent kinases (CDKs) are a conserved family of serine/threonine kinases that perform critical roles in regulating the step-wise progression through the eukaryotic cell cycle. The activity of CDKs is regulated through phosphorylation by other upstream kinases such as CDK Activating Kinases (CAKs) and most significantly by interaction with cyclins. In turn CDK-cyclin complexes are inhibited through the reversible binding of CDK inhibitors from the Cip/Kip and INK protein families, as well as through the cyclical degradation of cyclins during the cell cycle.

The cyclin D1-CDK4 complex regulates a key checkpoint during the G1/S transition phase of the cell-cycle. As a consequence, aberrant regulation of the CDK4-cyclinD1 pathway plays an important role in oncogenesis. Indeed over 90% of human tumours are characterized by dysregulation at the G1/S transition point. Inhibition of CDK4 therefore represents an attractive and biologically validated therapeutic approach to the treatment of cancer. Although X-ray crystallographic structures have been determined for various CDK-cyclin complexes, CDK4-cyclinD1 has remained highly refractory to structure determination. Here we report the first crystal structure of CDK4 in complex with cyclinD1.

Dysregulation of the CDK4-cyclinD pathway has been identified in many cancers. The CDK4 gene is amplified in a high percentage of liposarcomas, and breast cancers frequently exhibit high cyclin D1 levels, either through genetic amplification of the gene or due to overexpression. Translocation of cyclin D1 to the IgH promoter is a hallmark aberration in mantle cell

lymphoma. CyclinD1 translocations can also be detected in many cases of multiple myelomas. A mutation of CDK4 (Arg24Cys) that renders it refractory to inhibition by the tumour suppressor protein p16INK4a has also been identified and similarly, deletion or mutation of the p16INK4a gene results in defective CDK4 inhibition and dysregulated CDK4 activity. Finally, genetic inactivation of p16ink4 is among the most frequent tumor suppressor mutations found in human cancers. Taken together, these data indicate that an unchecked or hyperactivated CDK4-cyclinD1 pathway may be responsible for enhanced cellular proliferation in many cancers, and imply that CDK4 is a promising target for the development of anti-cancer therapies.