

	<b>Experiment title:</b> Crystal structures of the CDK5-p25 kinase with bound inhibitors	<b>Experiment number:</b> MX-267 MX-394
<b>Beamline:</b>  ID14-1 BM16 ID14-2	<b>Date of experiment:</b>  from: 28/07/2004 to: 30/07/2004 from: 10/02/2005 to: 11/02/2005 from: 07/05/2005 to: 09/05/2005	<b>Date of report:</b> 24/07/2005
<b>Shifts:</b>  6	<b>Local contact(s):</b> Elspeth GORDON, Gavin FOX, Petra PERNOT	<i>Received at ESRF:</i>
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## Report:

The cyclin-dependent kinases (CDK) CDK1, CDK2, CDK4, and CDK6 are serine/threonine protein kinases targeted in cancer therapy due to their role in cell cycle progression. The postmitotic CDK5 is involved in biological pathways important for neuronal migration and differentiation. CDK5 represents an attractive pharmacological target as its deregulation is implicated in various neurodegenerative diseases such as Alzheimer's, Parkinson's, and Niemann-Pick type C diseases, ischemia, and amyotrophic lateral sclerosis. We have generated an improved crystal form of CDK5 in complex with p25, a segment of the p35 neuronal activator. The crystals were used to solve the structure of CDK5/p25 with (*R*)-roscovitine and aloisine at a resolution of 2.2 and 2.3 Å, respectively. The structure of CDK5/p25/roscovitine provides a rationale for the preference of CDK5 for the *R* over the *S* stereoisomer. Furthermore, roscovitine stabilized an unusual collapsed conformation of the glycine-rich loop, an important site of CDK regulation, and we report an investigation of the effects of glycine-rich loop phosphorylation on roscovitine binding. The CDK5/p25 crystals represent a valuable new tool for the identification and optimization of selective CDK inhibitors.

## References:

Ahn JS, Radhakrishnan ML, Mapelli M, Choi S, Tidor B, Cuny GD, Musacchio A, Yeh LA, Kosik KS. (2005) Defining Cdk5 Ligand Chemical Space with Small Molecule Inhibitors of Tau Phosphorylation. *Chem. Biol.* **12**, 811-823

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