X	**Experiment title:** **Crystal structures of the CDK5-p25 kinase with bound inhibitors**	**Experiment number**: MX-129
Beamline: ID14-2 ID14-2	**Date of experiment**: from: 13/03/2003 to: 13/03/2003 from: 10/07/2003 to: 10/07/2003	**Date of report**: 28/08/2003
Shifts: 1 1	**Local contact(s)**: Joanne MCCARTHY Stephanie MONACO	*Received at ESRF:*

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Report:

Background

CDK5 is a Cyclin-dependent Ser/Thr kinase acting in the central nervous system (CNS). Its activity requires the interaction with a protein known as p35. Deregulation of CDK5 activity as a consequence of proteolytic processing of the p35 sununit to a p25 moiety containing the C-terminal portion of p35 has been reported. It is deemed that CDK5 deregulation is important for the development of neuro-degenerative diseases such as amyotrophic lateral sclerosis and Alzheimer's disease. We have previously reported the crystal structure of the CDK5-p25 heterodimer (Tarricone et al, 2001). We are currently concentrating on the study of crystal structures of the heterodimeric enzyme with known and newly identified inhibitors of CDK5, to understand their mode of action, and to identify possible differences with other CDK-inhibitor interaction that may lead to the development of selective inhibitors.

Results

We have determined the crystal structures of several CDK inhibitors bound to the active site of CDK5, using a trigonal crystal form with greatly improved properties relative to the initially identified monoclinic crystal form (Tarricone et al 2001). A manuscript describing the refined structures of three complexes of CDK5-p25 with small molecule inhibitors (Indirubin, Roscovitine, Aloisine) has been submitted for publication. We have also started a collaboration with the group of Ken Kosick (Harvard Medical School, Boston, USA)

aimed at identifying non-active site inhibitors of this kinase, and at characterizing the crystal structures of the most promising leads. Dataset from a first batch of these inhibitors have been collected.

References

Tarricone C, Dhavan R, Peng J, Areces L, Tsai L-H, and Musacchio A (2001) Structure and regulation of the CDK5-p25 complex, *Molecular Cell* **8***,* 657-669

Mapelli M, Tsai L-h, Meijer L, and Musacchio A. Crystal structures of the CDK5-p25 complex bound to classical and non-classical cyclin-dependent kinase inhibitors, submitted

Short summary of collected data

CDK5-p25 with Aloisine
Space Group $P3_221$
Unit cell (Å) $a=b=117.5$, $c=156.8$
Resolution (Å) 35.0-2.3

CDK5-p25 with Aloisine
Space Group $P3_221$
Unit cell (Å) $a=b=117.5$, $c=156.8$
Resolution (Å) 35.0-2.3

CDK5-p25 with Inhibitors 1, 2, and 3
Space Group $P3_221$
Unit cell (Å) $a=b=117.5$, $c=156.8$
Resolution (Å) 35.0-2.3