ESRF	**Experiment title:** Crystal structures of the CDK5-p25 kinase with bound inhibitors and substrate peptides	**Experiment number**: **LS2183**
Beamline: ID14-2 ID14-2	**Date of experiment**: from: 17-07-02 to: 18-07-02 31-08-02 to: 02-09-02	**Date of report**: 5 September 2002
Shifts: 3 6	**Local contact(s)**: Elena Micossi Joanne McCarthy	*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. Furthemore, we would like to be able to raise crystals of the CDK5-p25 complex with peptide ligands. The existente of co-crystals of the kinase with substrates will shed

light on the mechanisms of substrate recognition by this kinase, which are believed to be rather different from those of other known CDKs.

Results

The most relevant recent endeavor in this project was the identification of a new trigonal crystal form with greatly improved properties relative to the initially identified monoclinic crystal form. The trigonal form diffracts at significantly higher resolution (up to 2.0 Å) and the overall quality of the diffraction pattern is remarkably increased for what concerns spot shape and mosaicity. The identification of the new crystal form allowed the collection of several datasets of CDK5-p25 in the presence of inhibitors and peptide substrates. A list of datasets collected is reported here. Data processing and crystal structure determination of the corresponding inhibitors bound to the CDK5 kinase is underway.

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

Short summary of collected data

CDK5-p25-MeridianinE (1)
Space Group $P3_221$
Unit cell (Å) $a=b=117.6$, $c=156.6$
Resolution (Å) 35.0-2.3

CDK5-p25-MeridianinE (2)
Space Group $P3_221$
Unit cell (Å) $a=b=117.5$, $c=156.8$
Resolution (Å) 35.0-2.0

CDK5-p25-MeridianinE-Tau peptide
Space Group $P3_221$
Unit cell (Å) $a=b=117.3$, $c=156.4$
Resolution (Å) 35.0-2.0

CDK5-p25-MeridianinE-DARPP32 peptide
Space Group $P3_221$
Unit cell (Å) $a=b=117.1$, $c=156.5$
Resolution (Å) 35.0-2.1

CDK5-p25-alsterpaullone
Space Group $P3_221$
Unit cell (Å) $a=b=117.4$, $c=156.8$
Resolution (Å) 35.0-2.3

CDK5-p25-Hymenialdisine
Space Group $P3_221$
Unit cell (Å) $a=b=117.4$, $c=156.5$
Resolution (Å) 35.0-2.2

CDK5-p25-ADP-PNP
Space Group $P3_221$
Unit cell (Å) $a=b=117.2$, $c=156.9$
Resolution (Å) 35.0-2.2