X	**Experiment title:** **Italian Bag 1: Crystal structure of the Lissencephaly type dimer in complex with PAF-AH α2/α2 homodimer**	**Experiment number**: MX-129
Beamline: ID14-2 ID29	**Date of experiment:** from: 15/05/2003 to: 15/05/2003 from: 21/06/2003 to: 21/05/2003	**Date of report**: 24/06/2004
Shifts: 1	**Local contact(s)**:	*Received at ESRF:*

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Report:

Mutations in the *LIS1* gene cause lissencephaly, a human neuronal migration disorder. LIS1 binds dynein and the dynein-associated proteins NudE, NUDEL, and CLIP-170, as well as the catalytic α dimers of brain cytosolic platelet activating factor acetyl hydrolase (PAF-AH). The mechanism coupling the two diverse regulatory pathways remains unknown. We report the structure of LIS1 in complex with the α_2/α_2 PAF-AH homodimer. One LIS1 homodimer binds symmetrically to one α_2/α_2 homodimer via the highly conserved top faces of the LIS1 β-propellers. The same surface of LIS1 contains sites of mutations causing lissencephaly, and overlaps with a putative dynein-binding surface. NUDEL competes with the α_2/α_2 homodimer for LIS1, but the interaction is complex and requires both the N- and C-terminal domains of LIS1. Our data suggest that the LIS1 molecule undergoes major conformational rearrangement when switching from a complex with the acetylhydrolase to the one with Nudel.

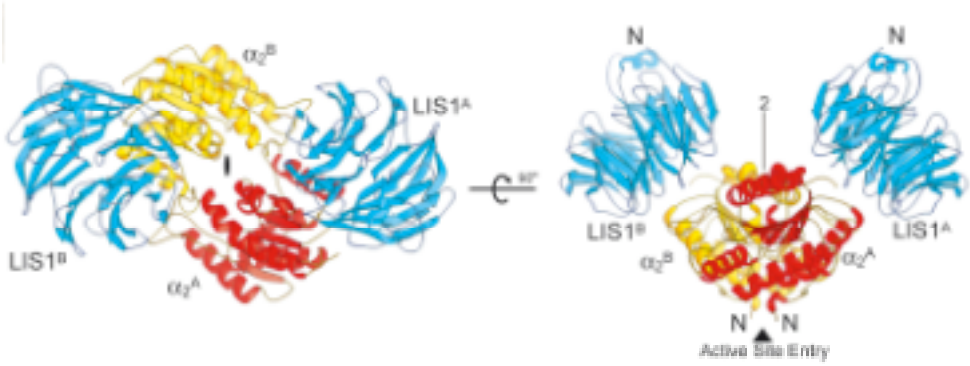

Figure 1 The Lis1$_2$/α_2 tetramer. Lis1 is blue, and the protomers in the α_2 dimer are yellow and red. The tetramer has 2-fold symmetry and the two views represent 90º rotations around the indicated axis.

References

Cataldo Tarricone, Franco Perrina, Silvia Monzani, Lucia Massimiliano, Myung-Hee Kim, Zygmunt S. Derewenda, Stefan Knapp, Li-Huei Tsai, & Andrea Musacchio (2004) Coupling PAF signaling to dynein regulation: structure of LIS1 in complex with PAF-acetylhydrolase, *submitted*