Experiment title	**Crystal structure of the human mineralocorticoid receptor ligand-binding domain**
Experiment number	**30-01-636**
Date of experiment	**1th - 3 April 2003**

The mineralocorticoid hormone aldosterone plays an important role in sodium homeostasis and in the regulation of blood pressure. Alterations of this regulation are associated with several pathologies (hypertension, cardiovascular diseases, heart failure). Aldosterone produces its effects through the mineralocorticoid receptor (MR) which is a ligand-activated transcription factor. Aldosterone antagonists bind to MR with the same affinity as aldosterone but maintain the receptor in an inactive conformation (1). Aldostérone and its antagonists binding site is located at the C-terminal domain of the MR, the ligand-binding domain (LBD). In the context of this project, we investigated first the structural study of the complex between deoxycorticosterone (a potent mineralocorticoid agonist) and the hMR_{LBD} that carry two point-mutations able to enhance the protein solubility.

Crystallization assays for the hMR_{LBD} resulted in reproducible cubs of about 300 µ. The protein crystallizes in the P31 space group with cell parameters a = 120.28 Å, b = 120.28 Å, c = 41.33 Å and $\alpha = \beta = 90.0$ °, $\gamma = 120.0$.

During the 30-01-636 experiment, two complete native data sets have been collected to 2.5 and 2.05 Å resolution (oscillation range 1°, 60 sec exposition). The statistics of the data collection for the best one are summarized in Table I.

Table I. Statistics of data collection.
The values in parenthesis are for the highest resolution shell (2.1-2.05 Å)

Resolution (Å)	2,05
wavelength (Å)	0.98
No. of observations	134236
No. of unique reflections	41704
R_{sym} (%)	7.9 (27,1)
Multiplicity	3.2 (2.7)
Completeness (%)	99.4 (98.8)
$I / \sigma (I)$	6.7 (2.5)

Molecular replacement in the $P3_1$ space group, using a truncated three-dimensional homology model of the hMR_{LBD} (ref), gave two clear solutions in the rotation function which are related

by a two fold symmetry axis. For each rotation solution, three translation solutions were found consisting in a cell composed of three translated monomers per asymmetric unit. The self rotation function suggested a two fold symmetry axis that was incompatible with the molecular replacement solutions.

Twinning analysis of the data in CNS, revealed a high twinning factor with the matrix (h, -h -k, -l) that agrees with an apparent supplementary two fold axis. Detwinning the data gave R factors around 34%. Refinement of the model is now in process.