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Laboratory of Structural Biology

Protein crystallography, HIV protease, antibody engineering

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Research topics

The Laboratory carries out structural work with various proteins of biological or medicinal interest. Among them, HIV protease, antibody fragments and galectins take a prominent position.

The HIV protease (HIV PR) research is focused on development of novel potent inhibitors as well as on understanding the structural basis of drug resistance acquired by mutations in HIV PR itself, in its target sites and elsewhere in the HIV polyproteins.

The antibodies include the antibody M75 (in Fab or scFv formats) specific to human carbonic anhydrase IX, a carcinoma marker. Several other antibody fragments of potential diagnostic and/or immunotherapeutic use (e.g. against CD20, CD44, CD3) have been cloned, expressed, purified and characterized in our laboratory with the aim to improve their radionuclide labelling or to introduce further useful properties.

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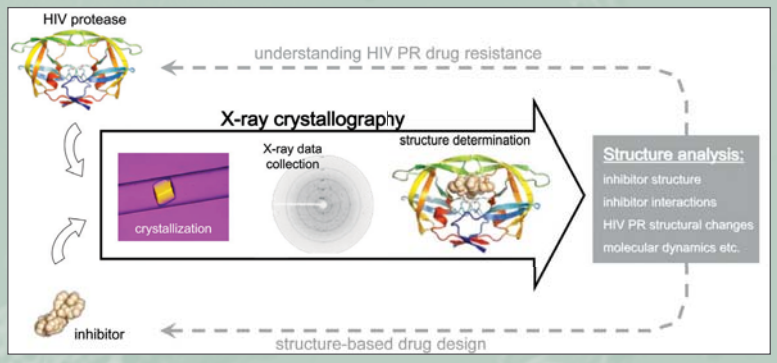
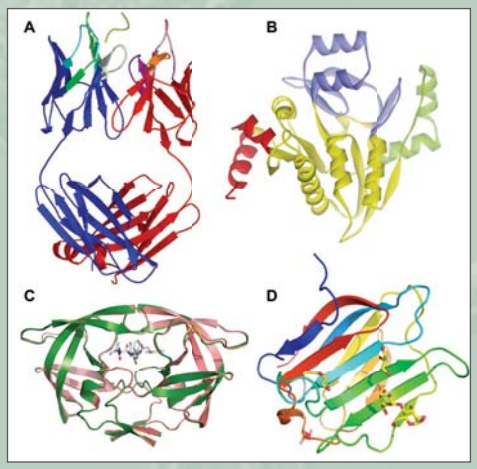
Selected recent papers

1. Krejčiříková V, Fábry M, Marková V, Malý P, Řezáčová P, Brynda J. Crystallization and preliminary X-ray diffraction analysis of mouse galectin-4 N-terminal carbohydrate recognition domain in complex with lactose. **Acta Cryst F.** 2008;64:665-667.
2. Řezáčová P, Kožíšek M, Moy SF, Sieglová I, Joachimiak A, Machius M, Otwinowski Z. Crystal structures of the effector-binding domain of repressor CggR from Bacillus subtilis reveal ligand-induced structural changes upon binding of several glycolytic intermediates. **Mol Microbiol.** 2008;69:895-910.
3. Kožíšek M, Šašková KG, Řezáčová P, Brynda J, van Maarseveen NM, De Jong D, Boucher C, Kagan R, Nijhuis M, Konvalinka J. Ninety nine is not enough: molecular characterisation of drug-resistant HIV-protease mutants with insertions in the flap region yielding resistance to protease inhibitors. **J Virol.** 2008;82:5869-5878.
4. Bartoňová V, Král V, Sieglová I, Brynda J, Fábry M, Hořejší M, Kožíšek M, Šašková KG, Konvalinka J, Sedláček J, Řezáčová P. Potent inhibition of drug-resistant HIV protease variants by monoclonal antibodies. **Antiviral Res.** 2008;78:275-277.
5. Král V, Mader P, Collard R, Fábry M, Hořejší M, Řezáčová, P, Kožíšek M, Závada J, Sedláček J, Rulíšek L, Brynda J. Stabilization of antibody structure upon association to a human carbonic anhydrase IX epitope studied by X-ray crystallography, microcalorimetry, and molecular dynamics simulations. **Proteins.** 2008;71:1275-1287.



A schematic depicting of individual steps involved in structural studies of HIV PR-inhibitor complexes. X-ray crystallography method is used to determine three-dimensional structures of HIV PR in complex with inhibitory compounds. Structural information is used to explain the mechanism of HIV resistance as well as for the structure-based drug design of novel inhibitory compounds.



*Selected crystal structures published in 2008: **A.** Fab fragment of anti-carbonic anhydrase IX antibody [ref. 5], **B.** the effector-binding domain of repressor CggR from Bacillus subtilis [2], **C.** HIV-1 protease with insertion E35EE [3], **D.** mouse galectin-4 carbohydrate recognition domain [1].*