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Laboratory of Structural Biology

Protein crystallography, HIV protease, antibody engineering

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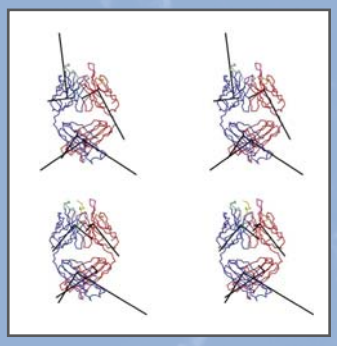

Global stabilization of the complex structure: changes in principal axes of the libration tensors for Fab M75 domains (VH, VL, CH, and CL) superimposed to stereo views of the crystal structures. Shown are Cα traces of the free Fab (upper block) and of the complex (lower block). The heavy chain is coloured mainly blue, the light chain mainly red, the epitope peptide yellow, the libration axes black.

Research topics

The Laboratory carries out structural work with various proteins and their complexes of biological or medicinal interest. Among them, HIV protease, antibodies and galectins take a prominent position. The HIV protease (HIV PR) research is focused onto 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. Also carried out is protein engineering work with therapeutic antibodies aimed to improve their radionuclide labelling or to introduce further useful properties.

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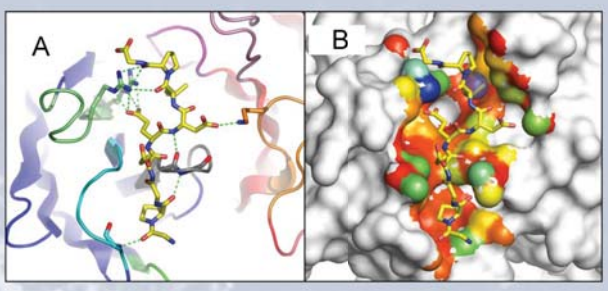
Selected recent papers

1. Cígler P, Kožíšek M, Řezáčová P, Brynda J, Otwinowski Z, Pokorná J, Plešek J, Grüner B, Dolečková-Marešová L, Máša M, Sedláček J, Bodem J, Kraeusslich H-G, Král V, Konvalinka J. From non-peptide towards non-carbon protease inhibitors: metallacarboranes as specific and potent inhibitors of HIV protease. **Proc Natl Acad Sci USA.** 2005;102:15394-9.
2. Dušková J, Dohnálek J, Skálová T, Petroková H, Vondráčková E, Hradílek M, Konvalinka J, Souček M, Brynda J, Fábry M, Sedláček J, Hašek J. On the role of the R configuration of the reaction-intermediates isostere in HIV-1 protease-inhibitor binding: X-ray structure at 2.0 A resolution. **Acta Crystallogr D Biol Crystallogr.** 2006;62(Pt 5):489-497.
3. Ondráček J, Mesters JR. An ensemble of crystallographic models enables the description of novel bromate-oxonian species trapped within a protein crystal. **Acta Crystallogr D Biol Crystallogr.** 2006;69 (Pt 9):996-1001.
4. Carey J, Brynda J, Wolfova J, Grandori R, Gustavsson T, Ettrich R, Smatanova IK. WrbA bridges bacterial flavodoxins and eukaryotic NAD(P)H:quinone oxidoreductases. **Protein Sci.** 2007;10:2301-5.
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.** Epub Nov 27,2007.



Structure of the antibody M75 combining site; the carbonic anhydrase IX epitope peptide, PGEEDLPGEEDL, is shown with the sticks model coloured yellow. Panel A: Hydrogen bonds formed between the antibody and the epitope peptide. Respective CDR loops are coloured blue/green for the heavy chain and magenta/mauve for the light chain. Panel B: Areas of protein surface at van der Waals radii buried upon the peptide binding; rainbow colouring from yellow (0<Å²) to blue (40 Å²); white (0 Å²).