Laboratory of Structural Biology

Protein crystallography, HIV protease, human carbonic anhydrase IX, antibody engineering

Pavlína Řezáčová

pavlina.rezacova@img.cas.cz

www.img.cas.cz/research-groups/pavlina-rezacova

The main interests of our group are structural studies of various proteins of biological or medicinal interest using the method of protein crystallography. We use the structural knowledge to understand the protein function and in some projects also in modulating its function by design of specific inhibitors.
In our structure-based drug discovery project, we target enzymes from pathogenic organisms as well as human enzymes (e.g. human nucleotidases or cancer-specific carbonic anhydrase IX); the knowledge of protein structures provides a platform for the rational design of specific inhibitors.
Our group also focuses on engineering recombinant antibody fragments of potential diagnostic use. We employ several approaches aiming at practical use of recombinant antibody fragments.

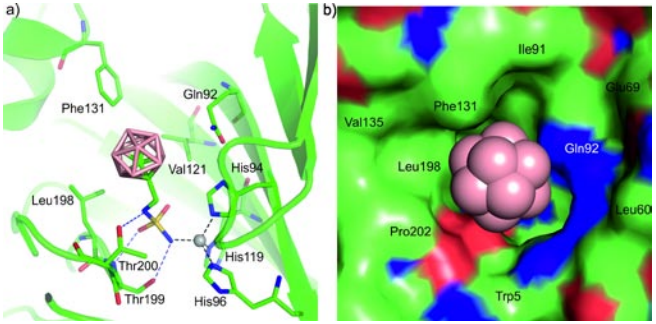

Fig. 1. Carborane-based inhibitors of human carbonic anhydrase IX were designed using a structure-based approach (reference 4).

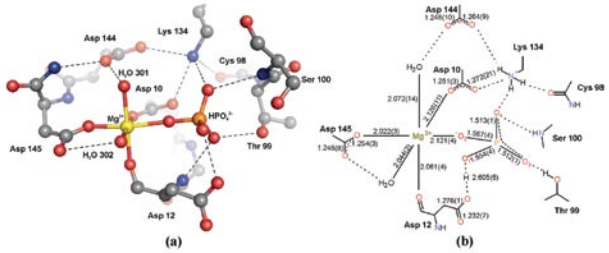

Fig. 2. High-resolution crystal structures of mitochondrial and cytosolic 5'-deoxyribonucleotidases with active site phosphate ions were used to estimate phosphate protonation and investigate differences in the active sites. These findings were applied to the design of a specific inhibitor (reference 2).

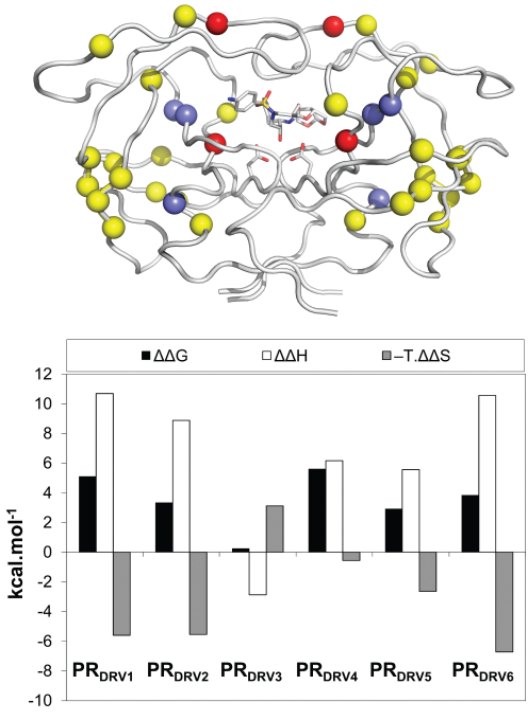

Fig. 3. Thermodynamic and structural analysis of HIV protease resistance to clinically used drug darunavir: analysis of heavily mutated patient-derived HIV-1 proteases (reference 3).

- TACR, TA02010797 – Labelling of recombinant antibody fragments with use of microfluidic systems, 2012-2014, J. Sedláček
- GACR, GA203/09/0820 – Structure-based drug design of specific nucleotidase inhibitors, potentially pharmacologically important compounds, 2009-2013, J. Brynda

1. Snášel J, Nauš P, Dostál J, Hnízda A, Fanfrlík J, Brynda J, Bourderioux A, Dušek M, Dvořáková H, Stolaříková J, Zábranská H, Pohl R, Konečný P, Džubák P, Votruba I, Hajdúch M, Řezáčová P, Veverka V, Hocek M, Pichová I: Structural basis for inhibition of mycobacterial and human adenosine kinase by 7-substituted 7-(het)aryl-7-deazaadenine ribonucleosides. **J Med Chem 2014** 23;57(20):8268-79.
2. Pachl P, Fábry M, Rosenberg I, Simak O, Řezáčová P, Brynda J: Structures of human cytosolic and mitochondrial nucleotidases: implications for structure-based design of selective inhibitors. **Acta Crystallogr D Biol Crystallogr 2014** Feb;70(Pt 2):461-70.
3. Kožíšek M, Lepsik M, Grantz-Saskova K, Brynda J, Konvalinka J, Řezáčová P: Thermodynamic and Structural Analysis of HIV Protease Resistance to Darunavir: Analysis of Heavily Mutated Patient-Derived HIV-1 Proteases. **FEBS J 2014** Apr; 281(7):1834-47.
4. Brynda J, Mader P, Šícha V, Fábry M, Poncová K, Bakardiev M, Grüner B, Cígler P, Řezáčová P. Carborane-based carbonic anhydrase inhibitors. **Angew Chem Int Ed Engl 2013** Dec 16;52(51):13760-3.
5. Tokárová V, Pittermannová A, Král V, Řezáčová P, Štěpánek F. Feasibility and constraints of particle targeting using the antigen-antibody interaction. **Nanoscale 2013** Dec 7;5(23):11490-8.

From the left standing: Petr Pachl, MSc / PhD Student, Petr Těšina, MSc / PhD Student, Juraj Sedláček, DSc / Research Fellow, Irena Sieglová, MSc / Research Assistant, Pavlína Maloy Řezáčová, PhD / Head of Laboratory, Assoc Prof Jiří Brynda, PhD / Research Fellow, Jitka Kredbová / Technician, Milan Fábry, PhD / Research Fellow
From the left sitting: Magdalena Hořejší, MSc / Research Assistant, Jana Škerlová, MSc/ PhD Student, Věra Mrkvičková / Technician, Vlastimil Král, PhD / Research Associate

Not in the picture: Veronika Krejčiříková, PhD / Postdoctoral Fellow (maternity leave)
Background: crystal structure of HIV protease in complex with a carborane inhibitor (PDB code 1ZTZ)