5. Jandova, Z., Trosanova, Z., Weisova, V., Oostenbrink, C., Hritz*, J., BBA - Proteins and Proteomics, 2018, 1866, 442-450.

6. Nagy, G., Oostenbrink, C., Hritz*, J., PLoS ONE, 2017, 12(7), e0180633.

7. Hritz, J., Byeon, I-J., Krzysiak, T., Martinez, A., Sklenár, V., Gronenborn, A.M., Biophys. J. 2014, 107, 2185-2194

# Friday, March 23, Session III

**L10**

## TRANSFORMING BIOMOLECULAR NMR TO STAY AT THE FOREFRONT OF STRUCTURAL BIOLOGY

**Konstantinos Tripsianes**

*CEITEC — Central European Institute of Technology, Masaryk University, Kamenice 5, Brno 62500, Czech Republic, kostas.tripsianes@ceitec.muni.cz*

The automation of NMR structure determination remains a significant bottleneck towards increasing the throughput and accessibility of NMR as a structural biology tool to study proteins. The chief barrier currently is that obtaining NMR assignments at sufficient levels of completeness to accurately define the structures by conventional methods requires a significant amount of spectrometer time (several weeks), and effort by a trained expert (up to several months). We have recently addressed both bottlenecks by presenting a complete pipeline for NMR structure determination using a minimal set of NMR spectra. Key to our approach was the development of 4D-CHAINS algorithm that enables fully automated assignments of NMR chemical shifts, at high levels of completeness and with a minimum error rate, from only two complementary spectra. In combination with autoNOE-Rosetta, 4D-CHAINS provides a robust approach leveraging a highly automated process to obtain reliable structures in a matter of days. Besides illustrating the merits of our pipeline for timely NMR structural studies, novel concepts in automation will be discussed aiming to harness the powerful advantages of the next-generation NMR spectrometers with magnetic strengths of 1.2 GHz.

**L11**

## CAPTURING DYNAMICALLY INTERACTING INHIBITOR BY PARAMAGNETIC NMR SPECTROSCOPY

**Pavel Srb,[1] Michal Svoboda,[1] Ladislav Benda,[2] Martin Lepšík,[1] Ján Tarábek, [1] Václav Šícha,[3] Bohumír Grüner,[3] Klára Grantz-Šašková,[1] Jiří Brynda,[1,4] Pavlína Řezáčová,[1,4] Jan Konvalinka,[1] and Václav Veverka[1*]**

*[1]Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences, Prague, Czech Republic*
*[2]Institute des Sciences Analytiques, UMR 5280 CNRS / Université Claude Bernard Lyon 1 / ENS de Lyon, 5 rue de la Doua, 69100 Villeurbanne (Lyon), France*
*[3]Institute of Inorganic Chemistry of the Czech Academy of Sciences, Husinec-Řež u Prahy, Czech Republic*
*[4]Institute of Molecular Genetics of the Czech Academy of Sciences, Prague, Czech Republic*

Transient and fuzzy intermolecular interactions are fundamental to many biological processes. Despite their importance, they are notoriously uneasy to characterize. Paramagnetic NMR provides an opportunity to amplify rather small indices of intermolecular interactions often observed with diamagnetic ligands. Here, we present an intricate case of a partially flexible protein dynamically interacting with a ligand where data obtained by standard approaches fail to provide detailed structural interpretation. We demonstrate, that a combination of paramagnetic NMR experiments, advanced quantum chemical calculations and molecular dynamics simulations offer a route towards structural characterization of a class of inhibitors based on substituted metalacarboranes with HIV-1 protease.

L12

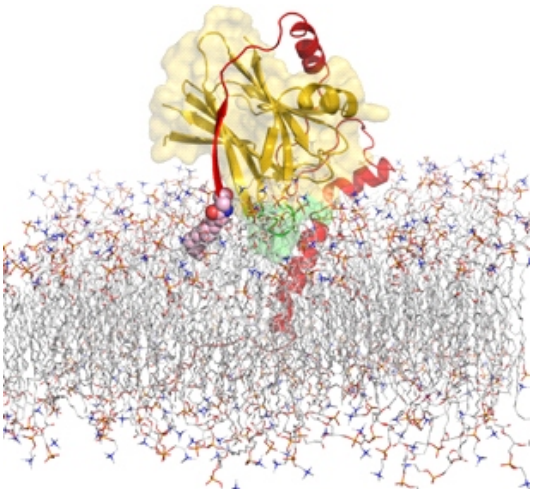
## STRUCTURAL BASIS FOR HIJACKING OF THE HOST ACBD3 PROTEIN BY PICORNAVIRUSES

**Martin Klíma[1,*], Vladimíra Horová[1], Dominika Chalupská[1], Bartosz Różycki[2], Miroslav Smola[1], Jana Humpolíčková[1], Evžen Bouřa[1]**

*[1]Institute of Org. Chemistry and Biochemistry, Czech Academy of Sciences, Prague, Czech Republic*
*[2]Institute of Physics, Polish Academy of Sciences, Warsaw, Poland*
**martin.klima@uochb.cas.cz*

Picornaviruses are small, positive-sense single-stranded RNA viruses including many important human pathogens as well as infecting a wide range of other mammals such as livestock. Within the host cell, these viruses replicate at specific replication sites called replication organelles. In order to remodel the host membranes and to create the replication organelles, these viruses hijack several host factors including the lipid kinase phosphatidyl-inositol 4-kinase beta (PI4KB, [1]) and the acyl-CoA-binding domain-containing protein-3 (ACBD3, [2]). Using X-ray crystallography, we solved the structures of the protein complexes formed by the non-structural 3A proteins from several picornavirus species and the appropriate interacting domain of ACBD3. We show that the viral 3A proteins act as molecular harnesses to enslave the ACBD3 protein leading to its stabilization at target membranes, which leads in turn to the recruitment and activation of the PI4KB kinase. Our structural analysis explains how these viral-host protein complexes assemble at the membrane and identifies new potential targets for antiviral therapies.

1. Klima, M., Toth, D.J., Hexnerova, R., Baumlova, A., Chalupska, D., Tykvart, J., Rezabkova, L., Sengupta, N., Man, P., Dubankova, A., Humpolickova, J., Nencka, R., Veverka, V., Balla, T. and Boura, E., Scientific reports (2016). 6: 23641.
2. Klima, M., Chalupska, D., Rozycki, B., Humpolickova, J., Rezabkova, L., Silhan, J., Baumlova, A., Dubankova, A. and Boura, E., Structure (2017). 25(2): 219-230.



Molecular dynamics simulation-based model derived from our crystal structure of the ACBD3 GOLD domain (mostly in gold, membrane-binding site in green) in complex with the 3A protein from human aichivirus (mostly in red, myristoylated Gly1 residue according to elements) on the lipid bilayer.

*The work was supported by the Czech Science Foundation (grant number 17-07058Y), Academy of Sciences of the Czech Republic (RVO: 61388963), and Ministry of Education, Youth and Sports of the Czech Republic (project InterBioMed - LO1302).*

L13

## TARGETING THE LEDGF/p75 ASSOCIATED PATHOLOGIES

**Lukáš Vrzal[1], Kateřina Čermáková[1], Vanda Lux[1], Subhalakshmi Sharma[2], Jan De Rijck[2], Milan Fábry[3], Sara El Ashkar[2], Frauke Christ[2], Pavlína Řezáčová[1], Zeger Debyser[2], Václav Veverka[1]**

*[1]IOCB CAS, Flemingovo nam. 2, 166 10 Prague, Czech Republic, veverka@uochb.cas.cz*
*[2]KU Leuven, Molecular Virology and Gene Therapy, Leuven, Flanders, Belgium*
*[3]IMG CAS, Prague, Czech Republic*

Lens Epithelium Derived Growth Factor/p75 (LEDGF/p75, or PSIP1) is a transcriptional co-activator that tethers other proteins to gene bodies. The chromatin tethering function of LEDGF/p75 is hijacked by HIV integrase to ensure viral integration at sites of active transcription. LEDGF/p75 is also important for the development of Mixed Lineage Leukemia (MLL), where it tethers the MLL1 fusion-complex at aberrant MLL targets to induce malignant transformation. In addition, LEDGF/p75 might be implicated in the Rett and MECP2 duplication syndromes (neurodevelopmental disorders). Here, we present the structural validation of the LEDGF/p75 binding interactions and targeting strategies for the LEDGF/p75 linked pathologies.