DOI 10.1515/hsz-2013-0250 — Biol. Chem. 2013; 394(11): 1353–1355

Guest Editorial

Highlight: NRW Research School BioStruct – Biological Structures in Molecular Medicine and Biotechnology

The International Research School *BioStruct – Biological Structures in Molecular Medicine and Biotechnology* – at Heinrich Heine University (HHU) Düsseldorf in Germany was initiated by the Ministry of Innovation, Science, Research and Technology of the German Federal State North Rhine-Westphalia (NRW) within the framework of the 'NRW Research School' program to establish a novel culture in post-graduate education in 2008.

It all started with the idea to combine modern structural biology with biotechnology and molecular medicine. Modern structural biology is no longer only structure determination but also examines the dynamics of the systems. Our idea was and is to combine the important and necessary 'classic structural biology', i.e., determination of the three-dimensional structure by X-ray crystallography or NMR, but also to relate this information to dynamics and function of the system under investigation. We decided to focus on two strong points of HHU – molecular medicine and biotechnology – research areas where our university has a long standing history. And obviously a combination of these two areas with structural biology represents an area of unlimited possibilities.

As a consequence, the NRW Research School BioStruct offered truly interdisciplinary research projects embedded in innovative PhD education in structural biology, provided with the expertise and research infrastructure present at the HHU, the Max-Planck Institute for Chemical Energy Conversion (Mülheim/Ruhr) and the Research Center Jülich.

The goal of BioStruct was 'very simple' – knowledge of the three-dimensional structure and the dynamics of the protein under investigation is decisive for understanding the protein's function and mechanism underlying its activity. Here, we selected systems that were the focus of the individual groups. This meant that the group focused on biotechnology or molecular medicine defined the questions for the groups strong in structural biology. A match in question was the basis for a project that was entirely based on curiosity and interest in a common question – how do these systems shape biotechnology or molecular medicine? In other words, for an application in biotechnology and molecular medicine, dealing not only with economic interests but human health, this type of profound knowledge is indispensable for optimization of the protein or the development of new drugs or inhibitors, respectively. Truly, this was and is an ambitious goal and could not be reached within a time frame of 5 years, but offered PhD students a high level education in many if not all aspects of structural biology as we define it today.

All articles presented in this Highlight Issue of *Biological Chemistry* cover different aspects of structural biology, the focus of the laboratory conducting the research and the wealth of methods and model systems, when combined within the research school BioStruct. Concurrently this selection reflects the broad range of proteins and systems that have been analyzed in the various research projects during the 5-year funding period. All projects tried and many if not all succeeded in elucidating previously unknown parts of molecular action of these fascinating machines, which guarantees processes pivotal to biotechnology and molecular medicine. Here is a summary of the details that will be presented in this Highlight Issue of *Biological Chemistry*.

Marbach et al. (2013) describe a simple, fast, and powerful tool to analyze prion protein (PrP)-trafficking as well as interaction studies of the cellular form of the prion protein (PrP^C) in its natural membrane environment. It also can serve for production of fully post-translational modified, GPI-anchored PrP^C. Dealing with the protein Disrupted-in-Schizophrenia 1 (DISC1), Yerabham et al. (2013) review its characteristic properties and propose DISC1 to be a tightly regulated and multi-faceted inhibitor of a wide range of enzymes from interrelated signalling cascades, which together contribute to neurodevelopment and synaptic homeostasis. The review by Amin et al. (2013) focuses on the current status of understanding the functions of Rho-ROCK pathways and various modes of regulation of Rho-ROCK activity, which plays an important role in cardiovascular, metabolic and neurodegenerative diseases, as well as in cancer. Thakur et al. (2013) summarize recent progress in understanding

the molecular mechanism of transforming acidic coiled-coil (TACC) 3 protein, a member of the family of centrosomal adaptor proteins, which are crucial for proper mitotic spindle assembly and dynamics to prevent faulty cell division and aneuploidy.

The review by Jaguva Vasudevan et al. (2013) nicely summarizes the biochemistry, biophysics and structural biology of the APOBEC3 family of DNA cytidine deaminases, which plays a vital role for innate defense against retroviruses like HIV. Also within the field of HIV research is the study of Do et al. (2013), which presents a solid-state NMR-based investigation of the full-length HIV-1 Vpu and its interaction with one of its target proteins, the human CD4 receptor, in phospholipid bilayers.

The reviews by Lenders et al. (2013) and Gawarzewski et al. (2013) summarize structural and functional data that provide molecular insights into the Type I and Type V secretion systems, respectively. Schünke and Stoldt (2013) describe structural insights about cyclic nucleotide-binding induced conformational changes in cyclic nucleotide-binding domains (CNBDs) and their potential coupling with channel gating. Khosa and colleagues (2013) dissect the operon structure encoding for nisin resistance, the prototype of lantibiotics. Comparing the *nsr* gene in different pathogenic and non-pathogenic bacterial strains that do not produce the corresponding lantibiotic, revealed an operon structure resembling the one of the immunity gene cluster found in nisin-producing strains.

From the crystal structure, one can deduce the static ligand orientation and location but the information about the dynamic of ligand binding and contributions from the residues forming the ligand binding site is missing. Saini et al. (2013) used molecular dynamics simulations and binding free energy calculations to analyze the species-selectivity of oxazolidinone antibiotics. This enabled them to identify 'hot-spot/residues' that govern the binding process, which in principle enables an improvement of binding and selectivity of antibiotics.

Höppner et al. (2013) present enzyme-substrate complexes of the quinate dehydrogenase from *Corynebacterium glutamicum*, which explain the strict dependency of a certain cofactor as well as its discrimination of the substrate, respectively. The concentration-dependent stabilizing effect of different compatible solutes on the membrane protein bacteriorhodopsin was studied by Roychoudhury et al. (2013) using single molecule force spectroscopy. The results provide in-depth information about the structure-dynamic relationship at the sub-nanometer scale of single proteins. The group of Scharf and Stoldt analyzed fibronectin fibrillogenesis from two different angles: Huynh et al. (2013) compare binding, unfolding and assembly of fibronectin by three integrins on platelets in suspension and adherent platelets in the presence or absence of platelet activating agonists. Nguyen et al. (2013) show the first study reporting shear-induced conformational changes in fibronectin.

Flavin-binding LOV domains (light, oxygen, voltage) are UVA/blue-light sensing protein units that form reversible flavin-mononucleotide-cysteine adducts upon light induction. Raffelberg et al. (2013) identified a residue directly interacting with the isoalloxazine methyl group and discussed their results with respect to biotechnological applications.

All this work has been supported by the Ministry of Innovation, Science and Research of the federal state of NRW, the HHU and the Entrepreneurs Foundation for the Promotion of Research and Young Scientists at HHU. We gratefully acknowledge their support.

We are looking forward to the presentations of these topics that will be given at the concluding symposium of BioStruct, scheduled for November 4–6, 2013. We hope that the readers of this Highlight Issue will enjoy it as much as we all enjoyed the period of BioStruct. The construction and operation of BioStruct initiated decisive developments at Heinrich Heine University towards a structured PhD program and certainly is to be continued.

References

Amin, E., Dubey, B.N., Zhang, S.-C., Gremer, L., Dvorsky, R., Moll, J.M., Taha, M.S.A., Nagel-Steger, L., Piekorz, R.P., Somlyo, A.V., et al. (2013). Rho-kinase: regulation, (dys)function, and inhibition. Biol. Chem. *394*, 1399–1410.

Do, H.Q., Wittlich, M., Glück, J.M., Möckel, L., Willbold, D., Koenig, B.W., and Heise, H. (2013). Full-length Vpu and human CD4(372-433) in phospholipid bilayers as seen by magic angle spinning NMR. Biol. Chem. *394*, 1453–1463.

Gawarzewski, I., Smits, S.H.J., Schmitt, L., and Jose, J. (2013). Structural comparison of the transport units of type V secretion systems. Biol. Chem. *394*, 1385–1398.

Höppner, A., Schomburg, D., and Niefind, K. (2013). Enzyme-substrate complexes of the quinate/shikimate dehydrogenase from *Corynebacterium glutamicum* enable new insights in substrate and cofactor binding, specificity and discrimination. Biol. Chem. *394*, 1505–1516.

Huynh, K.C., Stoldt, V.R., and Scharf, R.E. (2013). Contribution of distinct platelet integrins to binding, unfolding and assembly of fibronectin. Biol. Chem. *394*, 1485–1493.

Jaguva Vasudevan, A.A., Smits, S.H.J., Höppner, A., Häussinger, D., Koenig, B.W., and Münk, C. (2013). Structural features of antiviral DNA cytidine deaminases. Biol. Chem. *394*, 1357–1370.

Khosa, S., AlKhatib, Z., and Smits, S.H.J. (2013). NSR from *Streptococcus agalactiae* confers resistance against nisin and is encoded by a conserved *nsr* operon. Biol. Chem. *394*, 1543–1549.

Lenders, M.H.H., Reimann, S., Smits, S.H.J., and Schmitt, L. (2013). Molecular insights into Type I secretion systems. Biol. Chem. *394*, 1371–1384.

Marbach, J., Zentis, P., Ellinger, P., Müller, H., and Birkmann, E. (2013). Expression and characterization of fully posttranslational modified cellular prion protein in *Pichia pastoris*. Biol. Chem. *394*, 1475–1483.

Nguyen, H., Huynh, K.C., Scharf, R.E., and Stoldt, V.R. (2013). Shear-related fibrillogenesis of fibronectin. Biol. Chem. *394*, 1495–1503.

Raffelberg, S., Gutt, A., Gärtner, W., Mandalari, C., Abbruzzetti, S., Viappiani, C., and Losi, A. (2013). The amino acids surrounding the flavin 7a-methyl group determine the UVA spectral features of a LOV protein. Biol. Chem. *394*, 1517–1528.

Roychoudhury, A., Bieker, A., Häussinger, D., and Oesterhelt, F. (2013). Membrane protein stability depends on the concentration of compatible solutes-a single molecule force spectroscopic study. Biol. Chem. *394*, 1465–1474.

Saini, J.S., Homeyer, N., Fulle, S., and Gohlke, H. (2013). Determinants of the species-selectivity of oxazolidinone antibiotics targeting the large ribosomal subunit. Biol. Chem. *394*, 1529–1541.

Schünke, S. and Stoldt, M. (2013). Structural snapshot of cyclic nucleotide binding domains from cyclic nucleotide-sensitive ion channels. Biol. Chem. *394*, 1439–1451.

Thakur, H.C., Singh, M., Nagel-Steger, L., Prumbaum, D., Kalawy Fansa, E., Gremer, L., Ezzahoini, H., Abts, A., Schmitt, L., Raunser, S., et al. (2013). Role of centrosomal adaptor proteins of the TACC family in the regulation of microtubule dynamics during mitotic cell division. Biol. Chem. *394*, 1411–1423.

Yerabham, A.S.K., Weiergräber, O.H., Bradshaw, N.J., and Korth, C. (2013). Revisiting Disrupted-in-Schizophrenia 1 as a scaffold protein. Biol. Chem. *394*, 1425–1437.

Cordula Kruse
NRW Research School BioStruct,
Heinrich Heine University,
D-40225 Düsseldorf,
Germany,
e-mail: cordula.kruse@hhu.de

Dieter Willbold
Institute of Physical Biology,
Heinrich Heine University,
D-40225 Düsseldorf and
Institute of Complex Systems,
ICS6: Structural Biochemistry,
Research Center Jülich,
D-52425 Jülich,
Germany,
e-mail: dieter.willbold@hhu.de

Lutz Schmitt
Institute of Biochemistry,
Heinrich Heine University,
D-40225 Düsseldorf,
Germany,
e-mail: lutz.schmitt@hhu.de