A EUROPEAN JOURNAL OF CHEMICAL BIOLOGY

CHEMBIOCHEM

SYNTHETIC BIOLOGY & BIO-NANOTECHNOLOGY

Accepted Article

Title: ECBS and ICBS 2015 Joint Meeting: Bringing Chemistry to Life

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To be cited as: ChemBioChem 10.1002/cbic.201500684

Link to VoR: http://dx.doi.org/10.1002/cbic.201500684

A Journal of

ChemPubSoc Europe

www.chembiochem.org

WILEY-VCH

ECBS & ICBS 2015 Joint Meeting: Bringing Chemistry to Life

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The European Chemical Biology Society (ECBS) and the International Chemical Biology Society (ICBS) organized a joint meeting in Berlin. This meeting counted with more than 250 participants including: 4 keynote talks by Timothy Mitchison, David Tirrell, Carolyn Bertozzi and Jason Chin; 13 invited speakers, 20 selected oral talks and 30 speak talks selected from 90 posters. The meeting was distributed in six topics: chemoproteomics, epigenetics, conjugates for target delivering, antiinfectives, molecular imaging and probing the structure and function of posttranslational modifications.

The conference started with the introductory note given by Philip Gribbon (conference chair, EU-OPENSCREEN), and Melvin Reichmann (president elected of the ICBS). The scientific presentations initiated with the keynote lecture by Timothy Mitchison (Harvard Medical School), who discussed different aspects of mitosis in large cells and about the interactions of two drugs with microtubules: Pladitaxel (Ptx) and colchicine (CH). Ptx is an anti-tumor drug that acts on non-dividing cells killing tumorogenic spheroids.[1] Colchicine is an anti-inflammation drug that targets tubulin and is used to treat Gout.[2] He showed results on the activity of Ptx on the mitotic spindle using a H2B-GFP, which allowed the fluorescence imaging to follow the effect of the drugs to the mitotic spindle structures, chromosome behavior, mitotic arrest, and cell death.[3]

CHEMOPROTEOMICS

Studies to disclose the mode of action of small molecules and their interactions with proteins in their natural environment is becoming important for understanding the mechanism of action and development of new drugs. In this session different methodologies were presented to evaluate the interaction of drugs with proteins. Bernhard Kuester (TU Munich) started the session presenting examples of drugs-proteins interaction analysis using mass spectrometry-based protocols combined with ProteomicsDB, a data bank for real-time analysis of the human proteome.[4] He presented the use of this technology to study the interaction of drugs with protein signaling and proteomes,[5] the identification of toxicity targets,[6] the influence of post-translational modifications to the efficacy of drugs in cancer cells.[7] Benjamin Cravatt (Scripps Research Institute) followed this line introducing the activity-based proteomics (ABPP). He reported the use of ABPP to determine the functional state of enzymes in native proteomes and discussed its application in combination with other mass-spectrometry methods to investigate enzyme activities in physiology and metabolic disorders. He presented a study of the interaction of small-molecule inhibitors with BAT 5 and with ABHD12, which are involved in the regulation of the levels of lisophosphatidyl-serine (slyso-PS) in lymphoblasts and with potential therapeutic relevance for PHARC and other immunological and neurological diseases.[8]

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Figure 1. Audience by the lectures

An additional method to study the interaction of drugs with target proteins was introduced by Thomas Lundback (Karolinska Institute), who described the cellular thermal shift assay (CETSA).[9] The principle of this assay involves the thermodynamic stabilization of proteins after ligand binding and allows the study of proteins in cellular context without the introduction of any modifications that may affect compound selectivity and target identification. The stabilization is detected by heating ligand treated cells at different temperatures and separation of the soluble proteins.[9] He presented a test on thymidylate synthase using a cell base screening on MCF7 cells and discussed future application of this assay. Michel Bradshaw (Principia Biopharma) contributed a new method to discover inhibitors having extended target residence time, which enhance drug efficacy and improve safety of the molecules.[10] The process, called „residence time by design", involves the formation of a reversible covalent bond with a non-catalytic cysteine of the target protein with inhibitors containing acrylamide electrophiles. He illustrated this method for the identification inhibitors for tyrosine kinases BTK, which is target for B-cell cancers and possible autoimmune diseases. The final presentation of this session by Kasuke Dodo (RIKEN, Japan) involved the presentation of chemical probes bearing a small bifunctional O-NBD unit (NBD: nitrobenzoxadiazole), which can be turned into N-NBD unit that exhibits a strong fluorescence after reaction with the amine group of lysine in target proteins. To demonstrate the potential of this unit and its application in live cells, she described the attachment of O-NBD to ligands of the traslocator protein (TSPO) to Turn-ON the fluorescence and visualizes mitochondria expressing TSPO in HEK cells.[11]

EPIGENETICS

Epigenetic signals including chemical modifications of DNA and post-translational modifications of amino acids in histones regulate different processes. Chuan He (University of Chicago) reported on the methylation of RNA and the biological role of N^6-methyladenosine (m^6A) in the localization and decay of RNA.[12] He introduced the role of RNA demethylases, i.e. the fat mass and obesity-associated protein (FTO), which is a protein associated with human development and the gen regulatory activity of m^6A in low eukaryotes.[13] Angelina Measures (University of Oxford) discussed the modification of histone tails

and reported on the identification of low affinity inhibitors for the Tripartite motif protein TRIM24 using an AlphaScreen assay with peptides bearing a trimethyl- or acetyl unit at lysine residue.

Masatoshi Hagiwara (Kyoto University) discussed drug discovery using splicing therapy for genetic diseases. By using a splicing reporter assay, he reported on the visualization of pathogenic splicing in cells that allows the screening of small chemicals with the ability to correct the aberrant splicing of IKBKAP. He reported on the identification of the compound RECTAS, which can rectify the aberrant IKBKAP splicing in Familial dysautonomia (FD) patient fibroblasts and the reduced tRNA modification in FD, which can be quantified by LC-MS.[14]

Maria Duca reported on the inhibition of microRNAs **(**miRNA) as a strategy for cancer treatment.[15] She reported on two strategies to find inhibitors for the oncogenic miRNAs (miRNA-372 and -373) implicated in gastric cancer. The first strategy comprises the design and synthesis of RNA ligands that block the cleavage of miRNA precursors, the second involves the screening of 640 compounds library from the French National Chemical Library. She showed that the decrease of formation of the miRNAs induces the de-represion of LAST-2 protein in AGS cells, which is the target protein of those two miRNAs.[16]

In the second keynote lecture, David A. Tirell (CalTech) illustrated the use of non-canonnical amino acids to analyze protein synthesis in complex biological systems. He discussed the expansion of the amino acid set for protein synthesis and presented the bioorthogonal non-canonical amino acid tagging (BONCAT) and its applications. He presented studies involving qualitative and quantitative systems,[17] metabolic labeling, click chemistry, selective labeling of proteins in host-pathogen interactions and discussed the analysis of protein synthesis in time-resolved and cell-selective form. He presented an analysis to determine the order of injection of Yersinina outer proteins (YOPS) into mammalian cells.[18] Furthermore, he described the use of non-canonical amino acids in the metabolic protein labeling in animals and discussed cell and tissue specific labeling.[19]

CONJUGATES FOR TARGETED DELIVERY

The delivery of proteins and drugs to the correct place of treatment has been a hot topic in drug discovering and treatment of cancer. Dario Neri (ETH Zurich) introduced the use of immunocitokine-armed antibodies and their application in cancer therapy. He described the use of IL19-IL2 for locoregional applications and presented a combination of IL19-TNF for the treatment of soft tissue sarcoma.[20] He described the discovery of a micromolar binder for tumor vessel expressed markers using a stable dual-display DNA-encoded chemical library.[21]

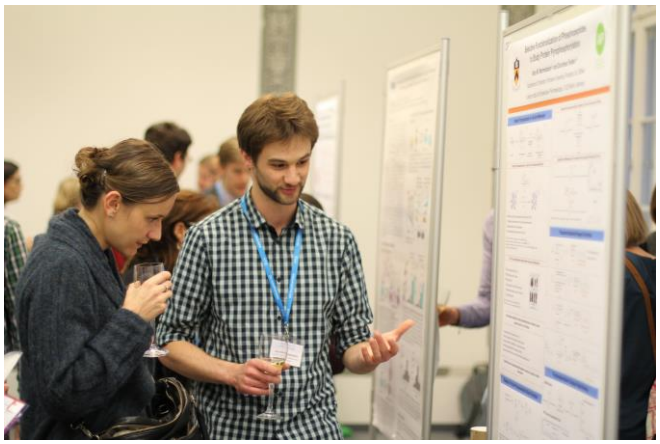

Figure 2. Discussion during a poster session.

In addition to the delivery problems, the transport of proteins through the membranes remains a big issue in the use of drugs for intracellular activity. To overcome this limitation, Jean-Phillip Pellois (Texas A&M University) introduced a new approach for the delivery of proteins and peptides into human cells by using co-incubation with cell penetrating peptides (CPP).[22] He presented the cytosolic delivery promoted by the CPP dfTAT and described the mechanism of incorporation of CPPs attaching proteins by disulfide dimerization, which improves their release from the endosomes. Henry Herce (TU Darmstadt**)** contributed mechanistic studies on CPP discussing the transport mechanism of CPP through the membrane, which is modulated by the protonation of fatty acids.[23] He described the targeting of the cell nucleus and presented results of the delivery of GFP-nanobodies into cells via chemical attachment of the cyclic TAT peptide to proteins.[24]

David Margulies (Weizmann Institute) presented synthetic receptors that communicate with proteins allowing protein detection in mixtures.[25] He described the use of optical cross-reactive sensor arrays, the so-called chemical “noses/tongues” approach, for the detection and analysis of proteins. He presented the application of a synthetic transducer that connects *in vitro* two unrelated proteins and allows programmable drug release.[26] Hilde L. Ploegh (Whitehead Institute) presented Sortase-catalyzed transformations of single strain nanobodies (VHHs) and the ligation of VHH with protein such as IL-2, and TNF,[27] as well as with fluorophores and radioisotopes.[28] He introduced the transformation of small VHHs and of full-sized antibodies and discussed its application in tracking different biological events.

RISING STARTS IN CHEMICAL BIOLOGY

In this established session at the Annual Meeting of the ICBS three selected up-and-coming chemical biologists presented the last results of their researches and were recognized for their achievements with the ICBS Young Chemical Biologist Award. Alessio Ciulli (University of Dundee) reported a compound for selective removal of the Bromo- and Extra-Terminal (BET) protein BRD4 that play important roles in transcriptional regulation, epigenetics, and cancer. The principle of the technique is the use of a proteolysis-targeting chimeric (PROTAC) molecule that achieves a rapid, time- and dose-dependent, long-lasting, and preferential removal of the target protein.[29] Evan Miller (UC Berkeley) discussed about the photoinduced electron transfer (PeT) for imaging Voltage in living cells. He described the design, synthesis and characterization of sulfonated Si-rhodamine and its use in voltage sensing applications.[30] In addition, he reported the use of this flourophores involving PeT as a molecular wire to improve the detection of BERST 1 and the visualization of neuronal activity.[31] Edward Lemke (EMBL Heidelberg) explained the use of protein and genetic engineering in protein labeling and studies of protein dynamics[32], as well as the use of the UAG stop codon for the introduction of unnatural amino acids containing functionalities such as alkynes and alkenes that allow protein site specific labeling using chemoselective reactions with fluorophores. He presented the application of this method for the visualization of insulin receptors.[33]

Following this session, Carolyn Bertozzi (Stanford University) reported on the imaging of bacterial peptidoglycan (PG) by using bioorthogonal chemistry. She described a chemical approach for probing PG via metabolic labeling by a bioorthogonal reaction of alkyne-functionalized D-Ala incorporated into the intracellular pathogen *Listeria monocytogenes* (*Lm*) *in vitro* and during

macrophages infection.[34] By using the same reporter strategy, she described the studies to determine the differences within the proportion of the *Lm* cell cycle in the division process when they grow in the host cell and in broth culture.[35]

ANTIINFECTIVES

An increasing resistance of diverse pathogens to antibiotics prompted the discovery of new molecules to combat infections. Rolf Müller (Helmholtz Institute) discussed the use of natural products for identifying antibiotic leads with new mode of action and presented cystobactanides as a new class of natural products against gram-negative bacteria. He reported on the efforts to identify new anti-tuberculosis agents using derivatives from griselimycin and presented studies made in order to understand the resistance of mycobacteria to this compound. Furthermore he explained that griselimycins inhibit the DNA Polymerase sliding clamp DnaN and reported on the low frequency resistance of tuberculosis to this drug.[36] Michael P. Manns (Hannover Medical School) reported on the treatment of Hepatitis C using protease inhibition. He discussed the inhibition of the nonstructural protein 5A (NS5A) using a combination of the drugs imeprevir and sofosbuvir,[37] He also explained that these drugs are well tolerated and can be used by patients with chronic HCV genotype 1 who did not respond to interferon-based therapy. Reiner Haag (FU Berlin) introduced the use of multivalent presentation of inhibitors in 1, 2 and 3-D scaffolds.[38] He reported on the synthesis of multivalent scaffolds containing sialic acid that inhibit the cell binding of influenza virus in density and size dependent form.[39] He also presented the use of graphenes for the attachment of carbohydrates and the multivalent presentation of carbohydrates for bacterial capture, release and thermal disinfection.[40] Maria Maneiro (Universidad Santiago de Compostela) presented studies with the Type-1 dehydrokinase enzyme from *Salmonella typhi* (DHQ1). She reported on a study of the irreversible inhibition of DHQ1 using epoxides and described two molecules that were designed to study the binding requirements of the linkage to the enzyme.[41]

CHEMINFORMATICS AND CHEMICAL SYSTEMS BIOLOGY

The collection, the experimental and the integration of informatics are gaining recognition and becoming relevant tools in research. Jordi Mestres (IMIM Barcelona) reported on current computational approaches to predict the proteome affinity profile of chemical structures to anticipate and compare the selectivity of chemical probes.[42] He presented distant polypharmacology and described the *in silico* target profiling of chemical probes from the NIH Molecular Libraries Program to identify probes with relevant affinities for proteins that are distant from the primary target.[43] Tudor Oprea (University of New Mexico) discussed the need to illuminate and to expand the druggable genome. He discussed the darkness genome, which according to his report corresponds to more than 40% of the human proteins. He presented studies showing the lack of therapeutic agents for around 70% of diseases and discussed recent studies demonstrating that drugs targeting is still focusing on the same protein families that have been analyzed frequently.[44]At the end of the session Prudence Mutowo (EMBL-EBI) introduced the navigation of the protein target space in ChEMBL using Gene Ontology (GO).[45] ChEMBL is free resource containing information on bioactive ligands, quantitative bioassay results and molecular targets of those molecules.[46] She described the ChEMBL target GO slim as a useful tool for navigating protein target space and gaining quick information on the drugs and the biology of the target proteins.

Figure 3. Carolyn Bertozzi giving a keynote lecture

Given the essential role of the quality of chemical probes in drug discovery, the topic was presented in two lectures. Albert A. Antolin (ICR London) discussed the perils of inappropriate chemical probes and the requirements of chemical probes and their selectivity for the target proteins.[43] He introduced the chemical probes portal and described activating cancer drivers and their druggability.[47] In the second talk Jonathan Baell (MIPS) discussed chemical probes and their required properties. Furthermore he introduced the chemical probes portal, which is a web-based resource for chemical biologists containing information on chemical probes and on the appropriate chemical probes for a given protein.[48]

MOLECULAR IMAGING

Visualizing and imaging not only the localization but also the in-time profile changes of a giving molecule is becoming important in the field of chemical biology.

Carsten Schultz (EMBL) presented the visualization of enzymes in real time with spacial resolution using fluorescent probes. He explained that small molecule dimerizers are powerful tools to study the kinetic of enzyme activity in intact cells.[49] Furthermore, he presented the visualization of diacylglycerol dynamics using oscillations by photo switchable diazobenzene containing-lipids. Venkata Pavan Kumar Kondapi (university of Alberta) presented ligands for the glucose transporter 5 (GLUT5) for the imaging of breast cancer. He described the labeling of GLUT5 binding hexoses with different near-infrared emitting dyes and the *in vitro* studies to obtain information on the ligands' potential as tracers and transport mechanism. Toru Komatsu (Tokyo University) reported on a new technique to reconstitute phagocytosis of inert cells using the display of proteins at the cell surface by small molecules inducing heterodimerization.[50] She described a system to display in a fast way a C2 domain of MFG-E8 protein, providing the cells with the ability to selectively bind to apoptotic cells through externalized phosphatidylserine in combination with the active Rac1 GTPase.[51] The session was completed by Peter Kele (TTK MTA Budapest). He reported on double functionalized self-labeling peptide tags that can be targeted with high selectivity with small molecule, dual-functional probes. He introduced the use of bisazide fluorogenic probes involving a dual role for the azides, as a fluorescence quencher for the aromatic cores and as a bioorthogonal handle for conjugation.[52]

PROBING THE STRUCTURE AND FUNCTION OF PTMs

Posttranslational modifications play an important role in protein structure, function and regulation**.** The role of these modifications has gained interest during the last years and is

becoming a stronger field in drug discovery and chemical biology. Hilal Lashuel (EPFL) discussed the role of α-Synuclein (α-Syn) aggregation in Parkison disease (PD) and introduced a method for the delivery of α-Syn into primary neurons using cell-penetrating peptides. He discussed TAT-s-s-α-syn nitration[53] and phosphorlyation and presented the use of phosphorylation as a therapy for clearance of α-synnuclein.[54] Carlo Unverzagt (university of Bayreuth) presented a semi-synthetic strategy for obtaining homogeneous glycoproteins. He discussed the synthesis and refolding of active human interleukin 6 (IL-6) and Erythropoietin (EPO),[55] the synthesis of complex glycans and the enzymatic elongation of glycans for obtaining glycans and glycoprotein libraries.[56] Dorothea Fiedler (FMP Berlin) discussed chemical approaches to elucidate the molecular mechanisms in diphosphoinositols polyphosphates (PP-IPs) signaling. She presented a strategy used to obtain non-hydrolyzable PP-IP bisphosphonate analogues and their benefit for the affinity purification of inositol polyphosphate binding proteins.[57] She also introduced a method applied to produce pyrophosphopeptides for developing enrichment and mass spectrometry-based detection of pyrophosphoproteins.[58] Yoawen Wu (CGC Dortmund) presented mechanistic studies dealing with the investigation of the anti-autophagy effector RavZ function using a combination of chemical, biophysical and cell biological tools. He discussed the semi-synthesis of modified LC3 proteins to study the structure-function relationship of RavZ-medicated cleavage and the establishment of a working model for RavZ.[59] Saptal Virdee (University of Dundee) presented a platform for building activity-based probes (ABPs) that profile the distinct transthiolation activity associated with particular steps of the ubiquitine conjugation cascade.[60] He presented ABPs for profiling the transthiolation activity between E1 activating enzymes and E2 conjugating enzymes that represent a significant help while understanding the regulatory mechanisms of the Parkinson's disease-associated E3 ligase.

The conference ended with a keynote lecture about the expansion of the genetic code for the incorporation of non-natural amino acids in eukaryotic and animal cells. Jason Chin (MRC Cambridge) presented the expansion of the translation machinery, including genetically encoded PTM's such as ubiquitination and phosphorylation.[61] He discussed the natural and non-natural incorporation of phosphorylserine and the protein labeling in living cells.[62] Finally, he reported on the bioorthogonal target oriented labeling for optically switchable control of protein function.[63]

Two poster sessions at the end of the first and secon day completed the scientific program and a select group of students presented speaks lectures of their posters. Six poster prizes, three from Wiley and three from Sanofi, were awarded in the closing ceremony to Benjamí Oller-Salvia (IRB Barcelona), Florian A. Mann (FMP Berlin), and Jan-Philip Schuelke (Pfizer, Boston), Elles Ostensen (University of Oslo), Abukakar Jalloh (Albert Einstein College) and Anuchit Phanumartwiwath (Oxford University).

The meeting offered different opportunities for an interaction between the participants. Besides the presentations and the interesting discussions, the poster sessions gave students and young investigators the opportunity to introduce their new results and to interact with the speakers. In addition, free time during the coffee breaks, lunch and a conference dinner at the Naturkunde museum could be used for exchanging ideas, meeting new colleagues and establishing future collaborations.

The meeting presented a huge amount of new strategies developed for evaluating the interactions of proteins with small molecules and offered a good balance of the different areas in chemical biology and of the rising role of chemistry for understanding living systems. I am looking forward for the next exciting meeting of the ECBS that will take place in Budapest, Hungary, in 2016.

Acknowledgements

I thank the Max Planck Society and the RIKEN Max Planck Joint Center for Systems Chemical Biology for the financial support.

Keywords: keyword 1 • ICBS • ECBS • Chemical Biology • Meeting Report

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ECBS & ICBS 2015 Joint Meeting: Bringing Chemistry to Life

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Bringing Chemistry to Life: Recently, the ECBS & ICBS organized a joint meeting in Berlin, Germany, which covered the different fields of chemical biology. This report describes the three days meeting and presents its scientific highlights.