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EMBO Conference Series: Chemical Biology 2014

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The European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany, hosted the fourth biennial Chemical Biology conference from August 20–23, 2014. The conference, featuring exciting, diverse advances in the field of chemical biology, was organized by three scientists from EMBL Heidelberg: Maja Kohn, Edward Lemke and Carsten Schultz, and one scientist from EMBL-EBI (Hinxton): John Overington. The sessions comprised 36 talks including three keynote lectures and 21 invited talks. In addition, 15 short talks were selected from abstracts—five each from students, postdocs and principal investigators. There were also nearly 200 poster presenters among the 300 participants at the meeting. The conference attracted a highly international audience, representing 18 countries from around the globe. The EMBL Corporate Partnership Programme also awarded ten travel fellowships to students attending from under-represented countries.

The conference was structured to provide ample time for discussions and networking. Two separate “Meet the Speakers” sessions were provided to give attendees the unique opportunity to informally chat with speakers (Figure 1). In addition, the posters were presented over three well-attended sessions that allowed sufficient time for viewing and discussion. At the end of the conference, three students were awarded prizes for outstanding presentations or posters; these were sponsored by *ChemBioChem*. The prize for short talk by a graduate student was presented to Elisabeth Storck Saha (Imperial College, London); the prize for short talk by a postdoctoral student was given to Malte Gersch (Technische Universität München); and the poster prize was awarded to Jacob Bush (University of Oxford).

Innovations in Therapeutic Discovery

As we find that patients are often unresponsive or develop resistance to therapeutic strategies, there is an increasing need to develop new approaches to enhance the responsiveness and efficacy of treatment. Many speakers presented integrative strategies to

maximize therapeutic effectiveness by taking patient variations into consideration. Olli Kallioniemi (University of Helsinki) presented a strategy involving individualized systems medicine to improve patient care for leukemia.^[1] In this approach, the researchers profiled the ex vivo responses of primary acute myeloid leukemia (AML) cells derived from patients to various treatment agents. This information was coupled with biochemical analyses to profile biomarkers of drug responsiveness with the goal of translating this information into a personalized treatment scheme for individual patients. Krister Wennerberg (Institute for Molecular Medicine Finland, FIMM) discussed his work on the design of an individualized systems-medicine program that integrates information on drug sensitivity in order to identify signal and/or network dependencies.^[2] Drug-sensitivity profiles were subsequently applied to patient profiles to identify possible drug combinations with improved efficacy. Rhys Taylor of the Sugiyama laboratory (Kyoto University) presented his work on the design of pyrrole imidazole polyamides with a high affinity for codon mutation sequences of KRas and demonstrated sequence-specific alkylation as a strategy to inhibit gene expression.^[3] Herwig Schuler (Karolinska Institutet, Stockholm) showed that, although ADP-ribosyltransferases are a highly sought-after drug target, these multidomain proteins have generally only been characterized by using small domain fragments. When studying the activity of each isoform of full-length proteins, differences in activity were elucidated due to allosteric regulation between the domains.^[4] These findings were applied to re-interpret PARP inhibitors for target selectivity.

Otto Wolfbeis (Universität Regensburg) gave an innovative keynote lecture on fluorescent sensing and imaging of oxygen.^[5] Although oxygen is an essential component for understanding biology, tools to sense oxygen in biological processes still need to be developed. He discussed the development of new materials for sensing including lanthanide-based nanoparticles, probes that are sensitive to two-photon excitation, and fullerenes. Some benefits of these new technologies include a lack of interference by proteins in biological systems and lifetime-based sensing measurements that are not dependent on probe concentration. The development of these materials greatly broadens the applicability of oxygen sensing to diverse backgrounds. Chris Lipinski (Meliior Discovery, Exton) gave a thought-provoking keynote lecture on the broad field of drug discovery (Figure 2). One point that was emphasized is that literature searches on lead compounds have significant value even if the compound has unrelated biology. The benefit is that principles in medicinal chemistry can be inferred and applied to the ligand chemistry of the new target. He also discussed the relationship between ligand efficiency and selectivity where ligand efficiency is measure of the efficiency of ligand atoms used for binding. He suggested that ligand efficiency, not IC₅₀ values, can lead to new insights for improved target selectivity.

Computational Methods

Computational methods provide a powerful means to integrate large masses of data into useful analyses. Bissan Al-Lazikani (Institute of Cancer Research, London) reported an in silico approach to integrate bioinformatics and data from experimental biology to create rankings as a means of prioritizing drug targets and assessing their suitability for drug targeting.^[6] This method was designed to balance technical and biological risks for potential targets so as to ultimately identify currently undrugged but potentially “druggable” targets.

She also presented the development of the canSAR knowledge-base (<http://cansar.icr.ac.uk>).^[7] This publically available database is fully annotated to include data from diverse sources including chemical, pharmacological, biological and structural sources to support translational cancer research and drug development. Patrick Aloy (Institute for Research in Biomedicine, Barcelona) described a bioinformatics approach to identify chemical scaffolds that are over-represented with particular properties including side effects, targets, and interactions.^[8] These models were built by using a combination of biological and chemical features with the aim of identifying scaffolds with favorable therapeutic properties and minimal adverse drug effects to aid in the process of drug design. Yvonne Martin (Martin Consulting, Waukegan) presented a very interesting historical perspective on drug discovery and the paradigm shifts that have accompanied computer-aided drug design over the last several decades. She also presented multiple current challenges in computational drug design, including accurately predicting affinity and potency and predicting potency for similar-in-structure and three-dimensional properties of in silico-designed compounds.

Cell Signaling

Chemical biology has proven to be a useful approach for perturbing signaling events in cells. Zhengjian Zhang (Janelia Farm) described his work to identify a chemical inhibitor of transcription factor IID (TFIID) that targets an out-of-pocket site. Through small-molecule screening, his group ultimately identified a tin-based cluster that binds an intrinsically disordered region and stabilizes DNA–protein interactions to ultimately inhibit TFIID-dependent transcription. Although cytokinesis is a fundamental process, Ulrike Eggert (King's College) pointed out that major questions still exist in terms of understanding the regulation and execution of this process (Figure 3). To address this, she has developed a set of small molecules that inhibit different components of the process. She discussed a few examples where these compounds were applied to study cytokinesis, including uncovering a new role for GPCRs^[9] and studying lipid accumulation in dividing cells.^[10] Rolf Breinbauer (Technische Universität Graz) presented an approach to probe lipid metabolism with a focus on adipose triglyceride lipase (ATGL), as this enzyme performs the first step in triglyceride catabolism (Figure 3). He presented the identification through small-molecule screening of the first small-molecule inhibitor of ATGL, atglistatin, which was applied as a synthetic strategy to inhibit triglyceride hydrolysis.^[11]

Zhong-Yin Zhang (Indiana University) discussed that although protein tyrosine phosphatases (PTP) are involved in many diseases, they are considered “undruggable” due to challenges in developing bioavailable and selective inhibitors. He and his colleagues developed functionalized moieties around a salicylic acid platform as non-hydrolyzable mimics of pTyr for PTP-based drug discovery.^[12] By additionally targeting peripheral pockets, PTP inhibitor potency and selectivity could be further enhanced. As phosphorylation-dependent protein-protein interactions (PPIs) are important interfaces in cell signaling, Shao Quin Yao (National University of Singapore) developed a phosphopeptide microarray to identify PPI inhibitors for various targets.^[13] Using phosphopeptides identified from the screen, he and his co-workers subsequently developed a cell-permeable, small-molecule-peptide hybrid inhibitor through a fragment-based

combinatorial approach to selectively target BRCA1.^[14] Eileen Kennedy (University of Georgia) described a peptide-based approach to disrupt the spatiotemporal regulation of kinases by using stapled peptides to block localization of PKA to A kinase anchoring protein (AKAP) complexes.^[15] She illustrated how these disruptors could be designed for isoform specificity and how they disrupted these signaling complexes in cell-based systems. Tom Grossmann (CGC/Technische Universität Dortmund) presented a synthetic approach to chemically crosslink a peptide with irregular secondary structure as a means to inhibit the interaction between human 14-3-3 and exoenzyme S.^[16]

Protein Chemistry and Engineering

Many exciting innovations are being developed to alter the functionality of a protein or regulate how it is post-translationally modified. John James (University of Cambridge) discussed the development of a chemically inducible receptor bearing FKBP/FRP domains that dimerize upon introduction of a rapamycin analogue.^[17] He showed that this strategy could be applied to synthetically control input to endogenous signaling by altering receptor density, rapalog concentrations and kinase binding sites. Lei Wang (Salk Institute, La Jolla) presented an inventive new approach for encoding proximity-enabled bioreactivity. In this approach, unnatural amino acids are incorporated into proteins and can react with natural amino acid target residues so as to form a crosslink when they are closely positioned near one another.^[18] Hilal Lashuel (École polytechnique fédérale de Lausanne) discussed his work on a one-pot synthesis to allow for the introduction of site-specific post-translational modifications by using protein ligation.^[19] He applied this method to develop a library of α -synuclein analogues with distinct post-translational modifications. This library can be used to identify modifications that are associated with particular cell-signaling events in normal and disease states. Ashraf Brik (Ben-Gurion University) discussed his work to synthetically create site-specific ubiquitylation of α -synuclein by using di- or tetra-Ub chains.^[20] These synthetic forms of α -synuclein were used to study various mechanisms of protein regulation and crosstalk as it relates to Parkinson's disease.

Virginia Cornish (Columbia University) presented several tools developed by her laboratory to expand the synthetic capabilities of yeast. One example was the development of "reiterative recombination" inside cells by endonuclease-induced homologous recombination with recyclable markers.^[21] This scheme can be applied to generate large libraries of multigene pathways from a defined locus. These tools provide the platform to engineer diverse pathways, including biosynthetic pathways, translational machinery and biosensors. Malte Gersch of the Sieber laboratory (Technische Universität München) discussed a strategy that combined synthetic, biochemical and structural methods^[22] to dissect the serine protease catalytic mechanism of the ClpP protease complex, and showed that acyldepsipeptides can stimulate ClpP activity. Suihan Feng of the Schultz group (EMBL Heidelberg) discussed the development of a reversible chemical dimerizer that localizes an enzyme of interest to a defined intracellular site.^[23] This methodology was applied to activate and inhibit PI3K activity in cells. Ivana Niki from the Lemke laboratory (EMBL Heidelberg) presented her work on encoding unnatural amino acids that have strained alkynes or alkenes that can be attached to tetrazine-functionalized dyes for rapid, dual-cover labeling in live cells.^[24] Gianluca Veggiani from the Howarth laboratory (University of

Oxford) showed that SpyLigase^[25] could be applied to build affibody tentacles linked by isopeptide bonds. These tentacles can then be covalently anchored on magnetic beads to capture tumor cells with very high sensitivity. Elisabeth Storck Saha from the Tate Laboratory (Imperial College, London) presented a approach to quantify protein prenylation by developing prenyl probes that can be used to metabolically label prenylated targets by using quantitative proteomics.^[26]

Herman Overkleeft (Universiteit Leiden) presented the design of activity-based probes for retaining glycosidases.^[27] This class of glycosidase forms a covalent enzyme–substrate intermediate. Taking advantage of this property, the group developed an activity-based profiling method using cell-permeable, small-molecule probes that covalently bind the active site in an activity-dependent manner. This approach can be applied in comparative activity-based glycosidase profiling to uncover the role of glycolytic enzymes in various cellular processes. Jennifer Kohler (University of Texas Southwestern Medical Center) presented her work on photo-crosslinking sugars^[28] to study host–pathogen interactions. Glycoconjugates mediate extracellular interactions, but because these interactions have low affinities, she developed photoactivatable crosslinkers that could be applied to covalently capture transient interactions. Using this approach, she and her co-workers pinpointed O-linked glycoproteins on the surface of intestinal epithelial cells that mediate interactions with cholera toxin and are required for various pathogenic processes.

Satoru Horiya of the Kraus laboratory (Brandeis University) presented his work on the development of a novel directed-evolution method to evolve a DNA backbone for in vitro selection of multivalent glycopeptides that cluster the 2G12 epitope on gp120.^[29] Liz Luenissen of the Hoenderop and van Delft laboratories (RIMLS, Nijmegen) presented her work on the development of more-polar derivatives of bicyclo[6.1.0]nonyne (BCN) as a means of selectively labeling extracellular glycans by strain-promoted alkyne–azide cycloaddition.^[30] Barbara Imperiali (MIT) gave an inspiring keynote lecture; prefacing her talk with, “Think of the most complicated thing you can think of and tackle it!” Indeed, Imperiali has made significant strides in the complex field of N-linked glycosylation. She covered several diverse topics, including the development of small-molecule inhibitors that target the intermediate steps of N-linked glycoprotein biosynthesis. These inhibitors can be used to study the virulence and pathogenic effects caused by cell-surface glycans. Another interesting approach that she presented was the development of a nanodisc model-membrane system as a platform to study the role of polyprenols in processes such as processivity and SAR by using diverse polyprenols and phospholipids.^[31]

Controlling and Engineering with Light

Using light to regulate and visualize cell-signaling events is an attractive tool for minimizing the perturbation of a cell. Klaus Hahn (University of North Carolina at Chapel Hill) started off the session by showcasing a variety of techniques to visualize and regulate cell-signaling networks. In one example, he presented a method of engineering allosteric control of kinases so that activation would be regulated solely by rapamycin. This was achieved by engineering a constitutively active mutant kinase catalytic domain that contained an inserted modified FK506 binding protein.^[32] In another example, he presented an approach to

control proteins with light by using “LOV-TRAP”, which traps a protein of interest in a membrane of interest so as to prevent it from interacting with its partners, as a synthetic approach to regulate protein activity. When irradiated, the protein is released from the site of sequestration. Jin Zhang (Johns Hopkins University) presented new methods for studying spatiotemporal regulation in living cells. She presented multiple ways to probe the localization of signaling molecules including cAMP, phosphoinositides and calcineurin by using genetically encoded FRET-based reporters.^[33] She also presented novel fluorescent reporters that are sensitive to intermolecular distances so as to allow for super-resolution imaging of dynamic enzyme activity.

Arnaud Gautier (École Normale Supérieure, Paris) discussed the development of fluorescent reporters that bind fluorogens that fluoresce only upon binding. This was achieved by developing a new family of fluorogen-activating proteins followed by screening to identify a shift in fluorescence upon binding the fluorogen dye. David Lawrence (University of North Carolina at Chapel Hill) presented an interesting approach to develop phototherapeutics:^[34] attaching a drug of interest to an alkylcobalamin. The cargo R group (drug, biological agent, etc.) can then be released in a wavelength-dependent manner by using long-wavelength fluorophores to induce cleavage of the Co–R bond of the alkylcobalamin. This scheme can be applied to a variety of drugs and allows the site and timing of release for drug delivery to be regulated. Finally, Laura Nevola from the Girault laboratory (Institute for Research in Biomedicine, Barcelona) presented the development of photoswitchable inhibitors to disrupt PPIs in clathrin-mediated endocytosis as a tool for studying the role of endocytosis in various cellular processes.^[35]

Perspectives

With a focus on the interface of chemistry and biology, this meeting emphasized the significance of each field on the other. Many speakers underlined the importance of integrating all known biology with chemical scaffolds in order to gain a better understanding of the biological effects of chemical structures. As the amount of data can be extensive, there is a critical need to integrate bioinformatics with biological and chemical data in order to gain meaningful insights. Many exciting innovations are being developed to probe the intricacies of biological processes. Such probes will allow us to study biology without perturbing the genetic background or these small molecules, biologics or light-sensitive probes can be designed to regulate biological events. The combination of chemistry and biology powerfully advances both fields towards a greater understanding of biology, the identification of new potential drug targets, and new strategies for inhibitor development. The next meeting, EMBO’s Chemical Biology 2016, is scheduled for September of that year and will surely be filled with all the latest developments and innovations emerging from this exciting field.

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Figure 1.
Meet the Speakers session.

Figure 2.
Chris Lipinski with the meeting organizers before his keynote session. Copyright: EMBL
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Figure 3.
Introduction of the Cell Signaling session.