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ICBS and ECBS Chemical Biology Meeting 2015 - Let Them Come to Berlin!

Toru Komatsu*,†,§ and Satpal Virdee*,‡

†Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan

§JST PRESTO, Tokyo, Japan

‡MRC Protein Phosphorylation and Ubiquitylation Unit, University of Dundee, Dundee, United Kingdom

Chemical biology largely concerns the development of chemically inspired tools for probing biological processes. Such tools range from small molecule probes that enable the selective perturbation of biomolecules involved in cellular pathways, to methodology that enables the construction of biomolecules themselves that are otherwise inaccessible. Researchers working at the chemistry and biology interface have contributed significantly to our understanding of biological phenomena and how they can be modulated for therapeutic benefit. The growth of this field has driven the assembly of a global network. The International Chemical Biology Society (ICBS) was launched with an inaugural conference held at the University of Kansas (USA, 2011). In 2015, ICBS jointly convened with the European Chemical Biology Symposium, a series of symposia organized since 2008 by the European EU-OPENSCREEN consortium. This first joint ICBS and ECBS conference was held in Berlin on October 7−9, 2015. During the meeting, ideas were exchanged over cutting-edge research that covered emerging topics in chemical biology, such as chemoproteomics, epigenetics, conjugates for target delivery, anti-infectives, chemoinformatics and chemical systems biology, molecular imaging, and post-translational modifications (PTMs). The three day meeting was held at Langenbeck Virchow House. The venue, restored to its 1915 state, was a real treat for the >250 participants from all over the world. The pleasure extended to a particularly memorable second evening at the Museum Für Naturkunde where participants dined in the Dinosaur Hall in awe of the fantastic exhibits on display.

On the first day, the meeting started with a welcome note by **Phil Gribbon** (Coordinator of EU-OPENSCREEN at **Leibniz-Institut für Molekulare Pharmakologie FMP in Berlin, Germany**) and **Mel Reichman** (**Lankenau Institute for Medical Research, USA**), President of ICBS. The scientific session began with a keynote lecture by **Timothy J. Mitchison** (**Harvard Medical School, USA**). His lecture started with the question, "How do anti-microtubule drugs work in man?" Taking taxanes, a commonly used class of anti-microtubule chemotherapy drug as an example, he discussed the difference in mode of function for single drugs *in cellulo* and *in vivo*.[1] For example, in culture, paclitaxel causes mitotic arrest and apoptosis of most treated cells, but this is not true *in vivo*, in part because of the differences in S phase cell populations and doubling time between these two settings. He introduced his latest studies aimed at filling this gap. The talk featured thoughtful insights explaining that even established taxane drugs have multiple and complex functions in controlling cellular phenotypes.[2−4] This plenary keynote lecture provided a stimulating opening to the conference.

CHEMOPROTEOMICS

The keynote lecture was followed by the first session entitled "Chemoproteomics." Chemoproteomics connects proteomics with pharmacology or chemical biology.[5,6] In previous decades pharmacology (modulation of protein function with tool compounds or drugs) was the major approach to understanding novel protein functions, but as a result of recent progress in genome sequencing, genetic studies are being used more frequently to discover direct connections between mutations and human disorders. The idea of chemoproteomics is to leverage the use of pharmacological or chemical-biological tools to facilitate target discovery. One of the important pillars of chemoproteomics is forward chemical genetics, or forward drug discovery. In this approach, compounds that give rise to cellular phenotypes are discovered, and the target protein is characterized afterward, so the chance of discovering novel protein functions is much higher.[5,7] However, in such a phenotypic screening approach, the bottleneck is target identification.[8] Many solutions to this long-standing problem have been developed, but so far there is no gold standard. One recently developed and promising technology is the cellular thermal shift assay (CETSA).[9] The assay is based on the biophysical principle of ligand-induced thermal stabilization. The application of thermal shift assays in a cellular format allows studies on target engagement of drug candidates in a cellular context. **Thomas Lundbäck** (**Chemical Biology Consortium Sweden, Sweden**) introduced CETSA techniques with successful research examples.[10] Next, **Bernhard Küster** (**Technical University of Munich, Germany**) described chemical proteomic strategies for profiling the specificities of kinase inhibitors.

Following those talks, **Ben Cravatt** (**The Scripps Research Institute, USA**) spoke on recent discoveries of novel protein functions, focusing on application of the activity-based protein profiling (ABPP) technique to serine hydrolases.[11] Serine hydrolases are an important class of proteins whose functions and relations to disease are poorly understood.[12,13] He introduced an elegant study aimed at understanding the functions of a poorly characterized enzyme named ABHD12.[14] He not only successfully characterized ABHD12 as lysophosphatidylserine lipase but also built on this finding to unveil the molecular mechanism of the neurodegenerative

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disease PHARC. He further proceeded to propose ways to treat the disease by the development of proof-of-concept inhibitors. This study represents a role model for studies aimed at connecting benchside to bedside.

Next, **Michael Bradshaw (Principia Biopharma, USA)** described the elegant development of a potent inhibitor of the tyrosine kinase, BTK. The key to achieving high potency was enhancing residence time at the enzyme active site.[15] This was realized by the use of "warhead chemistry" reported by Jack Taunton's lab that targets proximal cysteine residues in a covalent, but reversible, manner.[16] In principle, the described warhead chemistry can be applied to any inhibitor that binds proximal to a cysteine residue, rendering the inhibitor more potent and specific. It will be very interesting to see how these inhibitors fare during clinical development.

Technologies for labeling proteins with small fluorescent probes in living cells are invaluable for determining cellular localization and realizing the potential of super resolution microscopy. However, a drawback with classical methods is the background fluorescence from unreacted probe material. To address this, a number of probes that demonstrate turn-on fluorescence have been developed. However, these chemistries target specific tags or biorthogonal handles that need to be artificially introduced into the protein under study. Probes that can specifically target canonical amino acids with turn-on properties are lacking. For the last talk of the session, **Kosuke Dodo (RIKEN, Japan)** described a proximity-reactive *O*-NBD (nitrobenzoxadiazole) probe with turn-on fluorescence that targets the ε-amino functionality of lysine residues.[17] The utility of this technology was demonstrated by attaching the *O*-NBD moiety to a *N*,*N*-dialkyl-2-phenylindol-3-yloxylamide (PIGA) ligand that binds translocator protein (TSPO). The probe selectively labeled mitochondria expressing TSPO, and 2D PAGE analysis also revealed that a VDAC (voltage-dependent anion channel) was labeled.

EPIGENETICS

In the following session, four researchers discussed "Epigenetics." First, **Chuan He (The University of Chicago, USA)** introduced RNA methylation, which has been less characterized than the DNA counterpart.[18,19] The importance of RNA methylation was recognized, following his discovery of enzymes that reversibly control N^6-methyladenosine (m^6A) states on mRNA.[20,21] Besides enzymes that control methylation states, other important regulatory proteins in RNA methylation are methylation-specific binding proteins that control translation status or the lifetime of mRNA.[22,23] He introduced his discovery of these proteins, along with a novel member that mediates m^6A methylation on nuclear RNA.

Next, **Angelina Measures (University of Oxford, UK)** talked about the important role of "reader" proteins that recognize methylation/acetylation of histone lysine residues to control transcription.[24] She discussed the discovery of inhibitors of a reader domain using the AlphaScreen platform, supported by computational approaches. The tool compounds discovered should be useful to test the druggability of these domains, as well as providing tools to study the "epigenetic code" by modulating reader protein function.

The potential druggability of epigenetic proteins is still a matter of discussion,[25,26] though some interesting drug candidates have already been developed by pharmaceutical companies.[27] Under these circumstances, academic researchers have much work to do in driving forward our understanding of the intrinsic nature of epigenetic control of biological phenomena. Some pioneering work was next introduced by **Masatoshi Hagiwara (Kyoto University, Japan)**, who has been working on the development of novel ways to treat diseases by controlling the transcriptome. He compared drug discovery to the traditional Japanese sport of horseback bow-shooting. Hitting a target with an arrow fired from a running horse is not an easy task and requires good timing, sufficient skill, and great concentration, but fortunately there are many targets on the way, so even if the rider misses one target, another one is never far away. He described three small-molecule hits from a high-throughput screen and their optimization. The molecules controlled exon skipping (causative of genetic diseases such as Duchenne muscular dystrophy),[28] exon inclusion (causative of genetic diseases such as familial dysautonomia),[29] and the transcription of a broad spectrum of DNA viruses.[30] Despite the difficulties in achieving each goal, the results were promising and clearly illustrate the power of small-molecular drugs for controlling diseases related to epigenetic events. Another successful hit compound was reported by **Maria Duca (Institute of Chemistry of Nice, France)**, who described a small-molecular inhibitor that targets miRNA production.[31]

The second Keynote talk followed and was delivered by **David Tirrell (Caltech, USA)**. A testament to the utility of chemical biology tools is their ability to garner new biological insight. The talk described the validation and application of biorthogonal, noncanonical amino acid tagging (BONCAT) to a whole range of systems from microorganisms to animals.[32,33] BONCAT allows the incorporation of the unnatural amino acid azidohomoalanine (Aha) by the endogenous protein translation machinery. Aha pulsed into cultured cells, or animals, results in the incorporation of Aha into subsequently synthesized proteins. The biorthogonal azido group displayed by Aha can then be coupled to a biotin purification handle, or a fluorescent probe. A derivative of BONCAT employed an evolved synthetase that selectively incorporated the azido-functionalized amino acid (Anl). The use of specific promoters to drive transcription of the mutant synthetase thereby restricts Anl incorporation to specific cells and tissue types. These two approaches form the basis of a powerful platform for studying newly synthesized proteins in cells, animals, and host–pathogen systems.[34]

CONJUGATES FOR TARGETED DELIVERY

The second day began with a session entitled "Conjugates for targeted delivery." Antibodies are an important class of therapeutics, with excellent disease-homing properties. While antibodies alone can have potent biological activity, antibodies "armed" with additional functionality can be more efficient and serve as powerful therapeutic tools, representing an attractive field for chemical biologists. As an example, **Dario Neri (ETH Zürich, Switzerland)** introduced the art of fusing anti-inflammatory cytokines with disease-homing antibodies to generate immunocytokines.[35] The idea of boosting the activity of the immune system against tumors has been considered promising for a long time, but the use of cytokine alone is insufficient due to the lack of potency and selectivity for target tumor sites. The idea of immunocytokines is to utilize antibodies or antibody fragments as pharmacodelivery vehicles for cytokines. This approach is very effective, as was shown by a number of examples, including TNFα-conjugated anti-EDB-fibronectin human antibody L19 and IL-2-conjugated L19, agents that were confirmed to be effective in patients.[36] Besides

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these novel antibody-based therapeutics, he also outlined another project aiming to develop potent binders based on DNA-encoded chemical libraries. He has developed small molecules with ultrahigh binding affinity (sub-nM K_d) for their targets, rivalling that of antibodies.[37] Furthermore, by using fluorescent conjugates, accumulation in tumor sites of model mice was clearly observed. Bypassing antibodies enables facile handling, quality control consistency, optimization, and derivatization. In short, this is a powerful way to develop functional therapeutic tools based on chemical-biological knowledge.

A current limitation of biologics for cytosolic targets is their inefficient delivery across the plasma membrane. Cell penetrating peptides (CPPs) offer potential to deliver such cargoes, and the next two talks focused on developments in this area. **Jean-Phillipe Pellois (Texas A&M University, USA)** described a variant of the TAT peptide that could efficiently deliver a number of cargoes into the cytosol of mammalian cells.[38] The CPP consisted of a disulfide-linked TAT dimer conjugated to a tetramethylrhodamine (TAMRA) fluorophore. Cell uptake was demonstrated to be mediated by endocytosis followed by endosome escape. The inefficiency of this latter step has limited the utility of conventional CPPs, so this approach appears to be a significant advance. A somewhat conflicting talk followed from **Henry David Herce (Rensselaer Polytechnic Institute, USA)** describing cyclized versions of TAT that similarly enabled substantially enhanced delivery of protein cargoes.[39] However, it was proposed that endosome escape is not involved in CPP delivery, but rather direct diffusion through the plasma membrane. Together, these two strategies should increase the options available for macromolecule delivery into cells.

The next speaker was **David Margulies (Weizmann Institute, Israel)**. His talk described work on rewiring signaling pathways with chemical transducers. A potential application of this research is the development of novel modes of therapy. One interesting aspect involved the use of oligonucleotide (ODN)−small molecule conjugates that could be used to couple platelet-derived growth factor (PDGF) to activation of an enzyme, in this case, glutathione-*S*-transferase (GST).[40] Prodrug release could be programmed by Boolean logic such that GST activity and hence PDGF (where high levels are secreted by certain cancer cells) are both required. This technology was demonstrated as a proof of concept experiment in cell-free medium, so it will be interesting to see how these approaches can be extended to cells.

To wrap up the session, **Hidde Ploegh (Whitehead Institute, USA)** presented some of his latest work. Here, modified single domain antibody fragments (VHHs) were used as tools to detect immune cells and thereby use their infiltration of cancer cells to indirectly and noninvasively image tumors.[41] The small size of VHHs enabled their functionalization with a number of modifications such as PET tracers and fluorophores, using versatile sortase-mediated reactions.[42] The VHH format also enables cytosolic expression in mammalian cells, allowing measurement of phenotypic effects arising from perturbation of specific protein−protein interactions.

RISING STARS IN CHEMICAL BIOLOGY

A traditional component of ICBS meetings is a Rising Stars session, where up and coming young chemical biologists are given well-deserved recognition. This year's winners were **Alessio Ciulli (University of Dundee, UK)**, **Evan Miller (Berkley, USA)**, and **Edward Lemke (EMBL, Germany)**.

Alessio presented his work on establishing "bump and hole" approaches to Bromo and Extra-Terminal (BET) proteins.[43,44] Originally pioneered by the Shokat lab, the "bump and hole" approach is a chemical genetic method that can be used to obtain enzyme family member selectivity based on an otherwise pan-specific small molecule inhibitor.[45] BET proteins contain bromodomains that are dedicated recognition modules of lysine-acetylation marks on histone tails. Pan-specific inhibitors of BET family proteins have been developed (e.g., I-BET) that appear as a promising mode of therapy against several cancers and are currently in clinical trials.[46] While there has been keen interest in developing BET family member-specific inhibitors, it is not clear which family member to target. Alessio's approach involved mutating a conserved leucine residue in the bromodomain binding pocket to alanine.[43] This "hole" was then complemented by the introduction of an ethyl "bump" on the I-BET scaffold. The selectivity imparted by this approach toward a specific bromodomain in a BET family member was ∼2 orders of magnitude. The approach should prove valuable for probing the individual roles of bromodomains within specific BET family members. The next part of Alessio's talk described the development of novel proteolysis-targeted chimeras (PROTACs).[47] PROTACs are bifunctional compounds containing components that bind a target protein and a promiscuous E3 ligase. This permits reassignment of the E3 ligase to that of the target protein. The ubiquitination of the target protein results in its degradation by the proteasome. A key aspect of this strategy is that the protein is not simply inhibited, but removed from the cell in a substoichiometric manner (i.e., a single PROTAC can initiate the degradation of multiple copies of the target protein). Alessio's example utilized the VHL E3 ligase that was redirected to the previously discussed BET proteins.[48] Similar approaches have been reported by other laboratories highlighting the potential general applicability of this novel mode of therapy.[47]

The next recipient was **Evan Miller (Berkley, USA)**, who talked about the development of small molecule voltage sensors that can be used as probes of neuronal activity.[49,50] Membrane potential (V_{mem}) is classically measured with electrodes using patch clamp methods, which limits measurements to a single cell. Optical techniques are far less invasive and are amenable to higher throughput execution. However, existing optical approaches only provide an indirect measure of $V_{mem.}$ Evan described powerful probes such as BeRST that provide a direct measure of V_{mem}.[50] Variants that were photoactivatable, thereby conferring spatial resolution, were also described.[49] These probes should be valuable for the noninvasive and multicellular study of neuronal activity.

Edward Lemke (EMBL, Germany) spoke on bioorthogonal labeling of proteins in cells with fluorescent probes, with particular focus on methodologies that enable multicolor labeling.[51,52] His methods were based on the genetic incorporation of unnatural amino acids (UAAs) bearing strained ene and yne functionality. By tuning the kinetics of the popular strain promoted inverse-electron-demand Diels−Alder cycloaddition (SPIEDAC) reaction, a new and orthogonal variant was developed termed selectivity enhanced SPIEDAC (seSPIEDAC).[51] In conjunction with a bispecific UAA incorporation system, the utility of this approach was demonstrated by the labeling of two populations of the insulin receptor with two distinct probes.

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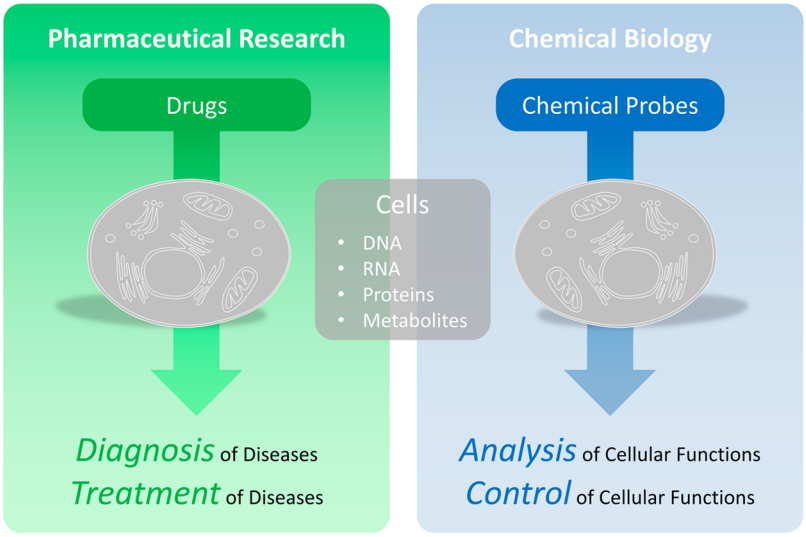

Figure 1. Similarities and differences between pharmaceutical research and chemical biology.

The session was rounded off with a Keynote Talk by **Carolyn Bertozzi (Stanford University, USA)**. Carolyn discussed the application of the revolutionary bioorthogonal chemistries her lab has developed to peptidodoglycan imaging.[53,54] This involved metabolic incorporation of unnatural D-amino acids, bearing click handles, into peptidoglycans and subsequent labeling with fluorescent dyes using bioorthogonal chemistry such as copper-catalyzed azide−alkyne cycloaddition (CuAAC). Her studies provided significant insight into peptidoglycan dynamics of *Listeria* in the context of infected macrophages. As an example, by monitoring the labeling of the bacterial pole and the septum upon macrophage infection, it was apparent that bacterial division was halted, and elongation becomes more pronounced.

ANTI-INFECTIVES

The Nobel Prize in Physiology or Medicine 2015 was awarded to three researchers who developed novel therapeutics for infectious diseases based on complex natural products. Discovery of natural products with significant biological activity has been one of the hottest areas in chemical biology, and in the session "Anti-infectives," excellent talks on constructing current and future therapeutics were presented. **Rolf Müller (Helmholtz Institute for Pharmaceutical Research Saarland, Germany)** talked about two great discoveries in natural product science, cystobactamids, which are highly potent novel antibacterial compounds,[55] and griselimycin derivatives, which are active against *M. tuberculosis*.[56] **Michael P. Manns (Hannover Medical School, Germany)** talked about how his team has been fighting hepatitis C by developing various forms of therapy, many of which have become standard care for hepatitis C worldwide.[57−60] These exciting talks were followed by those from **Lixin Zhang (Institute of Microbiology, China)**,[61,62] **Rainer Haag (Freie Universität Berlin, Germany)**,[63,64] and **María Maneiro (Concepción González-Bello group, Universidad e Santiago de Compostela, Spain)**,[65] who came up with novel ways and natural product compounds to fight various infectious diseases. Clearly, extensive background knowledge in this field is key to generating novel therapeutics in the continuing fight against infectious diseases.

CHEMINFORMATICS AND CHEMICAL SYSTEMS BIOLOGY

The next session was "Cheminformatics and Chemical Systems Biology," which included the special topic "Quality of Chemical Probes." The use of chemicals to control or monitor cellular phenotype has much in common with small-molecular therapeutics to control disease-related biomolecules (Figure 1).[66] The past decade of effort by academic researchers has advanced chemical biology, since it is a powerful way to fill the gap between the vast numbers of new genes that have been discovered and the lack of validated drug targets and ways to modulate them. The efforts have borne fruit, resulting in novel technologies, novel chemical tools to study cellular functions, and novel lead compounds for medicines, but the development of useful reagents with high potency, high selectivity, and a proven mechanism of action remains challenging. Indeed, some commercially available drugs, or historically established chemical probes, are nonselective when used in complex biological systems.[67] Under the circumstances, the important question is, how can we establish the selectivity of chemical probes and better evaluate the biological phenomena reported by their actions?

The first speaker in the session, **Jordi Mestres (Institut Hospital del Mar d'Investigacions Mèdiques, Spain)**, discussed how the effect of polypharmacology can be studied by computational approaches.[68] Polypharmacology, i.e., modulation of multiple targets at the same time by a single drug, is currently considered a unique advantage of small-molecule-based medicine over other modes of therapy.[69,70] The important question is, how can one evaluate the effect of polypharmacology correctly in order to predict the therapeutic efficacy? The speaker talked about the power of advanced bio- and chemo-informatics for this purpose. **Tudor Oprea (University of New Mexico School of Medicine, USA)** clearly described the status of current drug and protein discovery based on data acquired from over 100 omics and informatics sources, effort funded through a Common Funds initiative (NIH U54 CA189205). Using metrics derived from text mining, patent analytics, antibodies, and other sources, he categorized ∼38% of the human proteome (7681 proteins) as "Tdark," i.e., functionally enigmatic proteins or the so-called "ignorome."[71] Another 592 proteins (2.9%) have a confirmed

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mechanism of action for approved drugs ("Tclin"). Two other categories reflect levels of literature, functional and disease annotations ("Tbio," 53.1%) and knowledge about (potent) small molecules ("Tchem," 5.9%). He noted that there appears to be a knowledge deficit, i.e., we lack understanding of protein function for 38% of the human proteome, and that less than 3% of the human proteome is therapeutically addressed by drugs. Given our current understanding of disease concepts, he estimated that more than 70% of human diseases are currently unaddressed by a therapeutic agent. Thus, the field of drug discovery is wide open. Better chemical tool compounds are one of the key pathways to construct good drugs.[5]

Besides specialized informatics studies, the enrichment of public databases accessible to drug discovery scientists is an important way to facilitate the connection between chemical biology and drug discovery, and a study based on three public databases was introduced. ChEMBL[72] (https://www.ebi.ac.uk/chembl/) is an established database for chemical biology, along with PubChem, and **Prudence Mutowo (EMBL, Germany)** showed how the combination of the ChEMBL database and a gene ontology platform is valuable for navigating the target space of specified proteins, to understand which chemicals target a protein of interest, and to glean the biology influenced by the chemicals. **Albert A. Antolin (Institute of Cancer Research, UK)** pointed out the difficulty in target validation of tool compounds in cancer translational research. He demonstrated how the precise scoring of chemobiological data and its interpretation can be facilitated with the canSAR (https://cansar.icr.ac.uk/) database platform, assisting the study of deregulated proteins in cancer cells.[73,74] In the last session, **Jonathan Baell (Monash University, Australia)** introduced the relatively new public database, Chemical Probes Portal (http://www.chemicalprobes.org/), which was designed to address the above-mentioned problems of quality evaluation of chemical probes, which frequently gives rise to questionable compounds he has coined pan-assay interference compounds (PAINS).[66] In the database, researchers can access information such as the best available chemical probe for a protein of interest, along with the latest information on activity and selectivity, and suitable control compounds for biological studies. If the evaluation is done correctly and the probes are used properly, studies of various biological events could become more robust and reliable, so this database has the potential to aid the generation of valuable pharmaceutical drugs. This again stresses the importance of expanding this field and promoting worldwide communications and granting access to research data.

MOLECULAR IMAGING

The next session was "Molecular Imaging." **Carsten Schultz (EMBL, Germany)** introduced his latest discoveries concerning the development of tools to manipulate cellular function. Manipulation and visualization of cellular events are two important aspects in technology development, and his talk summarized how chemical knowledge can contribute to developing technologies in both areas, and how their combination can generate novel biological discoveries. As an example, he introduced his latest research results on understanding how lipid signaling, e.g., by diacylglycerol, is spatiotemporally mediated.[75,76] Development of another synthetic biological tool was discussed by **Toru Komatsu (The University of Tokyo, Japan)**,[77,78] and work on tools for bioimaging was presented by **Vankata Pavan Kumar Kondapi (University of Alberta, Canada)**, who described an effort to develop a smart tool to visualize GLUT5 activity using a GLUT5-selective sugar moiety,[79] and **Orsolya Demeter (Hungarian Academy of Sciences, Hungary)**, who developed a flexible platform for multivalent fluorogenic labels[80] *via* double-click techniques. As is popularly said, "seeing is believing," and fluorescence imaging is one of the ways that researchers can get valuable information on intracellular events by direct observation. Molecular imaging is being used more and more in drug discovery and development,[81] as well as disease diagnosis,[82] so we can expect a lot more progress in the field in the near future.

PROBING THE STRUCTURE AND FUNCTION OF PTMS

The next session was dedicated to post-translational modifications (PTMs). When studying substrates bearing PTMs, a common challenge arises from complications associated with the preparation of site-specifically modified substrates bearing a well-defined PTM. Another challenge is associated with the detection and enrichment of substrates modified with distinct PTMs. Chemical biology approaches have greatly advanced this area, and it was fitting that a session was dedicated to this topic.

The session was kicked off by **Hilal Lashuel (Ecole Polytechnique Federale de Lausanne, Switzerland)**. Hilal reported the total chemical synthesis of post-translationally modified forms of α-synuclein (α-syn). Parkinson's disease is associated with neuronal protein aggregates (Lewy bodies) which contain high concentrations of post-translationally modified α-syn. The identification of a PTM that is associated with pathogenicity will be an important discovery and could serve as a novel therapeutic target for Parkinson's disease. Hilal described the synthesis and characterization of an array of modified forms of α-syn.[83−87] The next speaker was **Carlo Unverzagt (University of Bayreuth, Germany)**. Carlo described work from his lab involving the convergent synthesis of homogeneous glycoforms of human interleukin-6.[88] Protein semisynthesis can present a number of technical challenges, and Carlo described a raft of chemical ligation strategies that were necessary for successful synthesis.[89] **Dorothea Fiedler (Leibniz-Institut für Molekulare Pharmakologie, Germany)** next spoke on her studies of the arcane PTM pyrophosphorylation. Dorothea's talk described the development of the tools necessary to study this poorly characterized PTM. These included nonhydrolyzable analogues,[90] production of pyrophosphopeptides,[91] and metal complexes for enrichment and detection.[92,93] The tools reported should be invaluable for studying pyrophosphorylation and establishing its cellular role. The next speaker was **Yao-Wen Wu (Chemical Genomics Centre of the Max Planck Society, Germany)**. Regulation of autophagosome formation is mediated by modification of the phosphatidylethanolamine headgroup, displayed on autophagosome membranes, with the ubiquitin-like protein, LC3. Removal of LC3 can be carried out by the *Legionella* effector protein RavZ, yet the mechanism is poorly understood. The talk described the semisynthesis of lipidated forms of LC3 which provided novel insight into how pathogenic effectors subvert the host's autophagy machinery.[94] **Satpal Virdee (MRC Protein Phosphorylation and Ubiquitylation Unit, UK)** spoke next and described the design and development of novel activity-based probes (ABPs) that profile the transthiolation activity associated with E1 activating enzymes[95] and

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ubiquitin E3 ligating enzymes.[96] In proof-of-concept work, he reported the profiling of the Parkinson's disease-associated E3 ligase Parkin, revealing a number of insights into the pathology and mechanism of this enzyme.[96]

The final talk was a Keynote Lecture from **Jason Chin (MRC Laboratory of Molecular Biology, UK)**. Jason discussed a large body of work from his lab using genetic code expansion approaches to interrogate PTMs and protein function in general. Genetic methods for directing the incorporation of PTMs are a powerful complement to chemical methods. In principle, genetic methods can be used to prepare site-specifically modified substrate proteins in the native state (i.e., no requirement for substrate assembly from constituent peptide building blocks followed by protein folding). In principle, this makes large substrates and those not amenable to artificial folding accessible. A number of strategies were described for genetically incorporating, or directing, a number of PTMs including acetylation,[97] ubiquitination,[98,99] and phosphorylation.[100] Approaches for acetylation and ubiquitination were used to provide novel biological insights into chromatin dynamics[97] and deubiquitinating enzyme specificity,[98] respectively. Jason also spoke about an exciting new technology dubbed genetically directed bioorthogonal ligand tethering (BOLT) for the selective and reversible regulation of protein activity in cells.[101] This provides an alternative but conceptually similar strategy to the "bump and hole" methods described earlier.[43,45]

An important part of the conference was the excellent poster sessions that were accompanied by short "speed" talks. Prizes were awarded, kindly provided by Wiley—Chembiochem and Sanofi, to those considered the best. The recipients were **Benjamí Oller-Salvia (IRB Barcelona)**, **Dominik Schumacher and Florian A. Mann (Leibniz-Institut für Molekulare Pharmakologie, Germany)**, **Jan-Philip Schuelke (Pfizer, Boston)**, **Elles Ostensen (University of Oslo, Norway)**, **Abukakar Jalloh (Albert Einstein College, USA)**, and **Anuchit Phanumartwiwath (Oxford University, UK)**.

The ICBS and ECBS are young organizations that were launched less than 10 years ago. The joint meeting held in Berlin was a testament to the momentum the societies have attained. The quality and diversity of science was a true reflection of the very best in international chemical biology and we look forward to what the 2016 meeting will bring, to be held in Madison, Wisconsin.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: tkomatsu@mol.f.u-tokyo.ac.jp.

*E-mail: s.s.virdee@dundee.ac.uk.

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