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Conference Report

EFMC-ISCB 2023

International Symposium on Chemical Biology

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The first International Symposium on Chemical Biology (EFMC-ISCB) jointly organized by the European Federation for Medicinal Chemistry and Chemical Biology (EFMC) and the Swiss Chemical Society, Division for Medicinal Chemistry & Chemical Biology (DMCCB) took place November 16th – 18th, 2023 at the Congress Center Basel in Switzerland. The symposium celebrates the great achievements and innovations in chemical biology.

The conference opened with remarks from one of the chairs of the organizing committee, Dr. Yves P. Auberson (Novartis) who then introduced the first plenary lecturer ***Dr. John Tallarico*** (Novartis). Dr. Tallarico's presentation was about the importance of target recognition of molecular glues during the development of degraders for the undruggable proteome. The presented examples highlighted that screenings looking into target recruitment are a key aspect of drug development. ***Dr. Markus Bantscheff*** (Cellzine/GSK) opened the first session about *Chemical Proteomics in Drug Discovery* with an overview of chemoproteomics, which relies on probe-based 'pull-out' assays from cell extracts. The talk also discussed studying target proteins with biophysical techniques such as thermal proteome profiling, cellular thermal shift, and quantitative MS. The next speaker, ***Dr. Stephan Hacker*** (Leiden University) presented competitive residue-specific proteomics mainly examining cysteine targeting, but a sampling for other side-chains was also shown. The importance of activity-based proteome profiling for lead identification was highlighted by ***Dr. Uwe Grether*** (F. Hoffman-La Roche) with the example of finding an inhibitor for monoacylglycerol lipase (MAGL), a key metabolic node in the central nervous system. The short presentation by ***Dr. Mikah Niphakis*** (Lundbeck) gave insights into how drug metabolism and pharmacokinetics for safe and efficient covalent drugs depend on understanding chemical and metabolic stability as well as proteome reactivity and selectivity. During the lunch break, the workshop from WuXi AppTec presented by ***Dr. Tao Guo*** gave insights about emerging modalities in drug discovery.

Fig. 1. The great atmosphere during the breaks, captured by F. Venturi.

After lunch and time for networking, the second session of the day (*Computational Chemical Biology*) commenced with the keynote lecture by ***Prof. Alessandra Magistrato*** (CNR-IOM), who emphasized the power of combining quantum mechanics/molecular mechanics (QM-MM) simulations for elucidating enzymatic mechanisms such as Group II intron splicing. The presentation highlighted the importance of combining experimental results with atomic-level simulations *e.g.* to understand the impact of metal ions in folding and the influence of mutations on RNA binding. Then, Martini coarse-grain models were introduced by ***Prof. Manuel Melo*** (University Nova de Lisboa), showcasing their potential through examples of investigating protein-DNA interactions to predict DNA recognition sites. Continuing with coarse-grained molecular dynamics, ***Prof. Vittorio Limongelli*** (Universita Della Svizzera Italiana) presented about combining it with funnel metadynamics to understand the activation and dimerization of G-protein coupled receptors upon ligand binding. After a short break, ***Dr. Richard Doveston*** (University of Leicester) opened the session about *Chemically Induced Proximity* with his presentation about native MS investigations on the interaction of 14-3-3 with MDM2 and the influence of phosphorylations. That enabled the development of covalent molecular glues. Afterwards, selective tumor targeting by antibody-based cytokine delivery was presented by ***Prof. Dario Neri*** (ETHZ, Philochem), highlighting the potential demonstrated by data from preclinical and clinical studies. His colleague ***Dr. Samuele Cazzamalli*** (Philochem) then gave insights into the application of small-molecule-based FAP-targeting therapeutics in PET imaging and drug development. The session was closed by the keynote lecture of ***Prof. Alice Ting*** (Stanford University), who joined by video conference and covered her seminal and recent work on proximity-labeling strategies. LOV-Turbo, a light-regulated variant of Turbo-ID, enables the labeling *via* nano-BRET technology, while LipoID uses LpIA-enzyme to install lipids with handles, such as azide or bromine, for further functionalization. Finally, the poster session was combined with a reception to cap off a spectacular first day.

Prof. Claudia Höbartner's (University of Würzburg) plenary lecture kicked off the second conference day. She gave insights into a methyltransferase ribozyme that catalyzes the installation of 1-methyladenosine into target RNA. In addition, SAM-analogue utilizing ribozyme (SAMURI) was applied for intracellular site-specific RNA labeling using engineered SAM cofactors. The following morning session about *Target Engagement and Mechanism of Action Determination* started with ***Dr. Rachel Grimley*** (Cancer Research Horizons (Cancer Research UK)), who highlighted the importance of understanding the structure-kinetics relationship during drug design in her keynote lecture. She concluded that drug-target residence models and potential conformational changes upon drug binding should therefore be considered in the drug discovery toolbox. ***Dr. Mikhail Savitski*** (EMBL) emphasized the effects of PTMs, such as phosphorylation, on the biophysical properties of proteins showing examples of thermal proteome profiling on mumps virus proteins. The synergies between transcriptomics and proteomics were highlighted

by ***Dr. Meha Singh*** (AstraZeneca), showcasing the potential for substrate identification of an E3 ubiquitin-protein ligase by analyzing proteome changes after degrader treatments. Then, ***Dr. Slava Ziegler*** (MPI of Molecular Physiology) presented cell painting assays to label different cell compartments with different dyes to enable the mapping of bioactivity cluster spaces.

In the afternoon, ***Prof. Dorothee Kern*** (Brandeis University) gave the first presentation in the session *Investigations of Protein Conformations: Beyond the Ground State*. She made the case that combining high-pressure NMR data and MD simulations can help to predict the active, high-energy, states of enzymes. She explained how studying protein conformational dynamics can help in understanding biological functions. Then, ***Dr. Anna Vulpetti*** (Novartis) highlighted how conformational change analysis *via* ^{19}F NMR spectroscopy can assist in hit findings and fragment optimization as shown for studies on interleukins. The investigations of intrinsically disordered proteins and protein regions by NMR were presented by ***Prof. Martin Blackledge*** (Institut de Biologie Structurale (IBS)), who showcased the potential of this technique in investigations on the replication machinery of Measles virus and avian influenza. ***Prof. Sebastian Deindl*** (Uppsala University) then underlined how single-molecule FRET *via* the local generation of NTPs (LAGOON) was applied to deepen the understanding of the dynamics of chromatin packing. After a break, the session about *Targeting Metabolism* started with an overview of how cancer metabolism is altered by ***Prof. Matthew G. Vander Heiden*** (MIT). We learned from him that carefully controlling media for cancer cell growth is critical because it can affect the efficacy of some drugs. In addition, to target the metabolism, intra- and extracellular conditions have to be adjusted to counterbalance effects such as altered cell redox states. ***Dr. Luca Laraia*** (Technical University of Denmark) then took over and introduced intracellular sterol transport proteins and how bifunctional molecules were used either to identify potent inhibitors or to stabilize proteins by shielding them from natural degradation. In the last talk of the day, ***Dr. Maren Heimhalt*** (LMU Munich) described how the activation of transcription factor ChREBP (which controls insulin sensitivity) can be modulated by a proteolytic cleavage site separating the inhibitory from the transactivation domain. In the evening, a lively poster session with many discussions set the stage for a wonderful symposium banquet at Schützenhaus Basel.

The final day was opened by ***Prof. Thomas Carell's*** (LMU Munich) plenary lecture about how cytidine methylations and oxidation products of those methyls in DNA represent a second dimension of the genetic code. He showcased how chemical synthesis of isotopically labeled and F-labeled nucleobases combined with MS experiments assist in deepening the understanding of these DNA modifications. Afterwards, the morning session about *Chemical Immunology and Checkpoint Inhibitors* commenced with ***Prof. Marc Vendrell*** (University of Edinburgh) with his presentation about the use of fluorescent amino acids and peptides. This technology was applied to selectively label macrophages for imaging live-cell interactions and cell sorting. This strategy could also distinguish exhausted and active T-cells and was used for in-human imaging of infection and inflammation sites. Next, two labeling strategies were introduced by ***Dr. Kimberly Bonger*** (Radboud University): enzyme-mediated nitrenium ion formation for reactions with biomolecules and the THRONCAT methodology, which uses β-ethynyl serine as a threonine analog to introduce an alkyne handle. ***Dr. Alberto Fernández-Tejada*** (CIC bioGUNE) presented SAR studies on QS-21 for the development of optimized saponin immunoadjuvants yielding an improved derivative assessable *via* a modular synthetic strategy. Before the lunch break, ***Dr. Rachel Hevey*** (University of Basel) showcased early lead-structure studies for the design of glycomimetic antagonists with improved drug-like properties against a C-type lectin important in the complement innate immune pathway.

The session about *New Understandings of Post-translational Protein Modifications* (PTM) began with ***Prof. Tom Muir's*** (Princeton) keynote lecture on new methods for investigating changes in chromatin interactions, PTMs and mutations in chromatin influence structure and intracellular interactions. Therefore, proximity-labeling strategies are applied and can be used for imaging, proteomics, and genomics. Protein pyrophosphorylation introduced by inositol pyrophosphate messengers was described by ***Prof. Dorothea Fiedler*** (FMP), who then presented synthetic approaches and analytical tools based on MS to study this PTM. In the following invited lecture, ***Prof. Beat Fierz*** (EPFL) presented the combination of synthetic protein chemistry and single-molecule fluorescence assays to directly investigate DNA repair mechanisms. He then discussed his studies on tubulin proteins looking into the crosstalk of enzymes installing PTMs (poly-glutamylation and detyrosination). First results for a photochemical approach to identify and investigate protein crotonylation *via* radical-mediated thiol-ene click chemistry were shown by ***Dr. Rita Petracca*** (Utrecht University).

Fig. 2. Photo taken at the banquet at Schützenhaus Basel on Friday by F. Venturi.

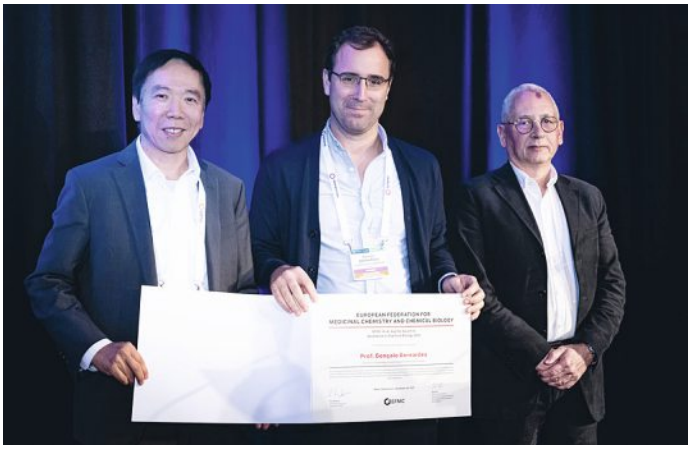

Fig. 3. Prof. Gonçalo Bernardes (middle) receiving the EFMC-WuXi AppTec Award for Excellence in Chemical Biology presented by Dr. Tao Guo (left) and Prof. Rui Moreira (right) (Photo by F. Venturi).

Prof. Gonçalo Bernardes (University of Cambridge and IMM Lisboa) received the EFMC-WuXi AppTec Award for Excellence in Chemical Biology presented by Prof. Rui Moreira and Dr. Tao Guo and gave a lecture with insights into different pro-

tein- and antibody-labeling strategies as well as a biorthogonal Pt-triggered bond cleavage for targeted drug activation developed in his lab. Moreover, he introduced the concept of click-degraders, small molecules targeting and irreversibly degrading RNA if in close proximity. This technology was applied to develop meCLICK-Seq, probing and mapping RNA methylation, and proximity-driven RNA degraders exemplified by targeting and degrading *e.g.* SARS-CoV-2 genomes.

The lecture was followed by another highlight: the announcement of the best poster awards by Prof. Yimon Aye (EPFL): ***Ivy Guan*** (University of Sydney) and ***Dr. Marko Cigler*** (CeMM) were honored with the first poster prize by EFMC and International Chemical Biology Society. In addition, ***Marie-Désirée Scheidt*** (University of Neuchâtel), ***Dr. Marta Serafini*** (University of Oxford), ***Matthias Bütikofer*** (ETHZ), and ***Dr. Zacharias Thiel*** (Novartis) received the second poster prize by Chemistry Europe.

Fig. 4. Poster prize winners and committee (from left to right): Prof. Zaneta Nikolovska-Coleska, Dr. Marko Cigler, Prof. Yimon Aye, Marie-Désirée Scheidt, Ivy Guan, Matthias Bütikofer and Prof. Claudia Höbartner (Photo by F. Venturi).

The conference was closed by the final remarks of Prof. Maja Köhn (University of Freiburg). Overall, it was an inspiring symposium with great contributions, and we are all looking forward to the next EFMC-ISCB on January 29th – 31st, 2025 in Basel, Switzerland.

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