Proceedings of the ICBS2018 Conference
September 24-27, 2018, Vancouver, Canada

SEPTEMBER 24, PREMEETING DAY

A year has flown by, and chemical-biologists from all over the world have gathered together again for the ICBS Annual Conference to share and discuss exciting achievements, cutting-edge technologies, and the biggest challenges in the chemical biology field.

The ICBS2018 meeting started in beautiful Vancouver with the Young Chemical Biologist's Forum opened by four lectures given by chemical-biology experts: Dr. Jonathan Baell (Monash University, Australia), Dr. Doug Auld (Novartis, USA), Dr. Scott Lovell (University of Kansas, USA), and Dr. Andrew Zhang (AstraZeneca, USA). In the opening lecture "PAINS and Nuisance Compounds: Sorting the Wheat from the Chaff in Bioactive Compounds" Dr. Baell highlighted the significance of identification of pan assay interference compounds (PAINS) for drug and chemical-probe discovery. Dr. Baell discussed different types of interference, including the chemical impurity and heavy metal contaminations. The appearance of PAINS compounds within the approved drugs and natural products was discussed, and the use of unbiased electronic filters to reveal the PAINS core structure was suggested to enhance the hit identification pipelines. The Eight Points Action Plan (EPAP) workflow specifically designed to facilitate hit discovery has been presented.

The challenges associated with the assay interference were further elaborated by Dr. Auld. In his talk entitled "Assay Development and Screening" Dr. Auld indicated different types of assay interference compounds and the ways to validate the hits in orthogonal assays. In addition to computational tools, different experimental approaches were presented, including the counter-screen, orthogonal, and multiparametric approaches. Dr. Auld discussed the assay-specific artifacts often observed in different biochemical, fluorescence-based, and gene reporter assays as well as different strategies to address the assay interference issues.

Dr. Lovell's talk has illuminated the significance of structural component in chemical-biology field.

A detailed overview of the protein structure analysis pipeline included considerations for initial protein construct design, protein purity analysis, crystallization screen assays, crystal imaging and analysis, X-ray diffraction data generation, and structure solution to build a 3D structure. Then, Dr. Lovell discussed the current approaches for the ligand complex crystallization exemplified by luciferase inhibitor crystallization, norovirus 3CL protease inhibitors, and application of structural analysis to design cyclic peptide inhibitors of iPGM protein that is often considered as an undruggable target. The presentation generated an interesting discussion about the methods to capture dynamical changes in protein structure as well as the advances in the field of crystallization of membrane bound proteins.

The Expert-Led forum was concluded by exciting presentation by Dr. Zhang entitled "Chemical Biology in Industry: Small Molecule Driven Target Deconvolution Strategies" that highlighted a critical role of chemical-biology in therapeutic development. Dr. Zhang discussed target discovery and selectivity profiling techniques, including lysis based and cell based proteomic approaches and methods of data visualization. Dr. Zhang presented the recent stories of discovery of MCT4 as target for lactic acid efflux, and design of photoaffinity probes for cell-based proteomics for hit prioritization, illustrated by the targeting of BCL6 protein-protein interactions.

The Student-Led session of the forum included ten outstanding talks given by students and young postdocs, and covered diverse aspects of modern chemical-biology. Kun Qian (Emory University, USA) has introduced the ICBS-Emory student chapter, the second student chapter in the US after University of Michigan, and presented the discovery of new inhibitors for YAP-TEAD protein-protein interaction that regulates proliferation, survival, and cancer metastasis. Eline Sijbesma and Sebastian Andrei (Eindhoven University of Technology, Netherlands) presented their approaches to discover new stabilizers of protein-protein interactions, specifically for 14-3-3 proteins. Ali Nejatie's talk (Simon Fraser University, Canada) was focused on chemical synthesis of new fluorogenic probes for sialidase from Aspergillus fumigatus pathogen that cause a severe respiratory disease in immunocompromised individuals. Phillip Danby (University of British Columbia, Canada) and Oluwafemi Akintola (Simon Fraser University, Canada) presented their research focused on the substrate design, synthesis, and kinetics studies to understand the mechanisms of glycosyl hydrolases. Elena Reckzeh (Max Planck Institute of Molecular Physiology, Germany) gave a methodological overview of thermal proteome profiling for target identification, including thermal proteome profile (TPP) and CESTA methods for target identification and confirmation. Karson Kump (University of Michigan, USA) and Thomas Garner **(**Albert Einstein College of Medicine, USA) presented their studies focused on discovery and validation of new inhibitors for BCL2 family. Michael Winzker (Max Planck Institute of Molecular Physiology, Germany) discussed the discovery, application, and challenges of small molecules to regulate protein degradation using the proteolysis targeting chimeras (PROTAC) and in-cell click-formed proteolysis targeting chimeras (CLIPTAC) approaches.

The day was continued with the Tech Talks: "Creating and Deploying Next Generation Informatics Solutions – What We've Learned Along the Way" by Dr. Whitney Smith (Collaborative Drug Discovery, USA) and "Antibody-Drug Conjugates" by Dr. Graham Garnett (Zymeworks, Canada).

Then, the ICBS2018 was officially opened by the keynote lecture "PROTAC-mediated Protein Degradation: Making Problem Proteins Go Away" given by Dr. Craig M. Crews (Yale University, USA). Dr. Crews is the Lewis Cullman Professor of Molecular, Cellular and Developmental Biology and holds joint appointments in the departments of Chemistry and Pharmacology at Yale University. Dr. Crews graduated from the U.Virginia with a B.A. in Chemistry and received his Ph.D. from Harvard University in Biochemistry. His laboratory pioneered the use of small molecules to control intracellular protein levels, and currently Dr. Crews is focused on a new 'induced protein degradation' drug development technology, PROTAC. In his exciting lecture Dr. Crews discussed specific structural and chemical requirements for efficient PROTAC degradation, such as inker-dependent target specificity and proper location of the target lysine residue. The successful application of the PROTAC approach was illustrated by many examples including the targeting of TBK1, EGFR, P38a, BRD4, and androgen receptor with newly designed PROTACs compounds. Dr. Crews has highlighted the application of PROTAC methods to selectively degrade cancer-related mutants and to target the undruggable proteome for cancer therapeutic discovery.

SEPTEMBER 25, DAY 1

The Conference Day 1 was open by the Degradomics session that included three exciting talk by Dr. Shaomeng Wang (University of Michigan), Dr. Ting Han (National Institutes of Biological Sciences (NIBS), China), and Dr. Eric Fischer (Dana-Farber Cancer Institute, USA). First, Dr. Wang overview the progress and challenges in targeting of transcription factors using the PROTAC approach. The successful application of PRATAC for challenging transcription factors was illustrated by newly synthesized PROTAC small molecule degraders for STAT3 and BET proteins. Then, Dr. Han presented the application and development of PROTAC degraders for target identification and discovery of specific

cancer biomarkers. As example, Dr. Han presented a recent story of identification of CUL4-DDB1-DCAF15 E3 ubiquitin ligase as a target for clinically-tested anti-cancer sulfonamides. It was demonstrated that cellular response to sulfonamides depends on the expression level of DCAF15 and specific mutations in RBM39 protein. Dr. Fischer's talk was focused on the mechanism of action and target identification for thalidomide-related drugs, known as IMiDs. A large-scale PROTAC-based screening approach reveled a key role of SALL4 protein in IMiD-induced disruption of a network of ZnF transcription factors. Furthermore, it was found that IMiDs inducen the degradation of SALL4 exclusively in humans, primates and rabbits, but not in rodents or fish. Dr. Fischer highlighted that linkers can regulate not only the protein selectivity but also species-specificity of PROTACs.

The day was continued by the Glyco Chemical Biology session. Dr. David Vocadlo (Simon Fraser University, Canada) described a new approach to monitor activity of Glucocerebrosidase (GCase) in live cells using specifically designed fluorescent chemical probes, Bis-Acetal-Based Substrates (BABS). The BABS combined with a through a high-throughput screening approach revealed new regulators of GCase to understand the glucocerebrosidase biology and develop new clinical strategies. Then, Dr. Jenifer Kohler (University of Texas Southwestern Medical Center, USA) discussed new approaches to characterize the interactions between bacterial toxins and host glycoconjugates. Dr. Kohler presented the design of new photocrosslinking analogs of monosaccharides, specifically sialic acid and N-acetylglucosamine analogs, and development of new strategies to incorporate these sugars into glycoconjugates in mammalian cells. This approach provides a new opportunity to discover the interaction partners of glycosylated molecules. The session was continued by Dr. Frederic Friscout (University of Bordeaux, France). Dr. Friscout gave an overview of the significance of glycosyology for chemical biology and biomedical discovery. New strategies to develop fluorescent probes for oligosaccharides were discussed and a novel chemical reporter system that utilizes 3,4-disubstituted sydnones was presented. This new system allows to better understand the mechanisms and roles of metabolic incorporation of monosaccharides into glycoconjugates in living mammalian cells. Then, the session was concluded by Dr. Cristina Zamora (MIT, USA). Dr. Zamora's presentation entitled "Human Gut Microphysiological System Illuminates the Role of N-Glycans in Host-Pathogen Interactions of Campylobacter jejuni". In her talk, Dr. Zamora discussed the Campylobacter jejuni (Cj) pathogenicity with a specific focus on molecular mechanics of Cj N-linked protein glycosylation (Pgl) pathway.

The Open Panel Discussion was focused on the different aspects, challenges and perspectives of the partnerships between the Academia and Industry to promote drug discovery through chemical biology.

The Computational Chemical Biology session was open by Dr. J.B. Brown (Kyoto University, Japan) who presented a new "active-learning" methodology to develop novel chemical probes through use of feedback-driven, dynamic modeling and prediction processes. This novel approach can be applied for different classes of proteins, including GPCR, kinase, nuclear hormone receptor, and CYP450 families to build highly predictive models of ligand-target bioactivity. Then, Dr. Albert Antolin (Institute of Cancer Research, UK) introduced the Probe Miner, a new computational recourse that through the data-maiming and analysis of pharmacological and medicinal chemistry databases allows rapid identification of the most reliable and validated chemical probes for more than 2,000 human proteins. The session was concluded by Dr. Andrey Ivanov (Emory University, USA) who presented a novel approach to discover and target new cancer-associate protein-protein interactions through integration of experimental high-throughput screening technologies with the bioinformatics and structural modeling. The method was successfully applied to discover first-in-class inhibitors for NSD3/BRD4 and NSD3/MYC protein-protein interactions.

The final session "Emerging and Other Topics" was led by Dr. Sally-Ann Poulsen (Grif th University, Australia). Dr. Pulsen overviewed the progress in a small molecule binder-based approaches for drug discovery and chemical biology. Different fragment-based approaches were discussed. The advantages and limitations of application of ESI-MS analysis for fragment-based screening were presented and exemplified with the discovery of new binding molecules for zinc metalloenzyme carbonic anhydrase.

Then, Dr. Milka Kostic (Dana-Farber Cancer Institute, USA) gave an exciting talk highlighting not only the importance of chemical probes for biomedical research but indicating a key role of communication between scientists, publishers, developers, vendors, and funders to promote the best practices and standard for chemical-probe use and development. The significance of structural component for chemical-biology field was discussed by Scott Lovell (University of Kansas, USA) in his talk entitled "Structure Guided Development of BfrB-Bfd Protein-Protein Interaction Inhibitors: a Novel Target for Antibiotic Development". The fragment-based NMR-screening in combination with X-ray crystallography enabled the discovery of new chemical probes to block the BfrB-Bfd interaction and disrupt iron homeostasis in P. aeruginosa. These newly discovered small molecules provide novel opportunities for antibiotic development. The final talk of the day was given by Jeremy Baskin, (Cornell University, USA). In his lecture Dr. Baskin presented a new chemical strategy termed IMPACT (Imaging Phospholipase D Activity with Clickable Alcohols via Transphosphatidylation) that enables a real-time imaging of phosphatidic acid synthesis by Phospholipase D enzymes in live cells. The application of IMPACT approach has revealed novel subcellular locations of PLD activity within individual cells and uncovered a heterogeneity of phosphatidic acid signaling across cell populations.

The discussions were continued during the exciting poster session and reception.

SEPTEMBER 26, DAY 2

The Conference Day 2 was open by the Medicinal Chemistry session that included four talks by Dr. Scott Wolkenberg (Merck, USA), Dr. Rima Al-awar (Ontario Institute for Cancer Research, Canada), Dr. Casey Krusemark (Purdue University, USA) and Dr. Masahiko Ajiro (Kyoto University, Japan). First, Dr. Wolkenberg overviewed the limitations of a diazirine-based photoaffinity labeling (PAL) by analyzing the published diazirine PAL probes and suggested that the synthetic access to them has a problem. Based on the background, he successfully found the Suzuki-Miyaura reaction conditions by the robustness screening that give high cross-coupling efficiency while not degrading aryl diazirines. Then, Dr. Al-awar presented the potent and orally bioavailable inhibitor for the WDR5 (WD40 repeat protein 5)/ MLL1 (mixed lineage leukemia 1) interaction, OICR11824. MLL1 is a methyltransferase that methylates lysine 4 on histone H3 (H3K4) and is a key epigenetic regulator of the haemopoietic system. WDR5 is a component of the multiprotein MLL1 complex and she demonstrated that it can be a novel oncology target. Dr. Krusemark presented the activity-based DNA-linked ligand libraries as a new assay approach. The linked DNA is used to identify the compounds by DNA sequencing analysis. He presented the selection approaches with these libraries for enzyme substrates for protein kinase, protease and transferase. Dr. Ajiro presented a new class of antivirus drug, cyclin-dependent kinase 9 (CDK9) inhibitor. Human papillomavirus (HPV) induces tumorigenesis through viral oncogenes, which depend on host cell factor CDK9 for their transcriptional activation. The inhibitor is expected to be a novel therapeutic for cervical intraepithelial neoplasia (CIN) phenotypes, and is also currently evaluated in the phase I/IIa trial for anti-HPV activity in viral warts.

The day was continued by the Synthetic Biology session. Dr. Jason Micklefield (University of Manchester, UK) described an excellent biosynthetic engineering approach to provide the rapid structural diversification of promising natural product scaffolds, including the selective alkylation of rapamycin with methyltranslation enzymes. Then, Dr. Michele Chang (University of California, Berkeley, USA) presented a synthetic biology approach to synthesize the fluorinated natural products with a simple fluorinated building block, F-acetyl-CoA. This site-selective fluorination can be a powerful technique for improving the efficacy of small-molecule drugs. The session was continued by Dr. Kaity Ryan (University of British Columbia, Canada). Dr. Ryan presented the biosynthetic pathways to non-proteinogenic amino acids. She reported that a heme-dependent enzyme catalyzes N-N bond formation to give L-piperazic acid from *N*-hydroxy-L-ornithine. She also reported an enzyme pair that converts L-arginine to D-dehydroarginine in the pathway to the antibiotic indolmycin, highlighting the key role an O_2-, pyridoxal phosphate-dependent oxidase. Then, the session was concluded by Dr. Florian

Mayerthaler (University of Münster, Germany). Dr. Mayerthaler presented the Förster Resonance Energy Transfer (FRET) spectroscopy to monitor the interactions between substrates, the adenylation and the peptidyl carrier protein (PCP) domain in nonribosomal peptide synthetases (NRPSs). He further presented the dynamics of the domain alternation mechanism of the adenylation domain.

The iPSC Chemical Biology session was open by Dr. Steve Haggarty (Harvard University, USA) who presented patient-specific iPSC (induced pluripotent stem cell) models of neurodegenerative and neurodevelopmental disorders and further small-molecule screens to find a compound, which regulates neurogenesis pathways. For example, he tried to find WNT/TCF4 pathway modulators in hiPSC-derived neural progenitor cells and discovered a novel TCF4 modulator for generating human neuronal cells derived from iPSC. This technology is highly useful to understand fundamental human disease biology and discover the pharmacological agents targeting the root cause of disease. Then, Dr. Anne Bang (Stanford Burnham Prebys Medical Discovery Institute, USA) introduced the phenotypic screening of human iPSC derived neurons, neurological disease models derived from patient cells. She also presented the multi-electrode array (MEA) assays to monitor electrical activity, model synaptic plasticity, and evaluate drugs on human neuronal networks of human iPSC-derived neurons. Dr. Paul Guyett (BraoXwll, Inc., USA) presented amyotrophic lateral sclerosis (ALS) drug discovery using iPSC-derived human motor neurons. The clinically relevant screening platform is established to identify compounds that return the expression of neurofilament light chain (NFL) to normal levels in ALS patient derived motor neurons. He successfully found the compounds that increase NFL expression by the high-throughput screening (HTS). The session was concluded by Dr. Kimberly Snyder (STEMCELL Technologies Inc., Canada) who demonstrated how the NaïveCult^{TM}-t2iLGö media system uses chemical inhibitors of histone acetyltransferases in combination with Wnt signaling modulators and small molecule inhibitors of mitogen-activated protein kinase kinase (MEK) and protein kinase C (PKC) to induce hPSCs to adopt a native-like state.

The ICBS business meeting was held.

The special session “Rising Stars” to showcase up-and-coming chemical biology young scientists was led by Dr. Haian Fu (Emory University, USA). In this year, three young scientists, Dr. Christina Woo (Harvard University, USA), Dr. Chu Wang (Peking University, China) and Dr. Michael Cohen (Oregon Health and Science University, USA) received the ICBS Young Chemical Biologist Award. Dr. Woo presented a method to control the post-translational modification by *O*-linked *N*-acetyl glucosamine (*O*-GlucNAc) on specific target proteins. She developed fusions of *O*-GlcNAc transferase (OGT) to nanobodies as proximity-directing agents to a target protein and increase *O*-GlcNAc levels in living cells. The evaluation of the effect of *O*-GlcNAc on some target proteins revealed altered subcellular localization. Then, Dr. Wang presented the anti-hepatic steatosis mechanism of a natural flavonoid, Baicalin, isolated from Chinese herbal medicine. Hepatic steatosis constitutes the early stage of non-alcoholic fatty liver diseases (NAFLD). He identified multiple targets by a quantitative chemical proteomic strategy with the Baicalin photoaffinity probe. These results suggest that flavonoids may serve as a common scaffold to develop novel drugs for pharmacological treatment of NAFLD. The final talk of the session was given by Dr. Cohen. In his lecture, Dr. Cohen presented the development of orthogonal NAD^+ analog-engineered PARP pairs for the identification of direct protein targets of individual PARPs. The orthogonal NAD^+ analog contains a benzyl group at the C-5 position of the nicotinamide ring, which interacts with a hydrophobic pocket in the engineered PARPs and an alkyne tag at the N-6 position on the adenosine ring for copper-catalyzed conjugation to a biotin-azide probe. By using these chemical probes, he identified the direct targets of the poly-PARP subfamily.

The poster session (even numbered presentations) was held and active discussions were conducted.

SEPTEMBER 27, DAY 3

On the Day 3, the initiating session (Session VIII) was on “Synthetic Chemistry”. The first talk was delivered by David Lupton of Monash University, Australia on “New Reactivity, New Structures……New Functions”. Dr. Lupton focused on new catalysts, particularly organic catalysts, to access new chemical space.

This talk was followed by a talk by Dawei Ma, Institute of Organic Chemistry, China on “New Strategies for Synthesizing Bioactive Alkaloids”. His talk focused on synthesis of gelsedine and Kopsia alkaloids.

The third talk of the session was by Shinichi Sato of Tokyo Institute of Technology, Japan on “Development and Application of Tyrosine Click Reaction”. Dr. Sato focused on a new click reaction of Tyrosine side-chain with N-methyl luminol. This may develop into a selective method for tyrosine modification of proteins and peptides.

The last talk of this session was by Namrata Jain, University of British Columbia, Canada on the topic of affinity-based and mechanism-based covalent inhibitors of Glycoside Hydrolases. She also described the underlying mechanism of modifications of some of these inhibitors.

This session was followed by one of the two keynote addresses. The second keynote address was delivered by Jorn Piel, ETH Zurich, Switzerland. The topic of the keynote addressed was “New Enzyme Tools from Uncharted Natural Product Space”. Prof. Piel described the metabolite space and extraordinary rich genomic diversity of the candidate genus entotheonella. This may open up development of novel tools for synthetic biology.

The keynote was followed by an open panel session Chaired by Paul Clemons of Broad Institute on “Target Identification and Mechanism-of-Action Studies Using Chemical Biology”. The panelists were Michael Finley of Jansen Research and Development, Bridget Wagner of Broad Institute, Andy Phillips of C4 Therapeutics, Scott Lovell of University of Kansas and Andrew Zhang of AstraZeneca.

Post-lunch, the first session (Session IX) was on Chemical Proteomics for Drug Target Engagement. The first talk of this session was by Andrew Zhang of AstraZeneca, USA on “Elucidating PARP inhibitor Selectivity Using a PARP family Affinity Matrix”. Dr. Zhang described the methodology of using an affinity matrix based competition assay to determine the selectivity of several PARP inhibitors.

The second talk was by Sherry Niessen of Pfizer, USA on “Applying Chemical Biology in the T790M-EGFR Program”. Dr. Niessen described development use of third generation of EGFR irreversible inhibitors against T790M EGFR mutants.

The third talk in this session was by Andy Philips of C4 Therapeutics on “Targeted Protein Degradation: Tools for Target Evaluation and Therapeutic Applications”. Dr. Philips talked about directed protein degradation and its therapeutic implications, particularly for BET bromodomain proteins.

Final talk in the session was by Y. George Zheng of University of Georgia, USA on “Bioorthogonal Chemical Probes to interrogate Protein Acetylation”. Dr. Zheng talked about relationship of the cellular acetylome and different members of KAT family.

The last session (session X) was on Biosensors and imaging. The session started with a talk by Jin Zhang of University of California at San Diego on “A Suite of New Fluorescent Biosensors for Dynamic Visualization of Cell Signaling in Living Cells”. Dr. Zhang described new designs of probes for super-resolution microscopy and activity biosensors.

This was followed by a talk by Robert Campbell, Uniersity of Alberta, Canada on “New Colors and Applications of Genetically Encoded Biosensors to Probe Cell Signaling”. Dr. Campbell talked about developments of new types of Ca^{+2} and K^{+} biosensors.

The third talk in this session was delivered by Ellen Sletten of UCLA, USA on “Shortwave Infra-Red fluorophores for Illuminating Biological Processes in vivo”. Dr. Sletten described her work on new shortwave infra-red fluorophores for animal studies.

Last talk of the conference was delivered by Poncho Meisenheimer of Promega, USA on “Selectivity Differences between Cellular and Biochemical Kinase Analysis”. Dr. Messenheimer talked about Quantitative assessment of target occupancy using nanoBRET, an energy transfer technique.

The new president of ICBS, Prof. Jonathan Baell in his concluding Remarks commented on activity and growth of ICBS and some of its future plans.