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ICBS 2017 in Shanghai—Illuminating Life with Chemical Innovation

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Shanghai, a city situated on the estuary of Yangtze River in east China (Figure 1), welcomed a gathering of diverse chemical biologists from around the globe at the sixth annual conference of the International Chemical Biology Society (ICBS; <http://www.chemical-biology.org/>) held October 17–20, 2017. The annual conference is the flagship meeting for the ICBS, an independent, nonprofit organization dedicated to promoting research and educational opportunities at the interface of chemistry and biology.

Following the successful annual meetings in 2012–2016 that were held in Boston,^{1,2} Kyoto,³ San Francisco,⁴ Berlin,^{5,6} and Madison,⁷ this year's conference was held in Shanghai at East China University of Science and Technology. The major themes of this conference included small molecule modulators, spectroscopic tools, bioorthogonal reactions, and natural product chemistry (Figure 2). In addition to four keynote lectures and 10 scientific sessions, ICBS 2017 had a premeeting in the first day, consisting of a Young Chemical Biologists' Forum and a Women Chemical Biologists' Forum. The conference also featured an ICBS President's Forum on synthetic biology and two roundtable discussions with different topics. About 200 posters were presented in the conference, among which 34 were selected for a quick oral presentation.

DAY 1—PREMEETING AND OPENING CEREMONY

Young Chemical Biologists' Forum.

Li Tan (Shanghai Institute of Organic Chemistry) described the development of a multikinase degrader. This heterobifunctional small molecule acts by binding a kinase target on one end and an E3 ubiquitin ligase on the other, thereby inducing ubiquitination of the target and subsequent proteasome-dependent degradation. Quantitative proteomics analysis showed that the designed degrader was able to induce the degradation of a fraction of the

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intracellular kinases.¹³ Their strategy in designing kinase-directed degraders also provides a roadmap to systemically survey other susceptible targets in a gene family focused fashion.

Xiaoguang Lei (Peking University) described designing a series of lysine-targeted cross-linker (called “Leiker”) molecules for the chemical cross-linking of proteins coupled with mass spectrometry analysis (CXMS). Leiker molecules contain a biotin tag, which allows cross-linked peptides to be efficiently isolated, and the tag can be subsequently removed to increase the response in LC-MS analysis. Examples in *E. coli* ribosome and *E. coli* whole-cell lysates demonstrated that the Leiker-based CXMS could be useful for analyzing the structure of large protein complexes and probing dynamic changes in protein structures.¹⁴

Chu Wang (Peking University) described using the quantitative activity-based protein profiling (ABPP) strategy to identify an enzyme involved in fatty acid metabolism as the target of a flavonoid compound isolated from a Chinese traditional herbal medicine, which is an effective antisteatosis agent. Regulation of fatty acid metabolism might be an effective approach to treat nonalcoholic fatty liver diseases (NAFLD), and the flavonoid may serve as a useful scaffold for drug optimization.

Youcai Hu (Institute of Materia Medica, Chinese Academy of Medical Science & Peking Union Medical College) described the biosynthetic study of rubratoxin A, a nanomolar inhibitor of protein phosphatase 2A (PP2A). By a combination of genetic knockout and biochemical studies, a series of redox enzymes was revealed to be responsible for the complex structure of rubratoxin A. These enzymes include three α -oxoglutarate dependent nonheme iron enzymes (RbtB, RbtE, RbtG, and RbtU), a flavin-dependent enzyme RbtA, and a ferric-reductase like enzyme RbtH.¹⁵

Christian Ottmann (Eindhoven University of Technology) presented an overview of small molecules that stabilize protein—protein interactions (PPIs). With the adapter protein 14—3—3 as an example, the strategy was used in the development of small molecules and supramolecular ligands that stabilize the interaction between 14 and 3—3 and the partner proteins, including C-Raf, TASK3, CFTR, and Cdc25.^{16,17}

Evripidis Gavathiotis (Albert Einstein College of Medicine) discussed chemical and structural biology studies of protein—protein interactions within the BCL-2 family, and particularly pro-apoptotic BAX, which contribute to the development of cancer and chemoresistance.¹⁸ This has led to the discovery of the lead compound BTSA1 that has promising pro-apoptotic activity in cancer cells and *in vivo* xenografts.¹⁹ These studies demonstrated the therapeutic potential of small molecules directly targeting BAX activation.

Yisong Guo (Carnegie Mellon University) presented the mechanistic study of AsqJ, an oxoglutarate dependent nonheme iron enzyme involved in the formation of 4'-methoxyviridicatin. Using a combination of transient kinetics, Mossbauer spectroscopy, and mass spectrometry, his lab demonstrated that AsqJ uses a high-spin Fe(IV)-oxo intermediate, which likely undergoes an oxo-hydroxo tautomerization process as revealed by ¹⁶O/¹⁸O isotope incorporation analysis.

Gao-Yi Tan (East China University of Science and Technology) described the efforts in increasing the production of coenzyme Q10 by an industrial producer *Rhodobacter spheroids*. They analyzed the complicated metabolic network in relation to Q10 production by a combination of genomic, transcriptomic, and metabolomics analyses. A more efficient electroporation method for genetic manipulation of *R. spheroids* was established, allowing for rational engineering of *R. spheroids* to increase Q10 production. The concept of the 5M strategy (Mine, Model, Manipulation, Measure, and Manufacture) may thus be fruitful in future bioengineering efforts.²¹

Changlin Tian (University of Science and Technology of China) described the total synthesis of ubiquitinated histone proteins by a hydrazine-based native chemical ligation (NCL) approach. The synthesized ubiquitinated histones were used for nucleosome reconstitution. Single particle cryo-EM studies suggested that two flexible ubiquitin domains protrude between the DNA chains of the nucleosomes.²² Mapping of ubiquitin-binding sites by the photoactivated chemical cross-linking of proteins coupled with mass spectrometry analysis (CXMS) was also discussed.

Kenjiro Hanaoka (The University of Tokyo) presented the development of silicon-substituted xanthene dyes and their application as fluorescent probes.¹⁰ In contrast to the normal xanthene dyes that work in the green to red wavelength, the silicon-substituted dyes work in the far-red to near-infrared region, while retaining the key advantages of the parent structures (Figure 2), including higher water solubility, fluorescence quantum yield, and molar extinction coefficient. Several examples suggested the potential of these novel dyes for imaging biological processes in living cells.

Evan W. Miller (University of California, Berkeley) presented the design, synthesis, and application of new voltage-sensitive fluorescent dyes, which use photoinduced electron transfer as a voltage sensing trigger to achieve fast and sensitive voltage imaging in a variety of biological contexts.²³ These voltage-sensitive dyes offer a new strategy to monitor dynamic changes in membrane potential in living systems.

William Pomerantz (University of Minnesota) described using ¹⁹F-NMR to screen protein–ligand interactions. In this approach, the aromatic amino acid residues were labeled with fluorine atoms, which are used to screen fragments that bind to the protein target.²⁴ For proof of concept, bromodomain-containing proteins BPTE and Brd4 were used to screen a library of fragments, leading to the discovery of some of the first selective ligands for BPTE and new submicromolar ligands for Brd4.²⁵

Women Chemical Biologists' Forum.

Yan Feng (Shanghai Jiaotong University) described the design and assembly of artificial biosynthetic pathways. With computer-assisted metabolic analysis, they have successfully assembled several artificial biosynthetic pathways, allowing for the production of the plant-derived ginsenoside in yeast and β -valienamine in a *Streptomyces* strain.^{26,27}

Xu Zhang (Nanjing University of Chinese Medicine) presented the mechanism of action of a Chinese herbal formula for the treatment of non-small-cell lung cancer. Working with a

xenograft mouse model, she showed that a Chinese medicine formula (Ke formula) blocked the cell cycle progression at the G1/S phase and induced apoptosis mainly by suppressing the PI3K/AKT pathway.²⁸

Yuhong Du (Emory University) reported the development of an organoid culturing system for high-throughput compound screening. This screening platform was established by using genetically engineered mouse pancreatic and colon organoids as a model system in 384-well plates and monitoring organoid growth by automated imaging.

Zaneta Nikolovska-Coleska (University of Michigan) described the development of small molecule inhibitors that target myeloid cell leukemia (Mcl-1), an important antiapoptotic protein.²⁹ Using an integrated high throughput and computational screening approach followed by *de novo* and structure-based design and modification, they found a class of Mcl-1 inhibitors containing a 2,4,5-substituted benzoic acid moiety. A lead compound exerts potent activity against Mcl-1-mediated drug resistance in colorectal cancer (CRC) cells and completely restores the *in vivo* sensitivity of the CRC tumor to regorafenib, an FDA-approved drug for treating CRC patients.

Jeannine Hess (University of Cambridge) described a structure-guided and fragment-based approach in the development of novel inhibitors of the CoaBC from *Mycobacterium tuberculosis* (Mtb). CoaBC is a bifunctional enzyme involved in CoA biosynthesis and is essential for bacterial growth. Because of the considerable difference of Mtb CoaBC from its human orthologue, this enzyme serves as a promising target for the development of antitubercular drugs. Several lead compounds were developed that inhibit Mtb CoaBC with nanomolar affinities.

Wenni He (Institute of Medical Biotechnology, Chinese Academy of Medical Science and Peking Union Medical College) described a method for the anti-MRSA activity-based screening of tanshinone derivatives produced by microbial biotransformations. More than 200 microbial strains were screened for their potential actions on tanshinone IIA, among them fungus *Mucor rouxianus* 3.3447 was selected because it yielded the most active fractions. Further MS/MS networking and large scale fermentation allowed identification of two tanshinone glycosides, both of which possess potent anti-MRSA activity.³⁰

Li Jing (Pfizer Inc.) described the finding of selective down-regulation of Janus kinases (JAKs) by PF-956980, a previously reported JAK inhibitor. This study revealed that PF-956980 not only is a pan-JAK inhibitor but also selectively down-regulated JAK2 and JAK3 mRNA in human primary immune cells, leaving other JAK family members (JAK1 and TYK2) unchanged.³¹ Therefore, many kinase inhibitors might be assessed for their ability to change target kinase levels in relevant cell types.

Shanshan Li (Institute of Microbiology, Beijing) described a key role of the intracellular triacylglycerol (TAG) pool in polyketide production. By temporal control of TAG degradation, they increased the titers of several polyketides from *Streptomyces*. The production of avermectin B1a from *Streptomyces avermitilis* was increased to 9.31g/L, the highest titer ever reported.

Jingyu Zhang (East China University of Science and Technology) described the efforts in the discovery of novel terpenoid natural products.³² A large scale genome mining from 106 sequenced fungi using bifunctional terpene synthase as a molecular probe led to the finding of a strain *Bipolaris* sp. 11134, which produces six novel terpenoids.

Open Ceremony.

Zixin Deng (Shanghai Jiaotong University and Wuhan University) presented a keynote lecture titled “Chemical Biology of DNA Modification by Sulfur” (Figure 3). The discovery of DNA phosphorothioation and the biochemistry involved in this process was recounted,^{33,34} followed by discussion of the possible physiological role of DNA phosphorothioation and its crosstalk to DNA methylation.³⁵ The lecture was concluded by highlighting the widespread occurrence of DNA phosphorothioation in prokaryotes and its possible biological functions.³⁶

DAY 2—CHEMICAL BIOLOGY MEETS SYNTHETIC BIOLOGY

ICBS Presidents' Forum on Synthetic and Systems Biotechnology.

Sang Yup Lee (Korea Advanced Institute of Science and Technology) presented strategies for metabolic engineering and bacterial strain development to produce natural and non-natural chemicals.³⁷ Several examples in the production of non-natural compounds were discussed, such as lactams, terephthalic acid, and non-natural polymers.

George Guo-Qiang Chen (Tsinghua University) presented the efforts in the development of seawater-based fermentation technology with *Halomonas*, a genus of halophilic proteobacteria. Several multiple-gene pathways have been assembled in *Halomonas* spp., allowing for the production of various biopolymers.^{38,39} The growth patterns of *Halomonas* spp. have also been manipulated, leading to morphological changes from rods to long fibers and even large spheres, allowing high production and easy recovery of polyhydroxyalkanoates (PHA) from *Halomonas* spp. The potential of this technology in an industrial setting for large production of PHA at low cost was also highlighted.

Jens Nielsen (Chalmers University of Technology) presented on the topic of synthetic biology for the production of fuels and other chemicals using *Saccharomyces cerevisiae*. Discussion included technologies for metabolic engineering to develop platform strains for production of bioactive compounds such as fatty-acid-derived products.⁴⁰ The lecture was concluded by highlighting the use of mathematical modeling for predicting genotype–phenotype connections to enable faster design–test–build cycles of engineered strains.

Eriko Takano (University of Manchester) discussed the different strategies in harnessing microbial genomes for identifying and producing novel natural products.⁴¹ She presented case studies in engineering microbial metabolism for the production of high-value chemicals, including orthogonal transcriptional control circuits and bacterial microcompartments, computationally aided analysis, and high-resolution mass spectroscopy for the detection, analysis, and debugging of the engineered microbial systems.

Haifeng Ye (East China Normal University) discussed the application of synthetic biology, engineering, and software tools for developing novel optogenetic designer cells for the monitoring and treatment of diabetes in mice. Examples included optogenetic engineered cells for correcting insulin resistance and glycemic control and hydrogel-LED implants that can release short human glucagon-like peptide 1 remotely through a smartphone program, with a view toward cell-based precision medicines.⁴²

Session 1: Expand Chemical Space.

Hung-wen Liu (University of Texas at Austin) presented work on the biosynthesis of spinosyn A, a polyketide-derived macrolide produced by *Saccharopolyspora spinosa*. Spinosyn A has a 22-member macrolactone ring fused into a perhydro-as-indacene scaffold and an aglycone portion with three intramolecular carbon—carbon bonds. An elegant enzymology study was presented by investigating secondary kinetic isotope effects in the reaction with various deuterium-labeled substrates.⁴³ The unusual enzymology that enables the generation of the complex scaffold of spinosyn A was also discussed.

Eung-Soo Kim (Inha University) presented work focusing on heterologous expression of natural product biosynthetic gene clusters in *Streptomyces*, including novel strategies for the overexpression of large-sized biosynthetic gene clusters in heterologous *Streptomyces* hosts.⁴⁴

Jason Micklefield (The University of Manchester) described development of biocatalysts and mechanistic investigation of several enzymes involved in natural product biosynthesis. Structure-based diversification through mutagenesis enabled switching regio-selectivities of enzymes such as halogenases,⁴⁵ catechol-O-methyltransferase,⁴⁶ and aryl malonate decarboxylases,⁴⁷ among others.

Feng Wang (California Institute for Biomedical Research) described a genetic encoding approach for incorporating phosphotyrosine and its nonhydrolyzable analog 4-phosphomethyl-L-phenylalanine (Pmp) to study tyrosine phosphorylation in the regulation of proteins and signal transduction.⁴⁸ The pro-peptide strategy to increase cellular uptake of O-phosphotyrosine and Pmp and the efforts in identification of the aminoacyl-tRNA synthetase/tRNA pair to allow their site-specific incorporation into recombinant proteins were also discussed.

Jiajia Dong (Shanghai Institute of Organic Synthesis) presented studies encompassing sulfur(VI) fluoride activity as an attractive reaction for click chemistry. Sulfonyl/sulfonyl fluorides were highlighted as ideal electrophiles for stability, accessibility, and reactivity with protons or silyl activators, enabling multiple applications in chemical biology.¹¹

Huw Davies (Emory University) gave an overview of the NSF Center for Selective C—H Functionalization, which brings 24 professors and 15 universities to work collaboratively on the development and adoption of C—H functionalization as a new approach in organic synthesis.^{49,50} Partnerships models were offered for engaging the pharmaceutical industry to broaden the scope of applications for C—H functionalization in drug discovery.

Session 2: New Chemical Modalities.

Xiyun Yan (Institute of Biological Physics, CAS) introduced nanozymes, a class of nanomaterials that have intrinsic enzymatic activity with potentially broad utility in biomedical translational and applied research. The talk focused on particular nanozymes developed in her lab and their characterization for tumor diagnosis and therapeutic application.⁵¹

Jiahai Zhou (Shanghai Institute of Organic Chemistry) described the crystal structure of an intact cytochrome P450 monooxygenase enzyme from *Rhodococcus sp.* ECU0066 with the FMN/NADPH/Fe₂S₂ fused to the heme domain. Approaches such as Forster resonance energy transfer (FRET) analysis provided further insights into the molecular architecture and electron transfer mechanism of cytochrome P450 monooxygenase, which catalyzes oxygenation of substrates by transferring electrons from NADP(H) through redox proteins to the catalytic heme center.

Zheng-Jiang Zhu (Shanghai Institute of Organic Chemistry) described a new improved algorithm for metabolite annotation using LC-MS/MS technology. This approach increased the number of annotated metabolites by 5–8 fold, or up to 1000–2000 metabolites per biological sample. The application of this technology to extract aging-related metabolic pathways was highlighted.

Byung-Kwan Cho (Korea Institute of Science and Technology) presented the application of sequencing data from *Streptomyces tsukabaensis*, including integration analysis with transcriptome and translome data. These studies suggested that secondary metabolite gene clusters and particularly the FK506 gene cluster undergo translational control with reduced translational efficiency.

Session 3: Chemical Biology to Address Undruggable Targets.

Jiangyun Wang (Institute of Biological Physics, Beijing) described genetic code-expansion approaches and bioorthogonal chemical reactions for efficient and nontoxic protein labeling in living cells to design more efficient metalloproteins. One example included the application of genetic incorporation of a Tyr-His ligand and Cu binding site into myoglobin, which recapitulated features of heme-copper oxidase having selective O₂ reduction activity and generating less than 6% reactive oxygen species (ROSs) at more than 1000 turnovers.⁵²

Cai-Guang Yang (Shanghai Institute of Material Medica) described chemical intervention of N⁶-methyladenosine (m⁶A) mRNA modification as a new mode of genetic regulation through targeting FTO demethylase. The work led to the discovery of the first small molecule FTO inhibitors, such as the natural product rhein, by using structure-based virtual screening and biochemical studies demonstrating reduced activity of m⁶A demethylation in cells.⁵³ Targeting FTO demethylation in RNA is a potential therapeutic strategy for the treatment of acute myeloid leukemia and potentially other cancers.⁵³

Andrei Ivanov (Emory University) discussed the development of a protein–protein interaction network for cancer-associated proteins, named the OncoPPi network, which connects therapeutically challenging cancer drivers (*e.g.*, tumor suppressor genes) to

druggable molecular targets.^{54,55} An example included the STK11 (LKB1) tumor suppressor that was revealed to directly interact with cyclin-dependent kinase 4 (CDK4), for which there are FDA approved drugs. Experimental studies validated the physical and functional interaction between STK11 and CDK4, suggesting that the status of STK11 may impact the CDK4 activity and its sensitivity to CDK4 inhibitors. The OncoPPi network is available through the OncoPPi Portal to explore tumor suppressor-actionable drug target connectivity, offering new strategies for exploitation of “undruggable” cancer dependencies.⁵⁴

Milan Vrabel (Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences, Czechia) presented efforts to develop novel fluorogenic, bioorthogonal reactions for bioimaging. The combination of organic synthesis, NMR analysis, and density functional theory calculations led to the development of novel fluorescent 1,4-dihydropyridazines, based on Diels–Alder reaction of 1,2,4,5-tetrazines with particular *trans*-cyclooctene (TCO) isomers, where the fluorophore is rapidly and directly built upon the chemical reaction.⁵⁶ New 1,2,4-triazines were also described with superior properties for bioconjugation reactions.⁵⁷

DAY 3—ADDRESSING CHALLENGES IN DISEASES WITH CHEMICAL BIOLOGY

Rolf Müller (Saarland University) gave the second keynote lecture summarizing the discovery of novel bioactive compounds targeting antimicrobial resistance. Various strategies in this endeavor were described, such as searching new chemical space from uncultured bacteria, and an omics-based approach for compound isolation and mode of action studies.⁵⁸ Structural optimization of a *Streptomyces*-derived nonribosomal peptide griselimycin (Figure 2D) led to some derivatives showing potent anti-Mtb activity by targeting the DNA polymerase sliding-clamp DnaN.¹²

Session 4: Determine Molecular Mechanism of an Active Compound.

Bridget Wagner (Broad Institute of MIT and Harvard) gave an overview of new methods to reveal the mechanism of action of small molecules that induce proliferation of insulin-secreting β -cells in human islets. She showed that 5-iodotubercidin (5-IT), an annotated adenosine kinase inhibitor, strongly and selectively increased human β -cell proliferation *in vitro* and *in vivo* and increased glucose-dependent insulin secretion after prolonged treatment. Kinome profiling studies revealed that 5-IT is a potent and selective inhibitor of the dual-specificity tyrosine phosphorylation-regulated kinase (DYRK) and cell-cycle-like kinase families.⁵⁹

Hiroyuki Osada (RIKEN) described a screening strategy for inhibitors of cancer cell metabolism, leading to finding unantimycin A, a novel natural product produced by an actinomycetes strain RK88–1355, which selectively inhibited the mitochondrial complex III with moderate potency (IC₅₀ value of 1.2 μ M).⁶⁰ The strain RK88–1355 also produces a known compound SW-163A that is a more potent inhibitor of the mitochondrial complex III, having an IC₅₀ of 15 nM.

Seung Bum Park (Seoul National University) presented the diversity-oriented synthesis of a chemical library containing pyrimidodiazepine or pyrimidine moieties. A compound was identified from this library that inhibits the protein–protein interaction (PPI) between LRS and RagD, a PPI that regulates the amino-acid-dependent activation of mTORC1 signaling pathway.⁶¹

Xuebiao Yao (University of Science and Technology of China) described a new signaling cascade in mitosis. In this pathway, CDK-cyclin B phosphorylates the Ser90 of the acetyltransferase TIP60, which elicits the TIP60-dependent acetylation of the kinase Aurora B at Lys215. This acetylation protects the activation loop of Aurora B from dephosphorylation by protein phosphatase 2A (PP2A), ensuring accurate chromosomal segregation and a robust, error-free metaphase-anaphase transition.⁶²

Youli Xiao (Shanghai Institute for Biological Science) described the identification of molecular targets for several pharmaceutically important natural products, including artemisinin,⁶³ celastrol,⁶⁴ gambogic acid,⁶⁵ and pseudolaric acid B.⁶⁶ The work was carried out with the aid of activity-based protein profiling (ABPP), a functional proteomic technology relying on small molecule-based probes.

Chengzhang Fu (Saarland University) discussed carolacton, a macrolide natural product produced by the myxobacterium *Sorangium cellulosum*, demonstrating it targets a key enzyme in folate-dependent C1 metabolism; the binding pattern has been well characterized by the crystal structure of the protein-carolacton complex.⁶⁷ Interestingly, carolacton also targets the human ortholog with nanomolar affinity. Potential applications of carolacton in the oncology field were discussed.

Steven Zheng (The State University of New Jersey) described the identification of a hotspot (L2185) in the ATP-binding pocket of mTOR kinase, a master regulator of cell growth and proliferation. This hotspot is distinct from the “gatekeeper” site known to cause resistance to tyrosine kinase inhibitors such as as gefitinib and erlotinib, and mutation of this hotspot rendered resistance to mTOR kinase inhibitors.⁶⁸ The functional roles of the hotspot and gatekeeper sites in mTOR kinase and the strategies to overcome drug resistance were further discussed.

Zongbao Kent Zhao (Dalian Institute of Chemical Physics) described engineering of the cofactor binding site in a number of nicotinamide adenine dinucleotide (NAD)-dependent oxidoreductases. Instead of NAD(H), the engineered enzymes favor the unnatural nicotinamide cytosine dinucleotide (NCD) cofactor, whose functions are orthogonal to NAD(H).⁶⁹ Using these enzymes *in vivo* offers the possibility to selectively fuel targeted redox reactions, without perturbation of NAD/NADH cellular balance.

Masatoshi Hagiwara (Kyoto University) gave the third keynote lecture describing the development of specific kinase inhibitors. Several promising candidate compounds were found for treating various diseases, such as viral infections,⁸ Duchenne muscular dystrophy,⁷⁰ and Down syndrome (Figure 2A).⁹ The talk highlighted successful strategies for academic laboratories for independently advancing new medicinal discoveries through the drug development process.

Session 5: Interrogate Diseases with Chemical Biology I.

Guo-Qiang Chen (Shanghai Jiaotong University) described novel molecular mechanisms of cell fate determination, showing FAM122A interacts with protein phosphatase 2A (PP2A), which is essential for cell proliferation and fate determination. The silencing of FAM122A inhibits cell growth while its overexpression enhances cell growth and colonyforming ability.⁷¹

Taosheng Chen (St Jude Children's Research Hospital) presented the screening efforts for the pregnane X receptor (PXR) inhibitors. PXR up-regulates drug metabolizing enzymes such as CYP3A4 and CYP3A5 and thereby decreases drug efficacy. By a combination of high throughput screening, X-ray crystallography, and *in vitro* and *in vivo* pharmacology, a series of potent PXR antagonists were discovered, showcasing a promising way to overcome cancer drug resistance.⁷²

Xiaodong Wang (Eshelman School of Pharmacy) described the discovery of small molecules that inhibit Mer tyrosine kinase (MerTK). Inhibition of this protein provides dual therapeutic effects against MerTK-expressing tumors (*e.g.*, nonsmall cell lung cancer, acute lymphoblastic leukemia, *etc.*) by reducing cancer cell survival, invasion, and metastasis, as well as stimulating antitumor immune responses. Several of the small molecule inhibitors were effective in various cancer xenograft models.^{73,74}

Wei Wang (East China University of Science and Technology) described synthetic biology efforts in spatiotemporal control of cellular signaling and functions, highlighting a novel technology termed environment stimuli-induced proximity (ESIP) for cellular engineering. This technology is based on the chemically induced proximity methods, utilizing artificially applied chemical inducers to control the proximity between two chosen cellular proteins and, in turn, control the downstream events resulting from protein association.^{75,76}

Danielle Skropeta (University of Wollongong) described the design and development of siyltransferase (ST) inhibitors, which are antimetastatic agents promising for treating pancreatic and ovarian cancer. By a computationally guided design and optimization, the inhibitors of three different ST subgroups (ST3, ST6, and ST8) were found.^{77,78}

Weishan Wang (Institute of Microbiology, Beijing) described using transcription analysis-aided promoter optimization for improvement in titer of natural products in *Streptomyces*. Compared to the conventional use of constitutive promoters in heterologous expression, this strategy improved actinohordin and oxytetracycline production by 1.3- and 9.1-fold, respectively.⁷⁹

Xu Fang (Shandong University) described the functional characterization of xylose transporters in a filamentous fungus *Trichoderma reesei* by heterologous expression in *Saccharomyces cerevisia*. This effort showed that among the three sugar transporters in *T. reesei* (Stp2, Stp3, and Gtp), the xylose transport capacity of Stp3 is significantly better than that of yeast endogenous transporter Gal2.

Robert Lund (Beckman Coulter Life Science) presented a screening system to identify microRNAs (miRNAs) that influence cancer cell growth and chemotherapeutic sensitivity. The screen fully automates the transfection of a library of miRNA mimics, the addition of chemotherapeutics and staining reagents, and cell imaging. This effort led to the identification of miRNA mimics that independently affect cancer cell growth and survival and alter the rate of effectiveness of cell killing by established chemotherapeutics.

Session 6: Interrogate Diseases with Chemical Biology II.

Demin Zhou (Peking University) discussed conversion of influenza A virus into live virus vaccines by introduction of multiple premature termination codons (PTCs) into the virus genome. While the resulting viruses were fully infective, they also elicited robust humoral, mucosal, and T cell-mediated immunity;⁸⁰ thus, PTC-based methodology could be a general strategy in generating live virus vaccines.

Cong Liu (Shanghai Institute of Organic Chemistry) presented a study on lipid-binding partners of α -synuclein (α -syn), the aggregation of which is the cytopathological hallmark of synucleinopathies, including Parkinson's disease. Different α -syn species (monomer, oligomer, and fibril) had distinct binding preference to lipid molecules, and a group of lipid molecules stabilize α -syn monomers, preventing aggregation by specifically binding to the N-terminus of α -syn monomer form.

Hanne Ingmer (University of Copenhagen) presented her study of the quorum sensing (QS) system in *Staphylococcus aureus* and its crosstalk with other staphylococcal species. She showed that nonpathogenic staphylococci produce compounds with unexpected efficacies for repressing the *S. aureus* QS system. These compounds are similar to autoinducing peptides (AIPs), showing strong affinity to the *S. aureus* AIP receptor and thereby competing with the binding of the *S. aureus* AIPs.⁸¹ She proposed that these AIP-like compounds produced by nonpathogenic staphylococci may play important roles in determining the ability of *S. aureus* to colonize humans and animals.

Bin Xu (Virginia Tech) reported findings on the plant natural products rosmarinic acid (RA) and baicalein as potent agents in disaggregating amylin fibrils and reducing amylin-induced cytotoxicity.⁸² Remarkably, RA and a synthetic RA analogue demonstrated efficacy in reducing amylin oligomers in the serum samples from diabetic patients. High throughput screening to identify general and subclass-specific inhibitors of amyloidogenic proteins was also presented.

Yousong Ding (University of Florida) reported the discovery of a novel glycine binding protein from the mushroom *Coprinus comatus* that exhibited selective and potent cytotoxicity toward human T-cell leukemia Jurkat cells as compared with a panel of cancer cell lines. Further structural and mutagenesis studies revealed the key residues in the glycine binding site of this protein,⁸³ which could be promising in cancer diagnosis and treatment.

Tilmann Weber (Technical University of Denmark) presented the study in generating allyl- and propargyl-substituted kirromycin by a precursor-directed biosynthesis strategy. An engineered malonyl-CoA synthetase from *Rhizobium leguminosarum*, which is able to

activate unnatural malonyl derivatives, was introduced to the kirromycin producer, allowing for the production of different kirromycin analogues by feeding with different malonates. The propargyl-substituted kirromycin was also used in a click reaction to generate a fluorescent coumarin-kirromycin conjugate. Intriguingly, all these kirromycin analogues retained their antibacterial inhibitory effects.⁸⁴

Two roundtable discussions were held on day 3 in the morning and afternoon, respectively. The theme of the morning session was “Global Chemical Biology Landscape,” which was chaired by **Masatoshi Hagiwara (University of Kyoto)**, with other panelists including **Lihe Zhang (Peking University)**, **Zaneta Nikolovska-Coleska (University of Michigan)**, and **Bahne Stechmann (EU OPENSREEN, Berlin)**. The theme of the afternoon session was “Chemical Biology in Pharmaceutical Industry,” which was chaired by **Christian Ottmann (Eindhoven University of Technology)**, with other panelists including **Yves Auberson (Novartis, Switzerland)**, **Rathnam Chaguturu (iDDpartners, USA)**, **Hong Shen (Roche Innovation Center, China)**, **Takashi Owa (Eisai Co., Ltd., Japan)**, and **Yanwen Liu (SPRIM, China)**.

DAY 4—CHEMICAL BIOLOGY INNOVATION AND APPLICATIONS

Session 7: Biological Insights with Chemical Biology.

Pinghua Liu (Boston University) first described a study on iron enzymes that catalyze the formation of two unprecedented C–S bonds and the utilization of these novel reactions in synthetic biology. The second part of the talk focused on the mechanistic study of a nonheme enzyme FtmOx1 that catalyzes an endoperoxide formation reaction.⁸⁵

Shi Chen (Wuhan University) presented a study on microbial epigenetics, showing the cross-talk of DNA phosphorothioation with DNA methylation and tRNA modification.³⁵ These findings raise the possibility of the coevolution of different epigenetic systems in prokaryotes.

Chengqi Yi (Peking University) described chemical labeling and high-resolution sequencing approaches developed for epigenetic analysis. These approaches allowed genome-wide sequencing of 5-formylcytosine in DNA and transcriptome-wide sequencing of pseudouridine and 1-methyladenosine in RNA.^{86,87}

Peng Wu (The Scripps Research Institute) discussed recent progress in chemoenzymatic glycan labeling, which combines glycosyltransferases and unnatural nucleotide sugar donors equipped with a bioorthogonal chemical tag to directly label specific glycan acceptor substrates *in situ* within biological samples.⁸⁸ Also discussed was application of this technique in imaging glycosylation patterns in patient tissue samples and modulating immunity.

Session 8: Molecular Biosensors and Actuators.

Wei-Hong Zhu (East China University of Science and Technology) described the development of near-infrared (NIR) fluorescent organic nanoprobe for bioimaging. These

include a ratiometric fluorescent H_2S probe with extraordinarily fast response times⁸⁹ and a probe for *in vivo* real-time tracking of the β -galactosidase activity in colorectal tumors.⁹⁰

Takanari Inoue (John Hopkins University) described the iPOLYMER strategy, a rapid induction of protein-based hydrogels inside living cells. Biochemical and biophysical analysis aided by computational modeling showed that the polymer network formed in the cytosol resembles a physiological hydrogel-like entity, which acts as a size dependent molecular sieve.⁹¹ Application of iPOLYMER in reconstitution of the nucleation of biologically functional entities, including RNA granules in intact cells, was also discussed.

Robert Campbell (University of Alberta) described synthesis of versatile fluorescent protein (FP) tools by protein engineering.⁹² These FPs have been used for optical control of protein activity and gene expression. Also described was the successful conversion of red and near-infrared FPs into biosensors for calcium ions, membrane potential, and neurotransmitters.^{93,94}

Yi Yang (East China University of Science and Technology) described using SoNar, a genetically encoded fluorescent sensor for NADH, in a high-throughput metabolic screen of compound libraries in cancer cell lines.⁹⁵ This effort led to finding several compounds that increased NAD^+/NADH ratios and that had marked cancer cell cytotoxicities. Among them, KP372-1 was found as a potent antitumor agent by causing extreme oxidative stress in cancer cells.⁹⁶

Session 9: Emerging Technologies.

Peng Chen (Peking University) described a “chemical decaging” strategy that controls protein activation in living cells. This strategy, relying on the bioorthogonal elimination reactions, is highly efficient for intracellular proteins and shows low cytotoxicity. Several applications of these chemical decaging strategies in manipulating protein activity within a native cellular context were discussed.⁹⁷

Surajit Ghosh (CSIR-Indian Institute of Chemical Biology) described the development of highly bioavailable short peptides that target tubulin. Some of these peptides inhibited *in vitro* and intracellular tubulin polymerization, induced apoptotic death of cancer cells, and inhibited 3D multicellular tumor spheroid (MCTS) growth, thereby showing promise as drug leads for cancer.^{98,99}

Chunyang Cao (Shanghai Institute of Organic Chemistry) described the structural investigation on APOBEC3G (A3G), a DNA cytidine deaminase that deaminates two cytidines at the 3'-end of single stranded DNA (ssDNA). By using chemically modified cytidine in ssDNA, they have successfully solved the NMR structures of the C-terminal catalytic domain of A3G (A3G-CD2) in complex with the substrate, intermediates, and products.¹⁰⁰ These results provide important insights into the mechanism and substrate specificity of A3G.

Liang Yang (Nanyang Technological University) presented an investigation of the antibiotic-resistant subpopulation of *Pseudomonas aeruginosa* by pSILAC (pulse stable

isotope labeling with amino acid), a proteomic strategy for global analysis of cellular protein translation.¹⁰¹ This investigation revealed that colistin-tolerant cells employ quorum sensing and type IV pili-mediated migration to initiate the formation of a new colistin-tolerant subpopulation, providing mechanistic insights into the formation of antibiotic-tolerant populations in bacterial biofilms.¹⁰²

Mikiko Sodeoka (RIKEN) described the design of a chemical probe for protein affinity labeling, which contains a small bifunctional O-nitrobenzoxadiazole (NBD) unit that selectively reacts with a lysine residue. She also discussed the potential application of the probe for fluorescent imaging of targeted proteins in living cells.

Session 10: Computational Approaches to Accelerate Chemical Biology Research.

Petr Bartunek (Institute of Molecular Genetics, Czech Republic) introduced the Probes & Drugs (P&G) Portal (www.probes-drugs.org) that aims to reflect the current state of bioactive compound space. Many characteristics of the P&G portal, such as integrated visualization, chemical intelligence, and user-defined sets make it a unique platform for bioactive compound discovery.¹⁰³

Luhua Lai (Peking University) described strategies for allosteric site identification and ligand design.¹⁰⁴ Her lab has identified several molecules that either allosterically activate or inhibit protein activity¹⁰⁵ with utility for probing protein function and metabolic network regulation, as well as scaffolds for further drug development.

Paul A. Clemons (Broad Institute of Harvard and MIT) challenged the dogma that chemical structure diversity always leads to diverse biological performance of a library. By using a combination of retrospective analysis of diverse high-throughput screening data, novel multiplexed phenotype profiling assays, and panel-based sensitivity assay of cancer cell models, important clues into small molecule screening and library construction were revealed.¹⁰⁶

Runhui Liu (East China University of Science and Technology) discussed using nylon-3 polymers (poly β -peptides) as effective antimicrobial agents. The nylon-3 polymers have a backbone similar to that of natural host defense peptides (HDPs) but unlike the former are resistant to proteolysis. Nylon-3 polymers have activities against various drug-resistant bacterial strains, as well as *Candida albicans* in planktonic cells and biofilms.¹⁰⁷

Young Chemical Biologist (YCB) Rising Star Awards.

The sixth Annual ICBS-YCB Awards session was sponsored by *ACS Chemical Biology* for recognizing the recent work by young chemical biologists, who were selected by a peer-review panel comprised of past awardees.

Qi Zhang (Fudan University) presented mechanistic studies on radical S-adenosylmethionine (SAM) enzymes. Biochemical assays with various isotopically labeled substrates and extensive mutagenesis analysis revealed novel chemistries of several radical SAM enzymes, including NosL,¹⁰⁸⁻¹¹⁰ ThiH,¹¹¹ and BlsE.¹¹² Also described was the ability

to tune the radical chemistry of NosL with various substrate analogues, demonstrating the remarkable catalytic promiscuity of the radical SAM superfamily enzymes.^{113,114}

Haitao Zhang (Zhejiang University) presented a structural study on G protein-coupled receptors (GPCRs) by serial femtosecond crystallography (SFX) with X-ray free electron lasers (XFELs). This innovative technique allowed structural characterization of the human angiotensin II receptors AT₁R and AT₂R, in addition to rendering “molecular movies” of these GPCR proteins.¹¹⁵ The potential of XFEL in structure-based drug discovery was highlighted.

Toru Komatsu (The University of Tokyo) presented a study using small molecular fluorescent substrate probes to report enzyme activities in biosamples.¹¹⁶ The methodology was deployed for characterizing disease-related enzymes in samples by globally monitoring their activities with a library of substrates, identifying those that specifically associated with disease.^{117,118} In one example, global monitoring of peptide-metabolizing enzymatic activities led to the finding that the activity of the endopeptidase neurolysin is highly elevated in human colorectal tumor tissue samples.¹¹⁹ The talk was concluded by highlighting that such “enzymomic” investigations will facilitate the characterization of disease-related proteins as potential drug targets or biomarkers.

After the Young Chemical Biologist Award session, **K. Barry Sharpless (The Scripps Research Institute)** presented the last keynote lecture. Besides the work on chiral oxidation reactions that won the 2001 Nobel Prize in Chemistry, Dr. Sharpless is also famous for his conceptual framework of click chemistry,¹²⁰ with the azide–alkyne cycloaddition reaction as the most representative example.¹²¹ Here, he presented a new family of click reactions termed sulfur(VI) fluoride exchange (SuFEx). SuFEx can be used to produce arylfluorosulfates from phenol and SO₂F₂ in the presence of an organic base (Figure 2C), which are usually stable in biological environments. However, the reactivity of arylfluorosulfates can be dramatically increased when they encounter a specific protein partner. This is due to the fact that transition of fluoride from a strong covalent bond to a leaving group requires the assistance of a proton (or a silicon center) under strict spatial and kinetic constraints.¹¹ He discussed several applications of SuFEx in chemical biology studies, such as affinity labeling and the discovery of small molecules with antiviral and anticancer activities.

CONCLUDING REMARKS AND OUTLOOK

Student Poster Awards.

The last scientific program was the Flash Poster Oral Presentation session comprising 34 speakers, from which the following students were selected for an award by a committee of several ICBS Board members. The winners were **Karson J. Kump (University of Michigan)**, **Xiaoyun Zhang (Peking University)**, **Hongtao He (Institute of Microbiology, Beijing)**, **Xin Zhou (University of California, San Diego)**, **Wansang Cho (Seoul National University)**, **Elena S. Reckzeh (Max Planck Institute of Molecular Physiology)**, **Eline Sijbesma (Eindhoven University of Technology)**, **Sebastian Andrei (Eindhoven**

University of Technology), Valentina Gonzalez-Pecchi (Emory University), and Ryosuke Koyama (Nihon University).

The sixth Annual ICBS Conference in Shanghai was attended by a record number of more than 400 participants from 17 countries and regions (Figure 4). The magnitude, quality, and scientific diversity of the podium and poster presentations reflect the multidisciplinary nature and influence of a discipline bridging chemical and biological basic, translational, and applied research. We look forward to the seventh Annual ICBS Conference, for which Vancouver, Canada (September 24–27, 2018) was announced as the next host location.

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Figure 1. Sunrise on Huangpu River at the Bund, a famous sight in Shanghai. Photo by Ying Huang (China Photographers Association, Mianyang, Sichuan).

Figure 2. Representative examples of the four major themes in ICBS 2017. (A) Two “Academia Drugs” developed by Hagiwara and coworkers. Tp80 exhibits potent antihepatitis C virus activity,⁸ and ALGERNON is promising in treating Down syndrome.⁹ (B) TokyoMagenta, a silicon-substituted xanthene dye developed by Hanaoka and co-workers as a far-red to near-infrared fluorophore.¹⁰ (C) Naltrexone derivatization by SuEFx, a novel type of click reactions developed by Sharpless and co-workers.¹¹ (D) Griselimycin and the synthetic analogues developed by Müller and co-workers, which are highly active against *Mycobacterium tuberculosis* by inhibiting DNA replication.¹²

Figure 3.

Keynote lecture by Prof. Zixin Deng. The DNA phosphorothioation activity was reconstituted *in vitro* by using the Dnd enzyme complex (photo by Jingyu Zhang).

Figure 4.
Part of attendees in ICBS 2017. Photo by Shanghai Shangpai Culture Communication Col, Ltd.