

The International Chemical Biology Community Synthesizes a New Society

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Built by Ewing Marion Kauffman with a desire to accelerate science and innovation into the marketplace, the Kauffman Center made a fitting setting for the Inaugural Meeting of the International Chemical Biology Society (ICBS), held on October 11–12th, 2011 in Kansas City, Missouri. The meeting was organized by Rathnam Chaguturu (University of Kansas), Haian Fu (Emory University), and a committee of volunteers (Table 1) with the goal of launching the ICBS, a new international chemical biology society composed of scientists from around the world working at the interface between chemistry and biology. Indeed, the inaugural ICBS membership represents more than 20 countries. Following a welcome speech by Lesa Mitchell (Vice-President, Kauffman Foundation), Chaguturu presented a brief history leading up to the inaugural conference, the mission of the society (Table 1), and letters expressing overwhelming support from chemical biology pioneers, such as Stuart Schreiber, and community members around the world. This opening was followed over the next two days by an impressive list of presenters covering the global chemical biology landscape.

“The time is right, the opportunity is enormous, and the need is great” were the words spoken by Christopher Austin, Scientific Director of the NIH Center for Translational Therapeutics (NCTT). His keynote presentation set the stage for creation of the ICBS. He noted “it is the best of times; it is the worst of times.” A plethora of genomic information is currently available, but there is a lack of ability to translate this information into biological insights and therapeutics. In addition, “in the rush to develop therapeutics, we do not understand the fundamental science of how small molecules and targets interact.” He challenged the ICBS to be the intellectual home for those committed to the study of chemicals in action and to focus on the most basic science of chemical biology with a disease agnostic approach. By increasing the fundamental understanding of the biological effects of small molecules, Austin hoped that ICBS members would impact the science of preclinical drug development and ultimately contribute to all areas of drug discovery.

How will ICBS members bring Austin’s forward thinking ideas to fruition? With a mission of promoting research and educational opportunities at the interface of chemistry and biology, and a motivated and enthusiastic Board of Directors composed of chemical biology experts from around the globe (Table 1), the ICBS is poised to act. And perhaps the themes of the meeting reflect the strategy by which the ICBS will impact chemical biology: by going global, working at the interface, and advancing technologies.

Table 1. Mission and Initiatory Organization of the International Chemical Biology Society (ICBS)

The International Chemical Biology Society	
Mission Statement: The ICBS is an independent, nonprofit organization dedicated to promoting research and educational opportunities at the interface of chemistry and biology.	
http://www.chemical-biology.org	
Contact: Rathnam Chaguturu (rathnam.chaguturu@sri.com) or Haian Fu (hfu@emory.edu)	
Board of Directors (Proposed)	
Rathnam Chaguturu (Founding President), Haian Fu (President-elect), Melvin Reichman (Chair), Jonathon Baell, Lixin Zhang, Petr Bartůněk, Masatoshi Hagiwara, Krishna Kodukula, *to be determined (3)	
ICBS Conference Organizing Committee	ICBS Organizing Committee
Haian Fu, Emory University (Chair)	Rathnam Chaguturu, University of Kansas
Jeffrey Aubé, University of Kansas	Petr Bartůněk, Center for Chemical Genetics
Petr Bartůněk, Center for Chemical Genetics	Jian Ding, Shanghai Institute of Materia Medica
Rathnam Chaguturu, University of Kansas	Haian Fu, Emory Chemical Biology Discovery Ctr
Masatoshi Hagiwara, Kyoto University	Masatoshi Hagiwara, Kyoto University
Krishna Kodukula, SRI International	Andrew Napper, Nemours Center for Childhood Cancer Research
Lixin Zhang, Chinese Academy of Sciences	Melvin Reichman, LIMR Chemical Genomics Ctr
International Advisory Board Members	
Steven BenKovic, Penn State; Sir Philip Cohen, Dundee; Jian Ding, Shanghai Institute of Materia Medica; Krishna Kodukula, SRI International; Chris Lipinski, Melior Discovery; Ferid Murad, George Washington U; Bernard Munos, InnoThink; Tetsuo Nagano, Japanese Society for Chemical Biology; Stuart Schreiber, Harvard; Axel Ullrich, Max-Planck Institute; Paul Workman, ICR-London; Leonard Zon, HHMI; Litao Zhang, Bristol Myers Squibb	

■ GOING GLOBAL

A primary theme at the ICBS meeting was “going global,” breaking through traditional geographical, intellectual, and even economic barriers to allow widespread scientific collaboration. Breaking through geographical barriers, the first session of the meeting focused on the chemical biology landscape around the world, opening the doors to collaboration. Also, in the natural products session, researchers traveled the globe to identify new compounds to enrich and diversify chemical space. Breaking through intellectual barriers, research presented at the ICBS meeting transcended scientific disciplines. Finally, breaking through economic barriers, Chaguturu chaired a session

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covering what were historically taboo academia-industry-government partnerships.

The first session of the meeting, titled “Current Global Chemical Biology Landscapes”, featured speakers from Australia, China, Europe, Japan, New Zealand, and the USA. Jonathan Baell (Walter & Eliza Hall Institute) highlighted the development of the Queensland Compound Library in Australia, a centralized compound library for Australian researchers containing both private and public collections (>200,000 natural products and >20,000 lead-like and diverse compounds in a rapidly expanding public collection garnered from universities throughout Australia, >350,000 in private collections mostly custom selected from a variety of vendors). Baell touted this as the “world’s best publically accessible screening library”, available by collaboration. Lixin Zhang (Chinese Academy of Sciences) gave an overview of the research institutes and funding agencies in China, and Masatoshi Hagiwara (Kyoto University) described the formation of the chemical biology field in Japan. Hagiwara noted the development of the Japanese Society for Chemical Biology in 2005, which now comprises more than 750 members. Dr. Petr Bartůňek (Institute of Molecular Genetics, Czech Republic) had the daunting job of presenting the chemical biology efforts of the more than 20 countries in Europe. He discussed the development of EU-OPENSREEN, the European Infrastructure of Open Screening Platforms for Chemical Biology, and also gave a brief overview of efforts in individual countries (Table 2). Paul Teesdale-Spittle (Victoria University) represented New Zealand, noting the unique flora and fauna in his country and, due to geographical isolation, the need for collaboration and ingenuity. He highlighted scientific efforts around the country, particularly stressing the marine natural products resources. Haian Fu (Emory University) rounded out the session with an overview of chemical biology activities in the USA, including Schreiber’s pioneering research, the national initiative laid out with the NIH Road Map in 2005, and then beyond the roadmap with the expansion of academic screening centers, research and educational programs in chemical biology, and the developing trend toward academic–government–industry partnerships.

The ICBS meeting also went intellectually global, transcending scientific disciplines with widespread collaboration to cover many areas of the chemical biology space. Fitting this theme, Bernard Munos’s keynote presentation on Day 2, titled “Open Innovation”, stressed the importance of collaboration and resource sharing in what he proposed as a new era of drug discovery. He argued that open innovation “empowers co-creation and increases efficiency through sharing resources and raising effectiveness”. He urged ICBS members to “collaborate on the science, compete on the products”, noting that open innovation enables alternative models, exploration, and risk taking. Scientific collaboration is a fundamental element of chemical biology, and this was evident in nearly every ICBS presentation.

Economic barriers to “going global” were addressed in a session titled “Academia-Industry-Government Partnerships”. Garnering the most discussion was a presentation by Melvin Reichman (LIMR), describing the development of a novel, for profit, open access infrastructure for providing pharmaceutical company-derived compound libraries to researchers. Reichman justified his institute’s development of this ready-to-screen compound library, which will be distributed for free with prior agreement on the IP developed from usage, by comparing a

Table 2. Web Links for Resources Cited during the Inaugural ICBS Meeting^a

country	resource	web link
Australia	Queensland Compound Library	www.griffith.edu.au/science-aviation/queensland-compound-library
	Center for Drug Discovery and Design, University of Queensland	cddd.imb.uq.edu.au
	Institute for Glycomics	www.griffith.edu.au/glycomics
China	Chinese Academy of Sciences	english.cas.cn
EU	EU-OPENSREEN	www.eu-openscreen.eu
Germany	ChemBioNet	www.chembionet.info
France	FR-OPENSREEN	www.salsce.cnrs.fr
Sweden	Chemical Biology Consortium Sweden (CBCS)	www.cbse.se
Norway	Nor-OPENSREEN/ChemBioNet Norway	www.chembionet.info
Finland	Drug Discovery & Chemical Biology (DDCB)	www.biocenter.fi
Poland	Polish Consortium	www.eu-openscreen.eu
Czech Republic	CZ-OPENSREEN	www.openscreen.cz
Austria	Platform Austria for Chemical Biology (PLACEBO)	www.chemical-biology.at
Spain	ChemBioBank	www.pcb.uv.edu/chembiobank
Japan	Japanese Society for Chemical Biology	www.jscb.jp
New Zealand	Universities (8 total):	web.chemistry.auckland.ac.nz/staffsites/BrimbleM
	Auckland University	www.fmhs.auckland.ac.nz/sms/acsrc/
	Victoria University of Wellington	www.bic.canterbury.ac.nz/
	Canterbury University	www.mauricewilkinscentre.org/
	Otago University Crown Research Institutes (8) Industrial Research Ltd.	www.irl.cri.nz/our-research/bio-manufacturing/pharmaceuticals-and-biotechnology
	Centres of Research Excellence	www.malaghan.org.nz/
	NIH Roadmap Initiatives:	commonfund.nih.gov
	MLSCN	
	MLPCN	
	NCI CBC	next.cancer.gov/discoveryResources/cbc.htm
United States	NCTT	nctt.nih.gov
	NCATs	www.nih.gov/about/director/ncats
	Academic Screening Centers	www.slas.org/screeningFacilities/facilityList.cfm
	LIMR Chemical Genomics Center	www.lcgcinc.com
	CTSA-IP	www.ctsaip.org

^aInaugural ICBS conference sponsors included Promega Corporation, Abbott, Center for Chemical Genetics, Emory Chemical Biology Center, Hamamatsu, Kauffman Foundation, LabCyte, LIMR Chemical Genomics Center, Perkin-Elmer, Roche, Sigma-Aldrich, SRI International, and University of Kansas/Medical Center.

stored library to a commercial aircraft sitting on the ground; the “aircraft” is simply depreciating unless it is “in the air”. This new model, allowing sharing of high quality compound libraries from pharmaceutical companies, is expected to enhance the productivity of new lead discovery in academia. Reichman’s model generated much excitement among attendees and emphasized the underlying interest in improving access to quality compound libraries. Scott Weir (University of Kansas) discussed the development of a translational research “village”, focused on the establishment of a balanced portfolio of projects for the Kansas drug discovery program, which hinges on a

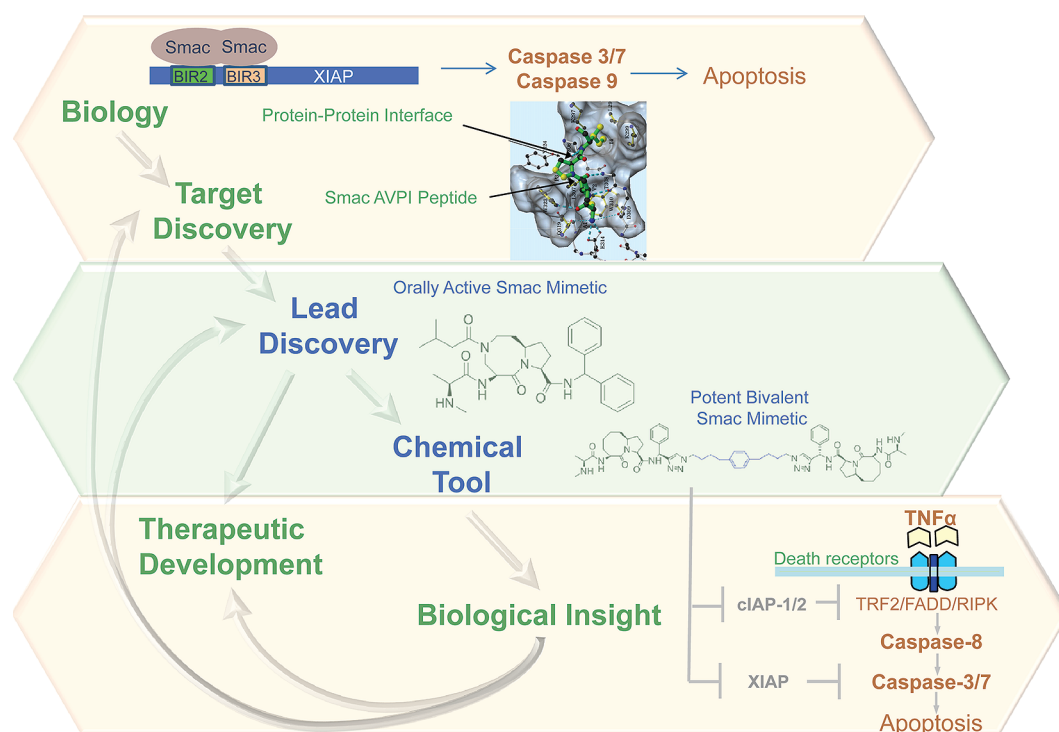


Figure 1. Research presented by Wang, demonstrating that Smac mimetics induce TNF α -dependent apoptosis by targeting both XIAP and cIAP-1/2, illustrates how chemical biologists use chemical tools to gain biological insight. In turn, these biological insights impact the many areas of drug discovery and therapeutic development.

“Learning Collaborative” partnership between the philanthropic Leukemia and Lymphoma Society, KU, and the government National Chemical Genomics Center (NCGC). In the same session, Mark Scheideler (HumanFirst Therapeutics) described the creation of the CTSA-IP Project, which facilitates intellectual property (IP) information exchange, linking providers of IP such as technology or resources to users. The goal of this project is to catalyze cross-institutional partnerships by stimulating collaboration and partnering.

“Going global” was clearly evident in the science presented at the ICBS meeting. A session on natural products highlighted researchers utilizing resources from around the globe to advance the tools available for chemical biologists. Lixin Zhang described research based on the isolation of novel compounds from two marine expeditions in the South China Sea, noting that while the trend in use of natural products is decreasing, the trend in use of marine natural products is increasing. His work has focused on the development of a marine microbes natural product library and characterization of the bioactive “co-drugs” in this library through high throughput synergy screening with existing drugs.¹ Similarly, Paul Teesdale-Spittle described the NMR-guided isolation and then characterization of unique compounds derived from materials gathered in undersea expeditions. Promising compounds included peloruside, an effective anticancer agent which disrupts microtubules using a mechanism that is synergistic with taxoid microtubule binders, and also pateamine, a compound with immunosuppressive and anticancer activity that, by chemical genetic profiling methods, appears to target eIF4A1/II and III.² Barbara Timmermann (University of Kansas) described her work in chemical discovery from plant biodiversity in North and South America. Following the guidelines of the United Nations Convention on Biodiversity, she described the gathering of novel materials during expeditions to Argentina,

Chili, Panama, and elsewhere. Through this work, she identified Withaferin A from the Argentinean plant *Vassobia breviflora*, and characterized its anticancer activity.³ Initially limited by availability of the material, she described bioprospecting efforts at locations in Kansas from which she identified new Withanolides, and is now trying to optimize the production of these novel compounds. On the other side of the world, Jinao Duan and Xu Zhang (both from Nanjing University of Chinese Medicine) described the efforts of the Chinese Herbal Resource Chemistry (HRC) to increase the production and utilization of Chinese medicinal herbs, and the characterization of traditional Chinese medicines, such as Jin’s Prescription, for use as therapeutics.

■ WORKING AT THE INTERFACE

Chris Austin noted that “the greatest revolutions in science happen at the interface of disciplines.” By definition, ICBS members work at the interface of chemistry and biology, using chemical tools for target discovery, lead discovery, therapeutic development, and ultimately, to gain insight into fundamental biology (Figure 1). Biological insights from chemical biology research impact the development and clinical use of therapeutics, poisoning chemical biologists at the interface of the bench and bedside.

Chemical biologists use chemical tools for target interrogation. For example, Shaomeng Wang (University of Michigan) and Yuhong Du (Emory University) each described work interrogating the protein–protein interaction interface, a new dimension of therapeutic target space, which has led to the identification of promising new therapeutics. The work described by Wang, focusing on the XIAP/Smac signaling pathway, illustrates the many areas in which chemical biologists work (Figure 1). Starting with the biology, XIAP and Smac are

part of an inhibitory cascade that negatively regulates apoptosis. Inhibition of the XIAP/Smac signal releases control of the apoptotic pathway, allowing induction of apoptosis. Therefore, regulation of this pathway forms a promising target for new cancer therapeutics. One approach for manipulating this pathway is by interfering with the XIAP/Smac interaction, which is mediated by a 4 amino acid peptide (AVPI) from Smac. To develop chemical tools, this small peptide was used a template for structure-based design of high affinity, orally active peptide mimetics, including SM-406. SM-406 turned out to be 50–100 times more potent than the Smac AVPI peptide. In preclinical work, SM-406 potently inhibits the growth of 15% of cancer cell lines, and its effects are synergistic with TNF α and other chemotherapeutic agents. SM-406 moved into clinical trials in 2010 and early results are promising.⁴ Further computational modeling indicated that a bivalent Smac mimetic, binding to both the BIR2 and BIR3 domains of XIAP, may be a more effective inhibitor of XIAP. A bivalent mimetic, SM-164, was synthesized by linking monovalent mimetics together using “click chemistry”. Indeed, the bivalent mimetic SM-164 was 100 times more potent than monovalent compounds.⁵ Wang also described the use of these chemical tools to probe the basic biology of the XIAP/Smac signaling pathway, aiming to understand what triggers apoptosis after the XIAP “brakes” are removed, and why only 15% of tumors are sensitive to the Smac mimetics. Studying the downstream caspase cascade, Wang found that caspase-8 and caspase-3, but not caspase-9, are essential for Smac mimetic activity. Since caspase-8 is part of the TNF α signaling pathway, it became clear that inhibition of both cIAP-1/2 (a regulator of the TNF α pathway) and XIAP are critical for Smac mimetic effects. Validating these observations, Wang found that only the sensitive breast cancer cell lines secrete TNF α . Thus, Smac mimetics induce TNF α -dependent apoptosis by inhibition of both cIAP-1/2 and XIAP. This biological insight may impact the use of Smac mimetics in the clinic, and the development of new compounds.

Also working at the protein–protein interface, Yuhong Du described the discovery of a novel class of 14-3-3 binding small molecule inhibitors through a high throughput screening approach. 14-3-3 is upregulated in a number of cancer types, including nonsmall cell lung cancer tissues; overexpression of 14-3-3 is correlated with poor survival of patients. Therefore, 14-3-3 is a potential target in cancer cells. Searching for inhibitors of 14-3-3, Du described the identification of a class of compounds (termed FOBISINs) which inhibit binding of 14-3-3 to its protein partners, such as Raf-1. One member of this novel class of compounds, FOBISIN101, was found upon exposure of the 14-3-3/compound crystals to X-ray to form a covalent bond with residue K120 in the 14-3-3 ligand binding site. Thus, FOBISIN101 may serve as a pro-drug for radiation-triggered chemotherapy.⁶

Other presentations included the use of chemical tools for lead discovery, focused at the interface of a small molecule and its molecular target. Charles Brenner (University of Iowa) described his work to identify direct small molecule inhibitors of DNA methyltransferase I (DNMT1), which will be used as anticancer agents.⁷ Thomas Smith (Donald Danforth Center) discussed the development of allosteric inhibitors of glutamate dehydrogenase (GDH) to control insulin disorders and possibly cancer. Smith presented a dynamic animation of the homohexamer GDH complex, morphing between an open and closed conformation, which visually demonstrated the effect of

inhibitor binding on movement and product release by the complex.⁸

Another area covered by ICBS presentations was the use of chemical tools to advance therapeutic development, at the interface between the bench and the bedside. Vance Lemmon (University of Miami), of the Miami Project to Cure Paralysis, described the development of a cell culture assay to identify compounds that promote neuronal growth on inhibitory substrates. Screening with a combinatorial library of 4,000 triazine compounds, his group identified 4 compounds which increase neuronal growth on inhibitory substrates, increase axon regeneration in an *in vivo* optic nerve crush assay, and stimulate growth of dorsal column axons in the spinal cord in an acute *in vivo* injury model. By transcriptional profiling, Lemmon's group was able to link the mechanism of action of one of these compounds, termed F05, to a class of antipsychotics. This class of antipsychotics, as well as Taxol, was found to promote neuronal regeneration.^{9,10} Thus, Lemmon's group identified a potential new use for these existing drugs with tested safety profiles, known as repurposing. Repurposing allows rapid advancement of biological insights into the clinic, thus it was a frequent topic at the ICBS meeting. Larry Sklar (University of New Mexico) also discussed repurposed drugs related to the regulation of leukocyte affinity and conformation by signaling and small molecules.¹¹

The main goal of chemical biologists is to utilize chemical tools to understand fundamental biology and then translate these biological insights to impact the treatment of disease. Bartůněk's presentation, on the use of small molecules in stem cell research, provided an overview of the use of small molecules as chemical tools for understanding biology. In the hematopoietic system, human stem cells undergo differentiation into the many different mature cell types comprising the hematopoietic system. Noting that phenotypic cell-based assays and reporter technology are powerful tools used by chemical biologists, Bartůněk described past work by his group and others which used phenotype-based assays to identify a number of small molecule inhibitors of pathways important in hematopoietic development. These chemical probes have allowed characterization of important signaling pathways, including the TGF β , Wnt, FGF4 and steroid receptor pathways, in stem cell biology. Masatoshi Hagiwara discussed the use of chemical tools to understand the regulation of mRNA splicing. His group has focused on kinase inhibitors which regulate splicing, and also has developed a reporter technology for drugs that affect splicing. Currently, his group is exploring the use of these inhibitors for diseases caused by aberrant mRNA splicing, such as the dystrophin gene in Duchenne's muscular dystrophy, viral replication of the Dengue virus, and cancer-specific splicing.¹²

■ ADVANCING TECHNOLOGY

The complete sequence of the human genome is available today due to exponential advances in sequencing technology that coincided with national efforts to define the human genome. The national effort now is focused on translating this rich genomic information into therapeutics to improve human health. As with genomic data, this translation into therapeutics is also going to require exponential advances in the technologies required for drug discovery. Glimmers of these advances were found in talks throughout the ICBS meeting.

Both a critical component of chemical biology and a bottleneck in the drug discovery process lie in the area of

medicinal chemistry. Talks by Jeffrey Aubé (NIH/MLPCN Specialized Chemistry Center, University of Kansas), Qingsong Liu (Harvard), and Hao Xu (Georgia State University) focused on novel chemistry to diversify screening collections. Aubé described three approaches for developing chemical/biological tools: natural products, synthetic methodology, and development of screening hits. Using a natural product approach, Aubé described the synthesis of 104 analogs inspired by an alkaloid traditionally used in Chinese medicine as an antitussive, similar to codeine.¹³ Aubé noted that manipulation of natural product structure can afford new agents with potential to be in the medicinal chemistry space. He also described the development of a novel synthetic chemistry utilizing basic principles, from which a 72-compound library was constructed. Compounds from this library turned out to be selectively active in an opioid receptor (KOR) assay.¹⁴ Working with collaborators in the Molecular Libraries Initiative at Scripps and Duke, Aubé and co-workers have also performed HTS for additional KOR chemotypes. They are now using 5 novel chemotypes to create analogues for probe/lead optimization.

Qingsong Liu (Harvard), representing his collaborative work with Nathanael Gray (Harvard), discussed the vast potential of the kinome and the use of a privileged library approach for the development of the selective torin1/2 small molecule inhibitors targeting mTOR, ATM, ATR, and DNA-PK. Liu demonstrated combinatorial effects of torin1/2 inhibitors with blockers of the Ras/Raf/Mek/Erk signal pathway in a transgenic K-Ras mutant lung cancer model.¹⁵ Hao Xu presented new catalytic methods for complex molecule synthesis. Xu noted that complexity, efficiency, and function are challenges in synthetic chemistry, and that ideal synthetic methods are simple and result in a wide variety of molecules. Using this thought process, Xu described new catalytic methods, inspired by functional molecules such as thiamine and cysteine, to transform starting materials into highly functional compounds with high purity.

Chemical libraries are a cornerstone of experimental work in chemical biology. Baell succinctly discussed the problem of nuisance HTS compounds present in nearly all compound libraries, designated as Pan Assay Interference Compounds (PAINS). He noted that the presence of these compounds is a worldwide problem in chemical biology. He stated that 480 classes of nuisance compounds have been identified, and these nuisance compounds are often published as “progress-able” HTS hits, when they are not. In Australia, they are attempting to address this issue by increasing the education of review committees, increasing the accessibility of methods to identify PAINS compounds, and providing PAINS negative control screening sets. These efforts may benefit the chemical biology field worldwide.

Advances in the drug discovery process will require improved assays. Doug Auld (Novartis) discussed assay design, noting that with the current linear “pipeline” model commonly employed in drug discovery, starting points will have a large impact on end points. Also, while assays drive drug discovery, “a lot happens between target and measurement”. Auld and colleagues have found that firefly luciferase inhibitors can show activation of luciferase activity in cell-based reporter gene assays due to inhibitor-based stabilization of the enzyme.¹⁶ Enrichment of firefly luciferase inhibitors among hits derived from a firefly luciferase-based screen can be up to 70%, depending on the assay. Auld also described ongoing work at Novartis where new reporter enzymes are being tested to identify those with reduced compound interference and/or with different

structure–activity relationships than those known to modulate firefly luciferase. These reporter enzymes could lead to improved reporter gene assay systems. He urged chemical biologists using bioluminescent reporter assays to carefully control for false positives derived from firefly luciferase assays. Auld also presented high-throughput transcript profiling platforms employing technologies, such as Panomics, as alternatives to reporter-gene assays for some applications.

Informatics-based approaches hold high promise for streamlining the identification and characterization of bioactive compounds. Phil Hajduk (Abbott) presented a targeted polypharmacology approach, “connecting” proteins into networks based on ligands.¹⁷ Robert Powers (University of Nebraska-Lincoln) described a systems-based approach, going beyond individual targets, to generate a metabolomics signature with FAST-NMR, leveraging the fact that proteins with similar functions have similar ligand binding sites.¹⁸ John Karanicolas (University of Kansas) discussed informatics strategies for protein–protein interaction pocket prediction, tying into chemical biology discovery efforts in this new therapeutic space.

Abreast with the trend toward personalized medicine, Krister Wennerberg (Institute for Molecular Medicine Finland) described efforts in Finland to provide integrated molecular profiling and drug screening for leukemia in Finnish patients. Collaborative efforts involving the Institute for Molecular Medicine Finland (FIMM), the Hematology Research Unit Helsinki (HruH) and the Finnish Hematology Registry and Biobank (FHRB) have led to the assembly of a concise, comprehensive, preplated screening collection of 240 approved oncology drugs and active substances. Leukemic cells from individual AML patients will be screened, using 5 doses of each compound. Initial data is promising, and will be used to increase understanding of the biology of the disease and for development of therapeutic strategies for individual patients. Such efforts could represent the future of planning chemotherapeutic strategies for cancer patients.

■ CONCLUSIONS

Many of the inaugural ICBS members expressed surprise that a society like the ICBS did not already exist. Now, with its global representation of experts in chemical biology and drug discovery, the ICBS is prepared to accelerate the effort to fill the intellectual void at the interface of small molecules and targets. The newly elected ICBS president, Rathnam Chaguturu, and president-elect, Haian Fu, implored the inaugural members to remember “This is your society,” so volunteer, give critiques, and move the field forward (contact information in Table 1). As the ICBS forms over the next year, the first official ICBS meeting currently proposed for Boston in 2012 promises to showcase the “revolution” in research occurring at the interface of chemistry and biology.

■ AUTHOR INFORMATION

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■ REFERENCES

- (1) Zhang, L., Yan, K., Zhang, Y., Huang, R., Bian, J., Zheng, C., Sun, H., Chen, Z., Sun, N., An, R., Min, F., Zhao, W., Zhuo, Y., You, J., Song, Y., Yu, Z., Liu, Z., Yang, K., Gao, H., Dai, H., Zhang, X., Wang, J., Fu, C., Pei, G., Liu, J., Zhang, S., Goodfellow, M., Jiang, Y., Kuai, J., Zhou, G., and Chen, X. (2007) High-throughput synergy screening identifies microbial metabolites as combination agents for the

treatment of fungal infections. *Proc. Natl. Acad. Sci. U.S.A.* 104, 4606–4611.

(2) Bordeleau, M. E., Matthews, J., Wojnar, J. M., Lindqvist, L., Novac, O., Jankowsky, E., Sonenberg, N., Northcote, P., Teesdale-Spittle, P., and Pelletier, J. (2005) Stimulation of mammalian translation initiation factor eIF4A activity by a small molecule inhibitor of eukaryotic translation. *Proc. Natl. Acad. Sci. U.S.A.* 102, 10460–10465.

(3) Samadi, A. K., Tong, X., Mukerji, R., Zhang, H., Timmermann, B. N., and Cohen, M. S. (2010) Withaferin A, a cytotoxic steroid from *Vassobia breviflora*, induces apoptosis in human head and neck squamous cell carcinoma. *J. Nat. Prod.* 73, 1476–1481.

(4) Cai, Q., Sun, H., Peng, Y., Lu, J., Nikolovska-Coleska, Z., McEachern, D., Liu, L., Qiu, S., Yang, C. Y., Miller, R., Yi, H., Zhang, T., Sun, D., Kang, S., Guo, M., Leopold, L., Yang, D., and Wang, S. (2011) A potent and orally active antagonist (SM-406/AT-406) of multiple inhibitor of apoptosis proteins (IAPs) in clinical development for cancer treatment. *J. Med. Chem.* 54, 2714–2726.

(5) Yang, D., Zhao, Y., Li, A. Y., Wang, S., Wang, G., and Sun, Y. (2011) Smac-mimetic compound SM-164 induces radiosensitization in breast cancer cells through activation of caspases and induction of apoptosis. *Breast Cancer Res. Treat.* Epub ahead of print, DOI: 10.1007/s10549-011-1752-3.

(6) Zhao, J., Du, Y., Horton, J. R., Upadhyay, A. K., Lou, B., Bai, Y., Zhang, X., Du, L., Li, M., Wang, B., Zhang, L., Barbieri, J. T., Khuri, F. R., Cheng, X., and Fu, H. (2011) Discovery and structural characterization of a small molecule 14-3-3 protein-protein interaction inhibitor. *Proc. Natl. Acad. Sci. U.S.A.* 108, 16212–16216.

(7) Syeda, F., Fagan, R. L., Wean, M., Avvakumov, G. V., Walker, J. R., Xue, S., Dhe-Paganon, S., and Brenner, C. (2011) The replication focus targeting sequence (RFTS) domain is a DNA-competitive inhibitor of Dnmt1. *J. Biol. Chem.* 286, 15344–15351.

(8) Li, M., Li, C., Allen, A., Stanley, C. A., and Smith, T. J. (2011) The structure and allosteric regulation of glutamate dehydrogenase. *Neurochem. Int.* 59, 445–455.

(9) Hellal, F., Hurtado, A., Ruschel, J., Flynn, K. C., Laskowski, C. J., Umlauf, M., Kapitein, L. C., Strikis, D., Lemmon, V., Bixby, J., Hoogenraad, C. C., and Bradke, F. (2011) Microtubule stabilization reduces scarring and causes axon regeneration after spinal cord injury. *Science* 331, 928–931.

(10) Usher, L. C., Johnstone, A., Erturk, A., Hu, Y., Strikis, D., Wanner, I. B., Moorman, S., Lee, J. W., Min, J., Ha, H. H., Duan, Y., Hoffman, S., Goldberg, J. L., Bradke, F., Chang, Y. T., Lemmon, V. P., and Bixby, J. L. (2010) A chemical screen identifies novel compounds that overcome glial-mediated inhibition of neuronal regeneration. *J. Neurosci.* 30, 4693–4706.

(11) Chigaev, A., Waller, A., Zwart, G. J., Buranda, T., and Sklar, L. A. (2007) Regulation of cell adhesion by affinity and conformational unbending of alpha4beta1 integrin. *J. Immunol.* 178, 6828–6839.

(12) Nishida, A., Kataoka, N., Takeshima, Y., Yagi, M., Awano, H., Ota, M., Itoh, K., Hagiwara, M., and Matsuo, M. (2011) Chemical treatment enhances skipping of a mutated exon in the dystrophin gene. *Nat. Commun.* 2, 308.

(13) Frankowski, K. J., Setola, V., Evans, J. M., Neuenswander, B., Roth, B. L., and Aube, J. (2011) Synthesis and receptor profiling of Stemonal alkaloid analogues reveal a potent class of sigma ligands. *Proc. Natl. Acad. Sci. U.S.A.* 108, 6727–6732.

(14) Frankowski, K. J., Ghosh, P., Setola, V., Tran, T. B., Roth, B. L., and Aube, J. (2010) N-Alkyl-octahydroisoquinolin-1-one-8-carboxamides: A novel class of selective, nonbasic, nitrogen-containing kappa-opioid receptor ligands. *ACS Med. Chem. Lett.* 1, 189–193.

(15) Liu, Q., Wang, J., Kang, S. A., Thoreen, C. C., Hur, W., Ahmed, T., Sabatini, D. M., and Gray, N. S. (2011) Discovery of 9-(6-aminopyridin-3-yl)-1-(3-(trifluoromethyl)phenyl)benzo[h][1,6]-naphthyridin-2(1H)-one (Torin2) as a potent, selective, and orally available mammalian target of rapamycin (mTOR) inhibitor for treatment of cancer. *J. Med. Chem.* 54, 1473–1480.

(16) Auld, D. S., Thorne, N., Nguyen, D. T., and Inglese, J. (2008) A specific mechanism for nonspecific activation in reporter-gene assays. *ACS Chem. Biol.* 3, 463–470.

(17) Metz, J. T., Johnson, E. F., Soni, N. B., Merta, P. J., Kifle, L., and Hajduk, P. J. (2011) Navigating the kinome. *Nat. Chem. Biol.* 7, 200–202.

(18) Shortridge, M. D., Bokemper, M., Copeland, J. C., Stark, J. L., and Powers, R. (2011) Correlation between protein function and ligand binding profiles. *J. Proteome Res.* 10, 2538–2545.