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EMBL Chemical Biology Meeting 2008: New Views and Interviews

Marlon J. Hinner*

Institute of Chemical Sciences and Engineering, École Polytechnique Fédérale de Lausanne, CH-1015 Lausanne, Switzerland

The largest conference to date on chemical biology was held October 8−11, 2008, at the European Molecular Biology Laboratory (EMBL) in Heidelberg. An impressive array of novel concepts and their application to biological problems was presented, with a clear trend toward complex systems and signaling. This report highlights the newest developments and presents interesting insights that the speakers shared with me in interviews after the talks.

"The most severe limitation is our brain. It is difficult for humans to get away from the reductionist approach of science," said Oliver Seitz from Humboldt University in Berlin, on the challenges and shortcomings in chemical biology. At the conference, 45 speakers from 11 countries and nearly 150 poster presenters nevertheless demonstrated their willingness to help overcome this limitation and showed ways how to do it. I took the opportunity to join in the popular discussion of what chemical biology actually is and to obtain the speakers' views on the origin and definition of the field and on its future directions. This part of the meeting report can be found in the accompanying boxes.

"We tried to make a snapshot of the field and to bring together topics that are normally shown on specialized conferences," said conference co-organizer Maja Köhn, an EMBL resident like the other organizers, Carsten Schultz and Joe Lewis. A second objective of the organizers was to encourage an exchange between the groups that use screening approaches and those that rely more on tools and single-molecule-oriented approaches. "It is still like two big camps," said Schultz. "It would be good if these would be brought together more closely." In the following, an overview for the different categories that were presented will be provided (*1*), with selected examples. A quick guide to all talks containing a short synopsis and the speakers' affiliations is given in an accompanying table in Supporting Information (*2*).

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Computational Approaches can be useful in chemical biology to help in drug discovery and design. This was shown in the talk of Karl-Heinz Baringhaus of Sanofi-Aventis, who demonstrated that a combination of the concepts of virtual screening using pharmacophore representations, homology modeling, and the fact that similar proteins bind similar ligands provides a robust strategy to find lead structures for ion channels and G-coupled-protein receptors.

A concept also based on computational approaches was presented by Vern Schramm. Through a combination of experimental work (determining kinetic isotope effects) and quantum chemical calculations, he is able to deduce a detailed structure of

***Corresponding author, marlon.hinner@epfl.ch.**

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Box 1. What is chemical biology?

The "birth of chemical biology" was announced in 1930 in a publication with this name (*15*). However, the usage of the term has changed and evolved with time (*16–20*), and the current meaning of the term cannot be traced back to a single source of definition (*21*). The EMBL conference on chemical biology showed that it may be the necessity of an *ad hoc* chemical synthesis to tackle a biological problem that provides a basic definition. This fits well with the background of those who actually think of themselves as chemical biologists; discussing with the speakers on the conference, it became clear that nearly all of those that consented to being chemical biologists had started out as synthetic, mostly organic, chemists. While basic biology can now be performed by chemists, most speakers agree that doing relevant chemical biology still requires the close collaboration with "true" biologists. In this collaboration, some perceive an imbalance between the effort that the synthetic part requires and the reward that can be gained by it in terms of acceptance by the biological community. According to Herbert Waldmann, there is the danger that this imbalance discourages organic chemists from dedicating themselves to the field. He said, "If the chemical biology community gives the major credit to the biology, and less credit to the chemistry, then one should not be astounded that the organic chemists pull back." He believes that chemical biology journals should make an effort to publish synthetic work that does not yet necessarily solve a biological problem. Some other thoughts from the speakers:

"A chemical biologist is someone who uses synthetic or analytical chemistry tools to tackle real biological problems." Benjamin Cravatt, The Scripps Research Institute

"I think a chemical biologist is a chemist who is using chemistry to solve biological problems." Scott Sternson, Howard Hughes Medical Institute, Janelia Farm Research Institute

"Chemical biology used to be making tools for biological questions. Originally, this implied that the chemist is just a hard worker making some tools for the biologist who is the nice guy that makes the bright experiments. This is changing now, although in some cases, it may still be more or less the way it goes."
"I think to be a chemical biologist, you need to know your chemistry and be aware of the fundamental problems in biology. This makes you able to design and make your own tools and to come up with original solutions for relevant biological questions." Maurice Goeldner, Université Louis Pasteur, Strasbourg

"I do not think that the chemical biology field has started a brand-new area that needed any term. Lots of established fields are lumped together into chemical biology. But I believe it is good to have a rallying point around a term that young scientists can associate with being an area that they might be interested in."
"I do not think it is possible for chemists to do biology without working with biologists. I believe you'll be hard pushed to find an example where a chemist has made a deep contribution to cell biology, for example, without the involvement of a biologist." Tom Muir, Rockefeller University

"Whenever chemists go into biology, they're doing a form of chemical biology. Chemical biology used to be natural products chemistry, and then it was structure and function, and then it become more pharmacology, and then it became biological chemistry, which was more mechanistically oriented. I think what chemical biology represents now is a union of the fields of biology, chemistry, and even engineering and physics. It is succeeding in bringing in the mechanistic as well as the integrative—instead of just the reductionist—approach." Glenn Prestwich, University of Utah

"Thirty years ago, I would have been called an enzymologist, and now I'm doing the same work and it is called chemical biology. Once the work progresses, it can be applied, and I think chemical biology means that the chemistry is being applied to biology. We see that more and more now, as we get smarter, we can apply the chemistry directly in biology." Vern Schramm, Albert Einstein College of Medicine

"The easiest way to be a chemical biologist is to be a chemist first, and a chemical biologist second; to be a biologist first is much the harder thing to do. The most important thing is that you need to be open to collaboration with biologists and want that really badly and, perhaps with that tag, you can call yourself a chemical biologist. You have to really want to apply chemistry to biological problems, and feel your prime issue is being driven perhaps differently, but still in tune with the biologists." Barry Potter, University of Bath

the transition state of enzymatic reactions. He uses this insight for the design of very powerful inhibitors. Schramm believes "There's going to be a resurgence in computational chemistry to understand inhibitor design for new and better targets."

High-Throughput Screening (HTS) approaches have recently been adapted by large research centers and spurred the birth of a field called chemical genomics, where the massively parallel power of HTS methodology is applied to find small molecules that help elucidate biological problems (*3*). For chemical biologists, this field is useful because it may help find new potential tools, and because assays and experiments of increasing complexity can be automated and performed in parallel using HTS. At the conference, the successful efforts of a number of institutions to establish HTS core facilities were described. For institutes lacking an HTS facility of their own, the European ScreeningPort might be of interest, a public–private partnership that provides HTS services to academic institutions, as presented by Philip Gribbon (*4*). The talks provided a good overview of the possibilities and pitfalls of HTS. Alykhan Shamji and other speakers addressed the problem of insufficient library diversity, causing failure to deliver useful lead compounds (see also ref 5). This is a general problem because different academic core facilities rely on the same commercial sources of compounds. Efforts are therefore being undertaken to increase the size and diversity of libraries by in-house synthesis.

Chemical biological **Tools, Assays, and Probes** may change the way drug discovery is done in the future. "One gets the impression that the groups that are presenting here produce tools that will aid in the drug discovery process," said Philipp Gribbon. "This conference is really about creating the tools of the future and the drugs of the future." An example for this was given by Gregory Verdine, who focuses his research on targeting

the so-called "undruggable" targets. Considered undruggable are protein−protein (e.g., transport proteins) and some protein−DNA (e.g., transcription factors) interactions, because these are mediated by extended and flat surfaces that are not easily mimicked by a small-molecule drug. However, whole proteins or polynucleic acids are not suitable as drugs because of insufficient permeability through membranes. Verdine discussed how an isolated peptide motif known to mediate a specific interaction can be stabilized outside its original protein framework. The solution is to synthesize the peptides chemically and to introduce cross-links that stabilize, for example, a helical conformation. As a welcome side effect, these stabilized peptides display favorable membrane transport properties. Verdine therefore now considers previously undruggable interactions targetable and declared "open season on transcription factors".

Measurement directly within complex environments is a continuing trend. "The days of performing HTS assays using purified biological components solely are over," said Roger Bosse of PerkinElmer. It was amazing to see how diverse ideas and concepts that require the interaction of chemically synthesized compounds and biomolecules can be translated into functioning systems. Yasuteru Urano and his group, for example, have generated the "Tokyo Green" fluorescent dyes by fine-tuning the electronic properties of fluorescein and managed to create a family of irreversible probes for hydrolases and small reactive molecules. Very recently, they succeeded in selectively imaging cancer cells by pH-activatable fluorescence probes (*6*). Elmar Weinhold showed how DNA can be labeled with organic molecules in a sequence-specific manner (*7, 8*). Kai Johnsson presented novel applications regarding small-molecule detection in complex environments based on SNAP/CLIP-tag technologies. The first is an indo-1-based calcium sensor that can be targeted to specific locations within a cell by specific reaction with localized SNAP-tag fusion proteins. The second is a proof-of-principle study on a semisynthetic FRET sensor concept for small molecules and ions. Gerard Marriott introduced a new high-contrast, background-free imaging technique (*9, 10*), termed optical lock-in detection (OLID). Benjamin Cravatt presented, in addition to his well-known concept of activity-based protein profiling, a very recently published method termed protein topography and migration analysis platform (PROTOMAP). The method allows the global mapping of proteolytic events occurring in natural biological systems, based on 1D SDS−PAGE gel electrophoresis and mass spectrometry (*11*).

A number of exciting examples were given where the **Chemical Synthesis of Biomolecules and Their Analogs** provided unique insights into biology. The power of this kind of approach lies in the possibility to study, on one hand, the interaction of a pure sample of a biomolecule with other biomolecules *in vitro* or *in vivo*. This is especially valuable in the cases where this biomolecule cannot be obtained in pure form from biological samples. On the other hand, one can also additionally synthesize non-natural, for example, stabilized or modified, analogs of the biomolecule to investigate which features of the structure or the chemical reactivity of the molecule are essential for its biological function. At the conference, an extensive list of examples impressively demonstrated how far chemical synthesis has come to provide diverse biomolecule classes, such as phosphorylated proteins (as presented by Luc Brunsveld), glycoproteins (Chi-Huey Wong, Peter Seeberger), small peptides used as inhibitors (Tom Muir), specifically damaged DNA fragments and stabilized analogs (Thomas Carell), and lipidated proteins (Herbert Waldmann). Some groups presented their work aimed at further expanding the toolbox for protein semisynthesis (Henning Mootz, Oliver Seitz) and for the construction of modified DNA bearing diverse functional groups at nucleobases (Michal Hocek) (*12, 13*). It became clear during the talks that the transition from developing the tools to applying them was a long-term commitment, and some of the truly astounding stories told at the conference (see Supporting Information for more detail) were efforts going on for 10 years or more.

Finally, the study of **Networks and Signaling** in complex systems, such as communication within the cell or between cells as in neuronal networks, may benefit enormously from chemical biological tools. The areas described in this and the preceding section overlap, and both require the synthesis of biomolecules and analogs. However, a possible differentiation is whether chemical biology is predominantly used to study what the biomolecule of interest does and what its precise mode of action is, or whether these tools are predominantly used to study the impact of the biomolecule (or an analog) on a signaling network and used to dissect this network. At the conference, there was a particular emphasis on phosphoinositide-mediated signaling, reflecting the universal importance—and the personal interest of conference co-organizer Carsten Schultz—of this class of molecules.

A general concept that may help categorize chemical biological tools used for the dissection of complex networks was presented by biophysicist Tobias Meyer. The goal of his research is to develop a unified model predicting cell specific functions in response to activation. In this model (recently reviewed in ref 14), the cell receives an input that is transduced *via* a number of signaling pathways to an output, the specific function of the cell. The framework of signal transduction is feedback, and the input/output behavior of cells can be explained as being the result of a number of single or combined positive and negative feedback loops. The general methodology that can be used to study such feedback

Box 2. The next big step in chemical biology.
Among the speakers who were interviewed, there was consensus that the challenge for chemical biology is studying complex systems like cell signaling networks or neuronal networks. Some groups are already involved in this endeavor, but more and better tools will allow an increasingly integrative approach.

"The big question for chemical biology will be to find a set of tools, of reagents, to systematically perturb complex biological systems." Herbert Waldmann, Max Planck Institute of Molecular Physiology

"The next big step is becoming more integrative rather than focusing only on mechanistic details." Glenn Prestwich, University of Utah

"I think interfering with protein−protein interactions is going to be a big advance in chemical biology." Vern Schramm, Albert Einstein College of Medicine

"I think the most important step for chemical biology is to develop probes for addressing as diverse biological questions as possible. We've seen examples for that already in this meeting. I'm very confident that chemists are the ones who will provide the tools of the future." Michael Famulok, Life and Medical Sciences Institute (LIMES), University of Bonn

"Regarding the computational tools that we make, they need to be adjusted to fit the requirements of chemical biologists; they are not yet exactly what people need. We have to understand the interface between chemistry and biology a bit better." Gabriele Cruciani, University of Perugia

"I think the major challenge is developing chemical tools and approaches that can probe and analyze increasingly sophisticated models, like whole organisms or the brain, and extract biochemical meaning out of them." Benjamin Cravatt, The Scripps Research Institute

"The biggest contribution will be toward systems biology, because small molecules will be essential to rapidly perturbate cellular signaling networks." Carsten Schultz, The European Molecular Biology Laboratory (EMBL) Heidelberg

"Not everything can be done with GFP. Sometimes you need unique functionalities that cannot be encoded. Therefore, research in the area of *in vivo* chemistry and specifically protein labeling with synthetic probes is something that we're very excited about." Gerard Marriott, University of Wisconsin

"To study orchestration of many interactions that happen simultaneously or in a sequential way, we require other technologies than we have available at the moment. We need more development on readout technologies and we need new conjugation methods to fuse reporter groups with biomolecules also inside live cells. We simply do not have enough methods available to do that." Oliver Seitz, The Humboldt University of Berlin

loops and to dissect signaling pathways is "perturbation and monitoring". First, the system has to be perturbed; then, the consequences of the perturbation on signaling events are monitored as the system relaxes back to equilibrium. This methodology critically relies on methods for perturbation and readout, the development of which clearly lies in the core competence of chemical biology (see above: Tools, Assays, and Probes). For perturbation, novel ideas will still be needed to provide methods that are rapid and selective; for probing, new approaches must be found that cause no side effects on the cell state and that exhibit improved signal-to-noise ratios.

An interesting example of such an approach in neuroscience was presented by Scott Sternson. Sternson and co-workers have adapted the "bump-hole" approach, demonstrated by Kevan Shokat for kinases, to nicotinic acetylcholine receptors. On the basis of a structural model of the interaction of the acetylcholine receptor with a known acetylcholine receptor agonist, they produced and tested a number of agonist analogs on acetylcholine receptor mutants. In the end, they managed to obtain a functioning agonist/receptor pair, with the agonist analog not acting on the wild-type receptor and the mutant receptor displaying a reduced responsiveness to the wild-type agonist acetylcholine. Thus, they have obtained tools for the specific chemical activation and silencing of neurons, which is a step toward dissecting the role of specific neurons in neuronal networks.

The first chemical biology conference in Heidelberg provided a comprehensive overview of different areas in chemical biology research. The attendees considered it well-organized and a big success. Although a number of conference participants were from industry, the overall attendance of representatives from the pharma companies was lower than expected. Co-organizer Carsten Schultz voiced his wish that there will be "more participants from industry" in the next EMBL meeting on chemical biology, which is scheduled for September 22−26, 2010. Philip Gribbon, who himself worked in drug discovery for major pharma companies before joining the European ScreeningPort, said, "It is unfortunate that more decision makers from the pharma companies were not here to see it all happen. If they had been here, they might have gone back with a lot of great ideas." Another thing to

wish for in 2010 is more room for the poster sessions, which some considered victimized by the tight schedule of the meeting. "I regret that we didn't allocate more time for the poster sessions," said co-organizer Maja Köhn. "We did not anticipate such a large number of presenters." More time for interaction between young and senior scientists will be available in 2010.

Chemical biology is not a completely new field. But as the conference showed, it is a buzzword that manages to attract scientists from different specializations that share common interests. "In a conference just like this one, you're exposed to really the finest science everywhere," said Oliver Seitz. "You pick up really fantastic stuff, that's very important and very stimulating." Glenn Prestwich was astounded at the number of chemists that have come to participate in clinical development. The final words of this report are left to him: "It used to be that chemists would just write it in their grant applications that they are going to cure cancer," he said. "Now they're actually in collaboration with physicians in their own institution to test new drugs, not just on animals, but on patients. I think that's an important new role that chemists have espoused for themselves: to be part of the biology, not just to hand it off."

Acknowledgment: I am indebted to the speakers that granted me interviews and that allowed me to quote them even though short quotes necessarily can not contain all the rigour and thoughtful deliberation that natural scientists are used to. I apologize that space considerations forced me to subjectively select only a few illustrative examples out of the many inspiring talks that were given at the conference. I thank Kai Johnsson, Christopher Chidley, Carolin Danner, and Arnaud Gautier for useful comments on the manuscript and the German Research Foundation (DFG) for funding under contract Hi 1363/1-1.

Supporting Information Available: This material is available free of charge *via* the Internet at http://pubs.acs.org.

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