Voices of chemical biology

We asked a collection of chemical biologists, "What is the most exciting frontier area in chemical biology and what key technology is needed to advance knowledge and applications in this area?" and reveal some of the perspectives we received.

I am glad to see that people are being increasingly bold in building complex biological constructs and viewing 'editing' of biology as being within our domain with even potentially therapeutic application. Organismal editing, if coupled with 'deep' (appropriately sensitive) mechanistic proteomics (to obtain quantitative measurements on complex, endogenous substrates) might enable not only direct tracking of the multiple effects of, say, pathology but also in vivo chemistry to edit, modulate and/or perturb such pathways.

Benjamin Davis
The Rosalind Franklin Institute, Oxfordshire, UK

The intersection of systems biology and chemical biology is an exciting emerging area poised to take off over the next five years. In particular, the development of new tools and techniques that can globally map the dynamics of protein–protein and protein–RNA interactions and gain insights into the functions and therapeutic relevance of these interactions is a key unmet challenge for chemical biologists. Such interatomic studies will almost undoubtedly require technical innovations in both chemical and photo-crosslinkers, including for small-molecule screening and crosslinking mass spectrometry. Innovations in data analysis and data integration are also going to be essential.

Keri Backus
University of California, Los Angeles, Los Angeles, CA, USA

I am particularly excited about the possibilities offered by functional genomics. Dramatic advances in the field of synthetic biology and highly multiplexed DNA synthesis will allow us to interrogate gene products at a single amino acid resolution with unprecedented speed and scale. Intersecting this type of data with modern-day docking studies should advance our understanding and serve as a highly valuable and probably faster alternative to structural elucidation.

Georg Winter
CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria

If we could design efficient artificial enzymes for any chemical reaction of interest, it would open the door to a wide range of applications in chemical biology. To advance knowledge and application in this area, I believe it will be essential to design all intermediates along the enzyme reaction coordinate instead of solely focusing on the transition state, as has been done in the past.

Roberto Chica
University of Ottawa, Ottawa, Ontario, Canada

The interplay between metabolites and proteins provides an important layer for the regulation of membraneless compartments in cells, but this has been poorly explored. The systematic identification and exploration of biological metabolites that regulate protein phase separation may inspire chemical intervention to strengthen functional membraneless compartmentation.

Dan Li
Shanghai Jiao Tong University, Shanghai, China

In establishing microbial cell factories for the production of natural chemicals, there are often unknown enzymes within the biosynthetic pathway, which is particularly true for complex natural products. For non-natural chemicals, there are often no known enzymes at all for some conversion steps. Thus, rapid, accurate, and efficient design, engineering, and even creation of necessary enzymes is the single most important technology needed by metabolic engineers.

Sang Yup Lee
KAIST, Daejeon, Republic of Korea

We are entering an era of 'human chemical biology' in which chemists will need to develop new genomics, proteomics, imaging tools and selective small-molecule probes to directly study human samples in a non-invasive manner to understand disease biology and patient-derived systems.

Chuan He
University of Chicago, Chicago, IL, USA

We need to develop new technologies that will enable us to ask, on a proteome-wide scale, why specific post-translational modifications (PTMs) were installed and how they execute their functions on a molecular level. Tools that enable PTM mapping in living cells with spatial and temporal resolution could provide insights into which modifications have meaningful phenotypic consequences and would allow us to develop a molecular-level understanding of what those consequences are. For example, targeting PTM capture tools to specific subcellular locations would enable generation of spatially resolved PTM maps that would shed light on how PTMs impact protein localization. This information would allow us to functionally prioritize PTMs for follow-up experiments and to dissect previously unappreciated functional nodes in biological signaling pathways.

Amy Weeks
University of Wisconsin. Madison, WI, USA

The restoration of structural stability and hence function of an essential protein rendered deficient by a single amino acid mutation remains extremely challenging. Understanding the biology of a system can inform small-molecule drug development to rescue defective proteins or enhance the activity of endogenous normally encoded proteins. Thus, the potential of molecular correctors to act as nanoprosthetics, while challenging, can be highly rewarding.

Christopher Overall
University of British Columbia, Vancouver, Canada

Plant researchers have been spending a lot of time producing plants with desired traits. This could be shortened by chemical biology approaches that identify molecules that can regulate physiological functions of plants, leading to efficient and sustainable food production.

Shinya Hagihara
RIKEN Center for Sustainable Resource Science, Saitama, Japan

The wealth of biotechnology we've inherited from evolution is enormous, but we shouldn't stop there! We need to reach past off-the-shelf components to build our own biological systems. Chemical biology needs to develop its emerging interplay with synthetic

biology into a symbiosis toward making new parts, including new functional biomolecules with capabilities not already found in nature. In my opinion, the less distinction we make between 'chemical' and 'synthetic' biology, the more we can all accomplish.

Ben Thuronyi
Williams College, Williamstown, MA, USA

A large fraction of our proteome remains uncharacterized in terms of its biological function in health and disease. Therefore, mechanistically understanding the biochemical, molecular and cellular functions of such unannotated proteins (enzymes) represents a grand challenge and a daunting task to modern chemical biologists. Obtaining this new information can lead to valuable new biomarkers that may facilitate early diagnosis of diseases or novel therapeutic paradigms in their treatment and/or clinical management.

Siddhesh Kamat
Indian Institute of Science Education and Research, Pune, India

One of the most exciting frontier areas is the continued development of RNA chemical biology-based ideas and approaches, as advanced and robust tools are still needed to study and engineer RNA. In particular, capturing RNA and ribonucleoproteins in situ within certain subcellular compartments in cells followed by spatiotemporal visualization with super-resolution imaging systems to cryo-technology revolutionized tomography will provide new insights into how RNA plays a role in organizing membraneless cellular granules.

Ling-Ling Chen
Shanghai Institute of Biochemistry and Cell Biology, Shanghai, China

Using cryo-EM to obtain the structure of protein complexes and medium–large individual proteins and enzymes will inform how these complex systems function at a molecular level. To accomplish this, new and more affordable microscopes and automatic computational methodologies will be required, which will in turn make cryo-EM affordable and accessible to everyone.

Ramón Hurtado Guerrero
University of Zaragoza, Zaragoza, Spain

We need to develop highly efficient technology that enables efficient cell and tissue delivery of protein–DNA–RNA complexes with cell-type or tissue specificity and minimal endosomal trapping.

Shao Yao
National University of Singapore, Singapore, Singapore

I think the integration of glycans into our understanding of proteins and lipids is still the most exciting frontier in chemical biology. We have so much to learn and still need better tools to consider the impacts of one on the other.

Lara K. Mahal
University of Alberta, Alberta, Canada

Imagine a single place where you could send a sample and they send you back everything that is happening in the cells in a form that is easily interpretable and rapidly guides the next round of design. This type of whole-cell debugging is crucial; we need to comprehensively 'see' the effects of engineering on the cell.

Christopher Voigt
Massachusetts Institute of Technology, Cambridge, MA, USA

Similar to recent advances demonstrating the ability to alter specific genetic modifications, dialing in post-translational modifications on proteins seems possible. Mass spectrometry and chemical proteomics will play a big technological role, as it's one of the few ways to directly measure protein modifications. To fully enable this capability, we will have to innovate new methods in chemical biology, which is the exciting part!

Christina Woo
Harvard University, Cambridge, MA, USA

Cellular metabolism—the playing field of much of chemical biology research—would reveal many secrets if we could detect metabolite levels and their fluctuations in subcellular compartments and organelles with high levels of confidence. Such analytical tools are key to understanding a range of diseases such as cancer, neurodegeneration and aging.

Erick Strauss
Stellenbosch University, Stellenbosch, South Africa

We need to develop comprehensive, efficient and rational technology that enables delivery of molecules to a precise cellular organelle.

Kazuya Kikuchi
Osaka University, Osaka, Japan

For new therapeutic modalities, such as targeted protein degradation, and new target types, such as RNA and biomolecular condensates, chemical biologists will need to design and synthesize the molecular tools necessary to enable development of the theories and paradigms that will guide the drug-discovery process toward the successful launch of new medicines.

Timothy Dore
NYU Abu Dhabi, Abu Dhabi, United Arab Emirates

The next frontier will be to devise molecules and methods that enable the complexity and heterogeneity of biological mechanisms within living cells or tissues to be interrogated and mapped with higher spatial and temporal resolution than is currently possible. To achieve this we will need clever designs of small molecules that are able to bind and modulate macromolecular conformations in vivo and physical methods capable of tracking the interactions of molecules with near-atomic resolution in real time in situ.

Sheena Radford
University of Leeds, Leeds, UK

Unravelling the functional roles of novel histone marks in epigenetic regulation is still the most exciting frontier area that can be advanced by the chemical biology community. To advance our understanding of these histone modifications, it is essential to identify the enzymes that add ('write') and remove ('erase') the marks and 'reader' proteins that interpret them. To address this challenge, technology that allows the detection or capture of histone PTM-mediated protein–protein interactions needs to be developed. In addition, nucleosome- and chromatin-based chemical biology tools can also provide a useful strategy to investigate the crosstalk of histone modifications within a nucleosome or between different nucleosomes.

Xiang David Li
The University of Hong Kong, Hong Kong, China

I think the most exciting frontier area is molecular optogenetics controlling specific molecules in living cells. Through the new generation of optogenetic tools, we can better understand cell signaling and cellular functions in living cells and animals.

Won Do Heo
KAIST, Daejeon, Republic of Korea

The realization that drugs can confer new properties to the proteins they engage has opened up a new dimension to chemical biology. In particular, small molecules can 'massage' proteins, creating large but also very subtle changes that can alter the protein's social properties, from inducing a tiny twist to efficiently engage an E3 ligase to short-circuiting two pathways. Even molecules with low affinity for their targets can now achieve great things.

Giulio Superti-Furga
CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria

Imagine if we could peer into the human body to better understand the molecular interactions and mechanisms that take place in various physiological states. Equipped with the tools derived from chemical biology to facilitate the analysis of single cells in their natural environment, scientists will be able to answer long-standing biological questions about aging, the mediators of disease and the threshold requirements of cells and molecules that change healthy states to diseased states.

Tara Deans
University of Utah, Salt Lake City, UT, USA

I think the most exciting area in chemical biology is the development of tools that allow us to monitor and modulate cellular functions and cell fate. Monitoring requires the development of imaging probes, synthetic or genetically encoded, to trace processes in living cells and chemical tags that allow omics identification of particular molecules and their modifications. Modulation reflects our ability to selectively tune pathways and metabolites in cells, in space and in time to understand how they affect functioning of the cells, tissues and organs.

Vsevolod Belousov
Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, Moscow, Russia

I think the next frontier will involve discovering new chemistry de novo and in vivo. The key technology is proteomics and deploying it in new ways that enable different ways of thinking about the data and how we define chemical probes. Coupling target discovery to lead compounds that operate by new mechanisms is where we can do better.

Megan Matthews
University of Pennsylvania, Philadelphia, PA, USA

Proteins and peptides have so much potential as tools, therapeutics, sensors and industrial catalysts. Our ability to design them to suit our needs, rather than use or tinker with what nature has provided, has enormous potential. We are already seeing an interesting convergence of inexpensive DNA synthesis and robotics-based high-throughput screening with energy function-based design and machine learning. However, all of these new techniques will only take us as far as our fundamental understanding of protein structure, function and dynamics allows us to go.

Colin Jackson
Australian National University, Canberra, Australia

The new frontier in drug discovery will be a merging of the two fields 'molecular glues' and heterobifunctional degraders to enable the design of interfacial binders. We may be able to drug protein complexes that normally interact with one another in a cell or create de novo protein complexes using small-molecule interfacial binders. The future is one where we view targets not as stand-alone entities but as one half of an interface that could be directed to any number of factors in a cell to activate, inhibit or degrade. The possibilities are endless!

Shiva Malek
Genentech, South San Francisco, CA, USA

While small-molecule modulation of protein activity is a pillar of chemical biology research, the equivalent for the nucleic acid world is only beginning to be discovered and used. A true frontier will be to develop potent and specific small molecules that target small nucleic acids, but not proteins.

Herbert Waldmann
Max Planck Institute for Molecular Physiology, Dortmund, Germany

Detailed understanding of how a polypeptide chain folds into the three-dimensional structure of a mature protein is an important and fundamental topic that still remains poorly understood. The key to this knowledge lies in basic protein-folding principles and, perhaps most importantly, in the behavior of proteins in their natural environment. Machine learning methods can give us tools to increase our understanding and predict these events, while wet-lab technologies will enable us to study proteins and other macromolecules at atomic resolution in their natural, crowded environment.

Anna Rising
Karolinska Institutet, Stockholm, Sweden

New technologies are emerging that will transform our ability to engineer ribosomes to manufacture new classes of enzymes, therapeutics and materials with diverse genetically encoded chemistry. I, for one, look forward to advances that enable ribosome-mediated polymerization of biopolymers containing exclusively mirror-image and backbone-extended amino acids. Such polymers could accelerate the discovery of next-generation therapeutics and materials.

Michael Jewett
Northwestern University, Evanston, Illinois, USA

Single-molecule experiments have revealed that the function of biological molecules fluctuates over time, and such fluctuations can be extremely long lived. Even though switching between long-lived functional modes appears to be a ubiquitous property of polypeptides and polynucleotides, its biological relevance has been unclear. I believe that mode switching will emerge as a generic mechanism for protein regulation. Investigating these phenomena requires functional assays able to directly observe single molecules for hours, including millions of individual functional events.

Dimitrios Stamou
University of Copenhagen, Copenhagen, Denmark

I hope that we will be able to know more about the sequence–structure–function relationships that allow us to accurately predict molecular interactions and reaction catalysis by enzymes and ultimately to modify sequences to change chemical output. To realize this aim, we need to develop the capability to test the output of a large number of sequence variations using sensitive and tailored detection techniques.

Emily Parker
Victoria University of Wellington, Wellington, New Zealand

Recently, chemical biology has been moving toward the quantum world, and our capacity to appreciate time-resolved dynamics of biological macromolecules such as those in biocatalysis is mostly underpinned on in silico first-principles simulations. In this scenario, experimental quantum chemical biology and disruptive imaging methods will emerge, providing a further level of molecular understanding of biological systems.

Mario Murakami
Brazilian Center for Research in Energy and Materials, São Paulo, Brazil

To me, the most exciting frontier in chemical biology is bridging living and non-living systems for biotechnology applications. Hybrid systems such as protocells, which incorporate living cells or organelles as functional elements, allow us to capitalize on the strengths of both biology and chemistry. Like any research area that is pushing the boundaries of knowledge, the key necessary technologies are analytical capabilities that allow us to have a detailed understanding of the behavior of these hybrid systems across time with high spatial resolution.

Karen Polizzi
Imperial College London, London, UK

The development of useful chemical–genetics and genome-editing tools coupled with new imaging strategies will help visualize target molecules and events with

high resolution in vivo, which is crucial in understanding brain functions and disorders in a quantitative manner.

Itaru Hamachi
Kyoto University, Kyoto, Japan

The most exciting current development in chemical biology is our increasing ability to design and engineer complex biological systems from the bottom up. This will transform biology from an analytical into a truly synthetic discipline. We will be able to create a whole new world of biological systems that feature completely novel chemistries yet retain the properties of living systems. These human-made chemical biological systems will provide alternative, more efficient solutions to natural processes or perform tasks not found in natural systems and thus could find applications in virtually all technological fields, including materials science, biotechnology and medicine.

Tobias Erb
Max Planck Institute for Terrestrial Microbiology, Marburg, Germany

An ultrasensitive technique such as single-molecule protein sequencing is needed. This opens exciting new frontiers to answer questions that we might not even know of yet and in doing so will revolutionize the fields of medicine, agriculture, biophysics and beyond.

Chirlmin Joo
Delft University of Technology, Delft, The Netherlands

Synthetic molecules, whether small or large, should be capable of executing most or even all of a protein's tasks if they are designed or explored well. Undrug-like synthetic molecules whose actions are governed outside of the lock-and-key theory could exert biological activities beyond our current imagination. Such discovery would require further development of chemical libraries beyond the rule of five and new simple technologies for direct identification of non-protein targets.

Motonari Uesugi
Kyoto University, Kyoto, Japan

The most exciting work I see in this area is describing novel binders and modulators of nodal signaling protein–protein interactions.

Rab Prinjha
GlaxoSmithKline, Stevenage, Hertfordshire, UK

The available methodologies for mapping and quantification of epitranscriptomic marks in low abundance RNA are far from perfect. A desirable technology, with the potential to significantly advance epitranscriptomics research and derived applications, is high-throughput direct sequencing of RNA, which will allow analysis of single long RNA molecules and sensitive and reliable identification of RNAs modifications.

Gidi Rechavi
Sheba Cancer Research Center, Tel Aviv, Israel

The challenge now is to expand progress in genomic, proteomic and metabolomic data to evolutionary chemical biology. The conservation of small-molecule–orthologue protein interactions in phylogenetically distant species suggests the importance of particular interactions, which, combined with omics data, may be correlated with developmental achievements during evolution.

Roberto Solano
Centro Nacional de Biotecnologia-CSIC, Madrid, Spain

Protein biochemistry benefits from a rich toolkit. I look forward to chemical biology breakthroughs thatwill transform our understanding of regulation of other macromolecules, especially lipids and metabolites. I anticipate great advances from improved detection and quantification (e.g., through emerging Raman imaging and mass spectrometry methods) to the identification of biosynthetic pathways in understudied and presently unknown organisms.

Brenda Schulman
Max Planck Institute of Biochemistry, Martinsried, Germany

Chemical biology is pioneering a new bridge between academia and industry. Given the complexity of biology, strengthening collaborations between industry and academic laboratories is going to be key over the next five years to continue this upward trajectory. We believe that chemical biology can serve as a powerful interface between academia and industry that facilitates the synergistic impact on both our fundamental understanding of pathological events as well as our capacity to treat them.

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