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Thoughts for the future

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As *Nature Chemical Biology* approaches its third decade we asked a collection of chemical biologists, "What do you think are the most exciting frontiers or the most needed developments in your main field of research?" – here is what they said.

It is impossible to precisely predict which new technologies will be developed in the future, or exactly how they will be harnessed to generate new knowledge. There is, however, some wisdom in crowds. With this in mind, *Nature Chemical Biology* reached out to researchers working in research areas that are representative of the work the journal covers. We asked them to contribute their vision of what the most important frontiers in chemical biology are, and what developments are needed to advance the field. Their comments highlight some of the challenges chemical biologists are addressing and we look forward to seeing how the field responds in the years ahead.

Lona M. Alkhalaf:

The advent of low-cost genome sequencing has propelled the field of natural product biosynthesis forward over the past 10 years, allowing scientists to identify and switch on silent gene clusters, detect novel biocatalysts, and elucidate the detailed molecular mechanisms of complex assembly lines. Current focus is on developing a more detailed understanding of how different parts of a biosynthetic pathway interface, how chemical selectivity can be rationally engineered, and whether we can use big datasets to learn any lessons from evolution, with help from machine learning technologies. The next exciting frontier will then be utilizing what we have learnt to manipulate these biosynthetic systems robustly, for the de novo synthesis of complex chemical scaffolds from simple building blocks.

Cheryl Arrowsmith:

Chemical probes are among the most useful tools to study the function of a specific protein

and/or its potential as a therapeutic target. However, discovery of potent, selective, cell-active compounds is currently time and resource intensive, and often encumbered by intellectual property restrictions, limiting their availability. To address these limitations, we should take inspiration from the recent success of 3D protein structure-prediction algorithms (such as AlphaFold2), which were trained on the thousands of experimental protein structures in the well-curated Protein Data Bank. Generation of high-quality experimental protein–small molecule interaction data at scale, and their deposition in machine-readable databases, coupled with benchmarking competitions, will enable machine learning models to predict drug-like molecules that can bind to a given protein. The goal would be to transition chemical probe discovery from an expensive, slow experimental endeavor to a largely computational exercise. Such an advance would eventually enable the discovery of chemical probes for most ligandable proteins, while also vastly accelerating drug discovery and our understanding of biological systems.

Emily P. Balskus:

Efforts to understand the many biological roles that complex microbial communities (microbiomes) have in ecosystems, including the human body, largely leverage descriptive, DNA sequencing-based approaches focused on identifying microorganisms. To gain a mechanistic understanding of microorganisms and microbiomes, we need better ways of characterizing and controlling microbial functions. This includes developing genetic and chemical tools that can be applied directly in natural microbial ecosystems. We also need better methods to infer biological and biochemical functions directly from microbial genome and metagenome sequencing data. This is a larger challenge we face in the genomic era of biology. Obtaining sequencing data is no longer a bottleneck – interpreting those data is now the major obstacle. With our ability to think about protein function at a molecular level and design molecules to interface with biological systems, I believe that the chemical biology research community is uniquely positioned to contribute solutions to these problems.

Giovanna Bergamini:

New modalities such as antibody–drug conjugates, bispecific antibodies and therapeutic oligonucleotides are revolutionizing drug discovery and development. They offer unprecedented precision in targeting diseases, enhancing efficacy and minimizing side effects, and innovations in chemical biology are driving these advancements. For antibody–drug conjugates, developments in linker technologies and payload optimization are crucial for targeted delivery and enhanced specificity. Bispecific antibodies are advancing with improved designs that enhance binding affinities and reduce immunogenicity. In therapeutic oligonucleotides, breakthroughs in chemical modifications and delivery mechanisms are key to overcoming stability and targeting challenges. These innovations promise more effective treatments and personalized medicine, significantly improving patient outcomes and expanding therapeutic possibilities.

Rashna Bhandari:

Inositol, a six-carbon ring with a hydroxyl on each carbon, provides a platform for

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combinatorial substitution of phosphate and diphosphate groups, creating an array of inositol phosphates (InsPs) and inositol pyrophosphates (PP-InsPs) in all eukaryotic organisms. Each of these metabolites can impact multiple cellular and physiological processes, many of which continue to be uncovered. InsPs and PP-InsPs regulate protein function via specific binding. Additionally, PP-InsPs can donate their β-phosphate to pre-phosphorylated proteins to generate pyrophosphoproteins, several of which were identified in a recent mass spectrometry-based detection of the human pyrophosphoproteome. Other advances in analytical methods are uncovering previously unidentified InsP and PP-InsP species – information on their functional roles will probably follow soon. Current tools for quantification of InsPs rely on conventional biochemical methods of extraction and isolation. Future breakthroughs in the in situ detection of InsPs and PP-InsPs, and their movement between subcellular compartments, will uncover new cellular biochemical secrets.

Christopher J. Chang:

Developing and deploying new chemical methods for mapping metals across varying biological-length scales will help us discover and decipher the foundational roles of these essential nutrients in health and disease across all kingdoms of life. Diverse imaging modalities, along with omics platforms spanning genomics, proteomics and metabolomics, represent key opportunities to advance our understanding of the chemistry and biology of the elements. These chemical approaches will inform new metal-dependent physiology, particularly at the interface between signaling and metabolism, as well as new metal-dependent disease vulnerabilities. In turn, this basic science knowledge in the chemical biology of metals can be translated to address some of the important societal issues facing our shared world today, from aging and age-related diseases such as Alzheimer's disease, cancer and metabolic disorders, to climate change and sustainability in food, water and energy.

Peng Chen:

Precise and programmable 'editing' of the proteome, such as sequence-specific proteolysis and site-specific post-translational modifications (PTMs), may offer an unprecedented capability for probing and modulating protein functions, localizations and interactions inside cells at will. Similar to the sequence-specific gene editing by using CRISPR systems, programmable proteases, PTM writers or PTM erasers could enable the remodeling and fine-tuning of protein functions within its native proteome context, which remains desirable yet challenging. In contrast to genetic alterations, the protein-level modulations provide more temporal and/or reversible control over protein functions and cellular processes. Empowered by the efficient protein evolution technology, I envision that reprogramming the specificity of proteases and PTM writers and erasers may ultimately revolutionize our ability to edit the human proteome with high accuracy as well as spatial–temporal precision, which may lead to an array of exciting applications in basic sciences and therapeutic innovations.

Xing Chen:

Like nucleic acids and proteins, glycans are a major type of biomacromolecule of cells. However, owing to the structural complexity and microheterogeneity, elucidation of glycan functions has long been challenging. For the past decades, chemical biology has provided powerful tools such as bioorthogonal chemistry and click chemistry for visualization and profiling of glycans in living systems in ways not possible before. From the perspective of technology, glycan sequencing and editing both at the single-cell and system levels remain lagging behind gene sequencing and editing and proteomics. Developments of these enabling tools will facilitate the answering of fundamental questions such as how glycan sequence is determined and what glycan functions are important in pathophysiological processes such as neurodegeneration and cancer.

Alessio Ciulli:

The success of PROTACs and molecular glue degraders, with >50 drugs in clinical trials today, is fundamentally underpinned by their remarkable ability to de novo induce protein–protein interactions or to strengthen pre-existing ones. We have just scraped the surface of what is possible with this new dimension of molecular recognition. I am excited about exploring the large space and potential beneath the tip of the iceberg, to pursue the true power of inducing molecular complexes as a strategy to probe biology and re-wire it for innovative pharmacology. Toward this long-term goal, I foresee that it will be important to develop new methods in integrative structural biology and biophysics, with a focus on gaining deeper insights into protein interactions and dynamics, and making better predictions thereof, as well as innovations in screening approaches for discovery in chemistry and biology. Together, these advances will combine to usher a clearer path toward more rationally designing the next generation of proximity-inducing small molecules.

Julia A. Cricco:

In recent years, advances in technology and experimental strategies have significantly expanded our understanding of metal ion trafficking and storage in different cells, tissues and organisms. However, the precise pathways of metal ion scavenging in real time and space, especially in pathogenic organisms, remain unresolved. Although a variety of proteins, chaperones and small ligands have been identified in several organisms, there is still a knowledge gap when it comes to pathogenic parasites. These pathogens rely on metal ions for their proliferation, while hosts regulate the availability and toxicity of these ions to combat infection. Unveiling the chemistry and biology of metal ion scavenging and trafficking in pathogenic parasites could lead to

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the discovery of new molecular targets, facilitating the development of novel therapeutic agents – or repurposing existing ones – that may serve as effective treatments against neglected diseases.

Benjamin G. Davis:

Genetics is axiomatically separated from true function in biology both in time and in space. It is therefore perhaps too blunt a tool to rely on, even with increasingly 'expanded' codes. The industrialization of oligonucleotide assembly (genome factories) may allow eventual progress to more precise control than is currently afforded by gene editing. However, none of these methods can control biology in the right place at the right time. One grand vision for chemical biology, as advanced chemical pharmacology, is the editing of life in its truly functional, post-translational state through bond forming and bond breaking directly inside living systems. This will exploit all the tools of chemistry, including catalysis and multiple layers of hierarchical selectivity. There is no reason that deficiencies caused by pathology, which inevitably emerge from even the most finely tuned genomes, cannot be corrected in this way. Crick warned against overreliance on genes in his invocation of molecular biology as dogma – chemistry now has the power, in the coming years, to step beyond this.

Martina Delbianco:

The frontier in carbohydrate materials lies in engineering well-defined glycans to harness their untapped potential across numerous fields. Interdisciplinary projects that integrate computational modeling, synthetic chemistry and advanced analytics are reshaping our understanding of glycan structures and their complex biological roles. Still, the exploration of glycans has just begun and tailor-made carbohydrates remain underexplored in materials science, organic chemistry and nanotechnology. A new era merging computer science and glycobiology is on the horizon, promising to accelerate glycan discovery and characterization even further. This process will unlock new functions and applications, allowing us to engineer carbohydrate-based systems that can intelligently modulate biological processes or function as programmable biomaterials. Drug delivery systems, catalysts for organic transformations, food additives and mimics of biological matrices are just some foreseeable applications, but many more opportunities may reveal themselves as research in carbohydrate materials progresses.

Natalia Dudareva:

Every day nearly one-fifth of the carbon dioxide fixed by plants is released back into the atmosphere in the form of volatile organic compounds that play key roles in plant–plant communication and interactions with insects and microorganisms. The next frontiers and challenges in volatile research are to understand how plants regulate the release of these compounds and to decrypt the messages plants convey through volatiles to other plants, insects and microorganisms. Unraveling the mechanisms behind this information exchange in the ecosystem will have a profound impact on sustainable agriculture, pest management, plant protection, biofuel production and improving crop nutritional value. This research is becoming increasingly crucial in the face of global climate change, as plant-emitted volatiles influence atmospheric chemistry and climate, while climate shifts substantially affect their production, emission and ecological functions.

Erin Dueber:

Advancements in peptide diversity display methodologies and synthesis strategies have expanded the range of peptide-based reagents, including the incorporation of an ever-growing list of non-natural amino acids and cyclization schemes that add conformational complexity and/or rigidity. These peptide reagents will be powerful tools for exploring the molecular mechanisms that underlie human biology and disease, and they could potentially serve as a means of therapeutic intervention for difficult-to-drug targets.

Fleur Ferguson:

Induced proximity modalities have raced from academic labs to the clinic, with numerous molecules in clinical trials. As the field advances, rational methods to screen for, validate and optimize this new class of molecules are emerging. Looking to the future, the next frontier is the development of methods that expand our ability to rationally discover molecular glues that rewire cellular signals, in particular those that go beyond ubiquitin. The field has rapidly leveraged cutting-edge medicinal chemistry, large-scale proteomics, protein complex modeling and machine learning techniques, and I am excited to see where these efforts lead in the next few years.

Priscila Oliveira de Giuseppe:

In lignin bioconversion, I think that the most exciting frontiers are the impact of lignin-derived compounds on the gut microbiota and health of humans and herbivores, and the molecular mechanisms used by gut microbial communities to break down and metabolize lignin under anaerobic conditions. Regarding the most needed developments, advances in mass spectrometry methods, combined with computational chemistry and machine learning for data interpretation, could enhance and accelerate our understanding of lignin structure and its transformation during chemical and biological breakdown processes. A dream would be to have a robust and fast method to sequence lignin macromolecules and oligomers, similar to that which exists for DNA and proteins.

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Itaru Hamachi:

Over the past 20 years, a variety of biomolecule-labeling techniques in living cells have been established, contributing to both basic biological research and drug discovery. Such selective labeling strategies with high chemical flexibility should be expanded toward living animals (in vivo) in the next decades. In particular, the brain remains an unexplored intriguing system due to its structural and functional complexity. The development of innovative tools such as optogenetics has unraveled the intricate neuronal networks of the brain. The use of in vivo covalent chemical tools may enable identification of metabolites with high spatiotemporal resolution to improve the resolution of the brain map. The description of such a molecular brain map can inform the creation of novel therapeutics to treat neuronal/brain diseases and to predict their potential side effects.

Ming Chen Hammond:

Foundational studies on ribosomal RNA–antibiotic and riboswitch–metabolite interactions built our understanding of RNA–small molecule interactions, which now have enabled the development of structured RNAs and/or small-molecule ligands for in vivo applications that require high specificity, including fluorescent tags, biosensors, gene regulators and targeted RNA degradation. However, an outstanding challenge remains to design bespoke RNA structures to bind any given small-molecule target with sufficient affinity and selectivity to be useful in the cellular context; equally challenging is the related problem of predicting the small-molecule ligand that would bind a given structured RNA. Although there are experimental methods that allow researchers to brute-force the solution through selections or screening, advances in RNA 3D structural prediction and design would be hugely enabling to the field and help accelerate the generation of RNA–small molecule interactions for truly novel functions.

Stavroula K. Hatzios:

Redox reactions govern essential processes within cells, from cellular respiration to the formation of post-translational modifications that modulate signal transduction. It is becoming increasingly clear that these electronic transactions can also mediate intercellular communication between microbial and host cells. Redox-active small molecules produced by the host can tune bacterial signaling and metabolism during infection, and vice versa. However, such processes are difficult to detect given the rapid and spatially controlled dynamics of redox reactions within biological systems. Integrating reactivity-based omics approaches with probes capable of capturing these dynamic events in situ will help illuminate this enigmatic facet of host–microorganism interaction and create new opportunities to control redox homeostasis in human health and disease.

Won Do Heo:

The most exciting frontier in the field of optogenetics is molecular optogenetics, which allows precise control over diverse cellular molecules using light-responsive proteins. Recent advances include the manipulation of receptor tyrosine kinases, intracellular proteins, second messengers such as calcium and phosphoinositides, mRNA, and intrabodies such as nanobodies and single-chain variable fragments. These tools enable the real-time study of cellular signaling pathways in cell biology and neuroscience fields, in which light can modulate cellular functions, animal behavior and memory. The capacity to regulate multiple molecular targets simultaneously opens new avenues for therapeutic applications, including treatments for neurodegenerative diseases and advancements in regenerative medicine. By controlling cellular processes with high precision, molecular optogenetics can influence neuronal activity and behavior in animal models, offering promising therapeutic potential for human applications. This expanding toolkit transforms our understanding of cellular function and drives innovative therapeutic strategies.

Jon Paul Janet:

Generative models for drug discovery need dynamics. The impact of generative models on life sciences has been dramatic, greatly increasing access to high-quality protein structures and widely recognized as a breakthrough (including the 2024 Nobel Prize). However, capitalizing on this information for drug discovery requires a connection to chemistry, identifying binding sites and accurately generating or finding chemotypes that can drug them. Progress has been made on this front, with a plethora of pocket-conditional generative models available, trained on static crystal structures and generally treating the receptor as rigid. However, proteins are both dynamic, in that they sample an ensemble of configurations, and flexible – this ensemble can be biased by the presence of a ligand. Incorporating these dynamic effects is a key outstanding challenge and exciting frontier for generative modeling to be able to account for entropic effects in binding, find cryptic pockets, and target 'undruggable' space.

Siddhesh S. Kamat:

A significant portion of proteins remain functionally unannotated. Of note, several incurable human diseases are associated with mutations and/or dysregulation of proteins (especially enzymes) whose physiological functions are hitherto unknown. Therefore, mechanistically delineating the biochemical and cellular functions of such disease-associated uncharacterized proteins remains an exciting challenge in the field of chemical biology. The past decade has seen an exponential increase in the development of new chemical tools, which, coupled with various omics techniques and defined genetic analysis, has substantially increased

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the throughput in assigning biological functions to such uncharacterized human proteins. Moving forward, continued efforts on this front will not only expand our understanding of context-dependent protein functions, but will most certainly lead to the development of newer and better therapeutic paradigms for currently untreatable human disorders.

Stefan Knapp:

The past decade has seen the emergence of exciting new targeting opportunities, including selective protein degraders and other bifunctional molecules that have immensely expanded our ability to interfere with cellular processes and developing new strategies for the discovery of new medicines. However, the vast majority of the human proteome remains unexplored. We now need to implement new technologies, especially machine learning and artificial intelligence, to accelerate the process of developing selective small-molecule modulators for the ever-expanding druggable proteome to take full advantage of these new discoveries.

Yamuna Krishnan:

We are only scratching the surface of biology. Nucleic acids can be molded into high-precision nanoscale architectures, and we can exquisitely control how they interact with, probe and program living systems. However, it remains unclear how nucleic acids translocate from organelle lumens into the cytosol and successfully traverse the blood–brain barrier. Given the success in mediating precise, cell-specific delivery of nucleic acid assemblies in macrophages, an outstanding challenge is how to re-route nucleic acids to other cell types. Another challenge is to target nucleic acids with subcellular precision, either to organelles on the secretory pathway or to specific cytosolic locations such as membrane-less organelles. These long-standing challenges remain to be addressed for nucleic acid nanotechnologies to achieve their full potential.

Kathrin Lang:

Within the past 20 years, the site-specific incorporation of non-canonical amino acids into proteins via genetic code expansion has become a widely used technology for decorating proteins with various functionalities. This expanded alphabet includes building blocks bearing bioorthogonal handles, crosslinker moieties and spectroscopic probes, as well as post-translational modifications (PTMs). Although genetic code expansion technologies have started to have impact on various fields, several challenges remain. I am especially excited to see how innovations in creative chemical probe design as well as advancements in protein and cellular engineering will enable efficient and multiplexed incorporation of diverse non-canonical amino acids mimicking PTMs in living cells. Smart combination of such technologies with advances in proteomic methods may allow system-wide interrogation of site-specific PTMs and high-resolution studies and control of signaling pathways. Our field's interdisciplinary culture, promoting collaboration between tool developers and users, will help overcome current challenges, deepen biological insights, and drive discovery beyond proof-of-concept studies.

Luca Laraia:

Significant advances in our understanding of how cells maintain lipid homeostasis have been made in the past decades. However, our ability to manipulate local lipid pools in specific cellular compartments remains challenging. Addressing this will require advances in chemical and genetic tools to inhibit, or more demandingly promote, the biosynthesis and trafficking of a given lipid, in a site-specific way. This will also have to be coupled with advances in tracking the fate of cellular lipids and exploring their interactome, in which improved imaging and analytical chemistry approaches are continuously being developed. Together, these tools will help us address diseases that have misregulation of lipid homeostasis at their core.

Reuben B. Leveson-Gower:

More classes of enzymatic transformations are possible than ever before and applications of enzymes in industry are increasingly providing economic and environmental value. Now we are even seeing examples of designed reaction pathways that are only accessible via an enzyme. Nevertheless, many gaps still exist in the biocatalytic repertoire. These missing puzzle pieces will only be found through effective cooperation between academia and industry to provide equal parts of daring and pragmatism. Protein structure prediction has already become a routine part of enzyme discovery and analysis workflows, and protein design can help improve poorly performing enzymes. Extensive and expensive directed evolution campaigns remain a hurdle for the widespread application of biocatalysis, but here machine learning is already making contributions. Enzymologists are probably not worried that machine learning will replace them, but major breakthroughs will likely result from a synergy between artificial intelligence and experts.

Xiang David Li:

My research focuses on developing chemical tools and approaches to address key questions in epigenetics. Epigenetic research is a complex and intricate field that primarily focuses on understanding how chromatin modifications such as DNA methylation and various histone modifications are established, maintained and modified in response to environmental cues, and how these modifications control gene expression and contribute to normal development, disease and aging. Although we have made substantial progress in understanding individual modifications, the interactions and crosstalk among various modifications are not fully understood. Even a comprehensive 'high-resolution map' illustrating the distribution of diverse epigenetic modifications throughout chromatin is still lacking. Therefore, novel techniques are required to profile chromatin modifications and their corresponding binding proteins in the native chromatin context at

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single-nucleosome resolution. Such information will pave the way for further elucidation of complex mechanisms of epigenetic regulation involving interplays between multiple layers of chromatin modifications.

David R. Liu:

There are more exciting opportunities for chemical biology than ever before, but a molecular problem of particular interest is the development of methods to deliver the many promising classes of protein, RNA and DNA therapeutics into any cell or tissue type of interest — potently, selectively and safely. Robust solutions may arise from co-opting natural cell entry mechanisms, from molecular engineering or evolution, and from the use of increasingly capable machine learning models. Breakthroughs toward solving this grand challenge would advance basic science and molecular medicine for the foreseeable future.

Mo-Fang Liu:

The Nobel Prize has twice acknowledged the discovery of small non-coding RNAs (sncRNAs), with microRNAs awarded in 2024 and small interfering RNAs (siRNAs) in 2006, underscoring their crucial roles in living systems. We now know that the small RNA world is vast, also including PIWI-interacting RNAs in animals, phased siRNAs in plants and various others. A key frontier in sncRNA research is its clinical application. In 2018, the US Food and Drug Administration (FDA) approved patisiran (Onpattro), the first siRNA drug for hereditary transthyretin-mediated amyloidosis with polyneuropathy, marking the transition of sncRNA research from theory to therapeutic practice, fostering the development of RNA-based treatments for diverse disorders. However, many challenges remain in transforming natural sncRNAs into effective and safe therapeutics. In particular, chemical modifications to stabilize sncRNAs or allow targeted delivery, as well as approaches to identify novel targets of sncRNAs, are expected to expedite the development of small RNA drugs in the near future.

Nir London:

Covalent binders offer the potential to target traditionally 'undruggable' proteins, such as those with shallow pockets or disordered regions. 'Electrophile-first' approaches for their discovery, including chemoproteomics and direct electrophile library screening, are at the forefront of covalent chemical biology. Two key areas could advance the field further. First, computational modeling of covalent binders needs to improve. Current methods for virtual screening are limited, focusing on static protein structures, whereas covalent binders often reveal cryptic, flexible pockets. Artificial intelligence-based structure prediction may help incorporate flexibility into binder modeling, uncovering new target opportunities. Second, expanding the range of electrophiles beyond cysteine is crucial. Although cysteine targeting remains dominant, discovering novel electrophiles for other amino acids, in a suitable reactivity range, will broaden the target scope and enable new applications in chemical biology and translational research.

Nilkamal Mahanta:

The advent of the genomic revolution and advances in computational tools to predict protein structures and functions have revitalized research on natural product biosynthesis. The investigation of biosynthetic pathways and engineering of enzymatic machinery for combinatorial biosynthesis, chemo-enzymatic synthesis and synthetic biology offers an attractive opportunity to harness the full potential of bioactive natural products. New natural products are being reported from underexplored domains of life such as complex marine environments, mysterious microbial kingdoms and extremophiles, which may lead to the discovery of novel biological activities and potentially new drugs. The modern genomic, bioinformatic and experimental skill sets have now enabled researchers to decode orphan enzymes, unravel hidden genomic spaces, and activate cryptic or silent biosynthetic gene clusters, which may possibly generate new therapeutic compounds. It is indeed exciting to witness total in vitro biosynthesis complementing the challenging chemical synthesis efforts in recreating nature's miracle molecules in the laboratory for pharmaceutical, agricultural or biotechnological applications.

Cristina Mayor-Ruiz:

Compound-induced protein proximity is an exciting and rapidly evolving arena in chemical biology. While prompting degradation by recruiting proteins to ubiquitin ligases has been a major focus, additional outcomes are being actively explored. I am excited about the prospect of novel proximity-inducing pharmacology able to orchestrate increasingly complex cellular rewiring with unique precision. Can we generate new synthetic cellular pathways with drugs that temporarily induce non-native protein complexes? A critical frontier lies in identifying and exploiting weak protein–protein interactions, with applications limited only by our imagination. By means of shape complementarity, these transient (often overlooked) interactions could be key to accelerate the development of chemical inducers of proximity. Integrating advanced computational methods with more sophisticated cellular screenings will be crucial to establish iterative discovery pipelines and deepen our understanding of induced proximity therapeutics.

Tom Muir:

Recent decades have witnessed remarkable progress in our ability to detect protein post-translational modifications (PTMs). Through advances in proteomics, we can now appreciate the staggering number of proteoforms created by PTMs. Although discovering novel PTMs is still an active area, we have reached a point where the next challenge is looming into view, namely what are all these modifications doing? Approaching this question is incredibly daunting, it is as if we have slogged up a mountain only to find that it was merely a foothill

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of the Himalayas. Comparative proteomics and emerging machine learning methods will have a role in prioritizing which PTMs to focus on in a specific context, for example a disease state. However, it will still be necessary to experimentally assign function to these PTMs, something that remains a difficult, bespoke undertaking. Developing methods that accelerate this work represents one of the great opportunities for the field in the coming decade. Although this will test the creativity of chemical biologists and our ability to work productively with investigators from diverse fields, the payoffs will be immense.

Mário Tyago Murakami:

The vast majority of microbial life remains an uncharted territory, with their genomes encoding numerous proteins of unknown function, a realm often referred to as 'microbial dark matter'. The inability to culture most of these microorganisms using traditional laboratory methods presents a significant challenge to microbiology. Understanding their metabolic capabilities is essential for advancing knowledge in microbial ecology, evolution and Earth's biogeochemical cycles. Deciphering the functions of these unknown proteins from uncultured microorganisms holds immense potential for biotechnology, with the possibility of revolutionizing sectors such as agriculture, healthcare, energy and biomanufacturing. By using advanced high-throughput sequencing techniques to recover high-quality genomes directly from environmental samples, alongside integrative chemical biology approaches, we can tap into this unseen microbial world. This endeavor could accelerate the bioeconomy, drive innovation across multiple industries, and contribute to addressing global challenges such as climate change and environmental sustainability.

Hyun-Woo Rhee:

In the past decade, proximity labeling techniques have shown great potential for

uncovering the spatial architectures of living organisms, ranging from atomic to intercellular interactions. In the future, I expect new proximity labeling tools to emerge, significantly enhancing our understanding of spatial biology in various organisms. These tools could also provide us with a good framework to understand spray-type modification events in our bodies. I believe that these potential new insights and spatial information will drive improvements in proximity-based therapies such as PROTACs or chimeric antigen receptor (CAR) T cells.

Matt Robers:

As the mode of action for new drug modalities becomes increasingly nuanced, sophisticated biophysical technologies are required to characterize drug pharmacology in cells and tissues. Traditional drug discovery focuses on isolated proteins, relying on binary drug–target interactions to guide medicinal chemistry. Although this strategy has been productive, it does not fully address the complexity of biomolecular assemblies that govern cellular physiology. Emerging drug modalities, such as protein–protein interaction stabilizers and molecular glues, exploit these higher-order assemblies and survey broader druggable space. In these cases, affinity for monomeric proteins may be modest, with high-affinity states only emerging within ternary or more complex assemblies. To fully realize the therapeutic potential of these interactions, new technologies are required to selectively interrogate biomolecular complexes in their native cellular context. If implemented in pathophysiological settings, these approaches could significantly accelerate the development of next-generation therapeutics.

Alex Satz:

The pharmaceutical industry strives to tackle undruggable intracellular targets and has thus taken to new modalities including oligonucleotides, bifunctional degraders and

macrocyclic peptides. Unfortunately, these molecules are problematic with regards to their optimization, as few guidelines exist for improving the cellular uptake of molecules that reside in chemical space beyond the rule of five. The obvious solution is to synthesize thousands or even millions of analogs, and test everything in a high-throughput cellular assay. But the cost to synthesize such libraries by traditional methods is prohibitively expensive. Alternatively, such libraries can be produced by combinatorial one-bead-one-compound DNA-encoded chemical library synthesis, in which the potential drug molecule can be released from the bead, and its activity in a cellular functional assay monitored. Such libraries have already been produced and successfully screened in biochemical assays. The next step however, robust screens in cellular functional assays, remains to be accomplished.

Brenda A. Schulman:

An exciting frontier in chemical biology is the development of 'degrader' molecules that harness the ubiquitin–proteasome system to elicit proteolysis of disease-causing proteins. Several recent breakthroughs have expanded the breadth of degrader mechanisms and their physiological utility. Examples include allosterically modulating protein structures to expose degrons, prodrugs enabling accessing E3 ligases not traditionally used for targeted protein degradation, and development of molecules crossing the blood–brain barrier. As more sophisticated chemical probes and small molecules are developed, we can gain deeper insights into these systems functioning in real time. However, chemically inducing proximity between previously undruggable targets and optimal E3 ligases remains a challenge. The integration of artificial intelligence with chemical design, structural biology, cell biology, sophisticated mass spectrometry and imaging will be crucial for deciphering the intricate mechanisms in physiologically relevant settings, to guide new

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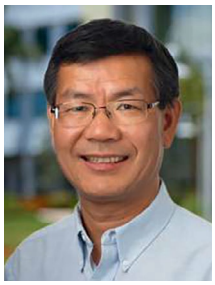
treatments for diseases such as cancer and neurodegenerative disorders.

Ben Shen:



Natural products continue to inspire chemistry, biology and medicine. Progress in DNA sequencing and microbial genomics has fundamentally transformed the current paradigm of their discovery, revealing the vast diversity of biosynthetic gene clusters that far exceed the number of natural products known to date. We are truly on the brink of transforming natural product discovery from the time-honored art of grind-and-find approach to hypothesis-driven science in which the structural complexity and rich functionalities of natural products could be rationally targeted and exploited. To realize this potential, predictive strategies made possible by 'big data' science would be transformative. Artificial intelligence and machine learning-based tools to map the global natural product landscape, predict their structure and function, and unlock the intricacy of biosynthetic gene cluster regulation and expression would set forth a new age of targeted natural product discovery, whereby natural products can be isolated at scale and speed and, most importantly, translated into clinic drugs to impact society.

Brian Shoichet:

Structure-based ligand discovery has matured from a conceit of molecular biophysics to an everyday practice. The advent of make-on-demand libraries has expanded the molecules available to virtual screening by 10^5, into the tens of billions, improving hit rates and affinities. A challenge will be expanding these libraries by further log orders, into the many trillions. Reliable prediction of ligand binding free energies, long a focus, will improve exploitation of these vast new spaces. Integration of structure-based discovery with pharmacokinetics, including permeability, metabolism and free fraction, will increase the biological impact of new ligands. The application of generative methods in artificial intelligence may make de novo ligand design pragmatic, if challenges in affinity prediction and synthesizability can be overcome. The integration of structure-based methods with some of the most exciting frontiers in chemical biology, including protein recruiters, glues and macrocycles, will expand its domain of use.

Erick Strauss:

Antimicrobial resistance is a pressing and growing health threat. The recent application of targeted protein degradation (TPD) as a new strategy for antimicrobial drug discovery is a very exciting development that could spur much needed innovation in the field. As TPD makes use of ligands that interact with a protein of interest (POI) in any manner, and does not require the ligand to show a specific inhibition profile for the POI, the scope for finding potentially useful POI-engaging ligands is greatly increased. However, advancing this methodology to general implementation will require a much better understanding of bacterial protein degradation pathways — specifically how they are regulated and the best strategies by which these regulation mechanisms can be hijacked for TPD.

Tsutomu Suzuki:

One of the most exciting challenges in my field is the discovery of novel RNA modifications from various sources and mapping them using epitranscriptome sequencing. To date, approximately 150 types of RNA modification have been identified across all domains of life, and it is expected that the chemical diversity of RNA modifications will continue to expand in the future. Sequencing RNA modifications has been a significant challenge in our field. The National Academies of Sciences, Engineering, and Medicine (NASEM) recently published a comprehensive study report highlighting the global need for epitranscriptome sequencing. This initiative aims to generate a research movement comparable to the Human Genome Project by involving national projects, industries, the third sector and international collaborations. If RNA modifications can be efficiently explored transcriptome-wide, it is expected that this will significantly advance research into RNA modopathies, human diseases caused by aberrant RNA modifications. Among the various methods developed so far, nanopore-based epitranscriptome sequencing has been progressing rapidly. In the near future, even complex tRNA modifications, which have been particularly challenging to sequence, would be profiled in clinical specimens.

Pratyush Tiwary:

The celebrated progress of artificial intelligence in structural biology has largely been limited to predicting static structures at room temperature, rather than generating the full range of ensembles under varying physiological conditions crucial for both biomedical and basic science. This is where integration with molecular dynamics could help — enabling more accurate sampling of proteins, nucleic acids and other biomolecular systems. However, many systems, especially nucleic acids and disordered systems, suffer from limited training data, meaning that artificial intelligence alone cannot yet fully capture their complex energy landscapes. Here, traditional molecular dynamics and theoretical statistical physics approaches will remain crucial for filling gaps in data and providing actionable insights. The excitement lies in the future: as interdisciplinary efforts in both training and research continue to unite expertise in statistical physics, chemical biology and artificial intelligence, we can anticipate breakthroughs in predicting dynamic conformational landscapes, transforming our understanding of proteins, nucleic acids and other challenging biomolecules.

Herbert Waldmann:

Chemical biology research will become more complicated because biology is becoming more complicated. In order to meet this challenge,

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chemical biology will have to go beyond the established one protein–one reagent or one tool approach and extend to the use of chemical methods for the investigation of entire cell states. This evolution will be empowered by multiple large-scale analysis methods, including novel mass spectrometric techniques on a proteomic scale and multiparametric imaging techniques. As in other areas of science, such development of the field will require ever more powerful computational methods. In addition, a current limitation of chemical biology research is that its chemical basis often is rooted in and relies on chemistry and compound collections developed decades ago. A new phase of applying the current organic synthesis methods to improve compound collections for both chemical biology and medicinal chemistry research will be rewarding and create novel opportunities.

Thomas R. Ward:

Artificial or repurposed enzymes (ArtRepZymes) have attracted increasing attention in the past 20 years to complement the somewhat limited reaction repertoire of natural enzymes. Although directed evolution has been widely applied to improve the performance of ArtRepZymes, their prowess often remains well below that of natural enzymes that emerged from prolonged evolutionary processes. To overcome this limitation, we predict that de novo enzyme design, combined with in vivo continuous evolution at high mutation rates, may produce ArtRepZymes with unrivaled catalytic performance and broad substrate scope. The perspective of endowing any catalytic transformation with an evolvable genetic memory would allow for vastly broadening the synthetic biology portfolio toward producing high added value chemicals.

Amy Weeks:

The ability of proteins to undergo dynamic spatial reorganization is an essential feature

of eukaryotic cell signaling that often goes awry in human disease. To probe this process, chemical biologists have established robust systems to exert spatiotemporal control over protein function using triggers such as exogenous small molecules and light. Exciting recent developments can program protein localization based on endogenous cues that lead to the installation of post-translational modifications on specific proteins. To push this exciting frontier, we need to develop new chemical biology tools to dissect how post-translational modifications impact protein localization in response to biological signals on a proteome scale, an effort that will require innovation in mass spectrometry and chemoproteomic approaches. Deciphering this code will enable the design of synthetic biology and synthetic chemistry approaches for precision control of protein function that will advance biological discovery and open new avenues for drug discovery.

Eranthie Weerapana:

The functions of cellular proteins are intricately regulated by post-translational modifications, protein–protein interactions and endogenous inhibitors. These mechanisms are vital for maintaining cellular homeostasis, and disrupted protein regulation is often a defining feature of many pathologies. A detailed mechanistic understanding of these regulatory pathways can help to identify protein targets and ligandable sites for therapeutic development. Recent advances in chemical probes and chemoproteomic pipelines have significantly enhanced our ability to map key functional sites on proteins. Continued innovation in technologies that enrich and precisely identify protein regions involved in post-translational regulation, allosteric modulation and protein interaction interfaces will open new avenues for targeting dysregulated cellular processes in disease.

Georg Winter:

In the field of targeted protein degradation, it is fascinating to witness the breadth of mechanisms of how molecular glue degraders can co-opt proteolytic circuits. I expect that deep mutational scanning will increasingly be leveraged to systematically probe the topology of target proteins and E3 ligases to identify 'glueable' hotspots. Sparked by these mechanistic insights and further empowered by protein interface predictions, I envision that generative artificial intelligence approaches will increasingly be leveraged for rational degrader design. Moreover, I anticipate these insights and experimental strategies to cross-fertilize other modalities that rely on proximity induction, including approaches dependent on steric disruption, targeted (de-)phosphorylation or drug-induced changes in protein localization. Finally, I anticipate that direct chemical rewiring of transcription regulation will have the biggest therapeutic impact from the variety of emerging proximity inducing modalities.

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