frontiers | Frontiers in Chemical Biology

TYPE Field Grand Challenge
PUBLISHED 15 December 2022
DOI 10.3389/fchbi.2022.1108654

OPEN ACCESS

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RECEIVED 26 November 2022
ACCEPTED 06 December 2022
PUBLISHED 15 December 2022

CITATION
Crans DC (2022), Grand challenges in chemical biology: Past, present and future.
Front. Chem. Biol 1:1108654.
doi: 10.3389/fchbi.2022.1108654

Grand challenges in chemical biology: Past, present and future

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KEYWORDS

chemical biology, biological problem, grand challenge, chemistry, interdiscipinary studies

What is chemical biology?

Chemical Biology is an interdisciplinary field that is limited only by the imagination of its practitioners. For chemists, Chemical Biology provides a field to explore new chemistry with biological relevance. For biologists, Chemical Biology provides a field in which to consider how chemical principles can be applied to fundamental biological questions. The value of such studies has become apparent with the onset of the worldwide spread of COVID SARS-CoV-2. This pandemic forced scientists to consider regulatory processes involved in infection and to develop novel chemistry for the preparation of vaccines and treatments that modulated those processes. Moreover, COVID has taught us that the chemistry of biology systems, as a function of mutations and evolution, is constantly changing to create biological organisms displaying improved survival and adaption mechanisms. The journal *Frontiers in Chemical Biology*, by placing chemistry on center stage, will emphasize the development of new innovative approaches to the study of biological problems at the intersection of chemistry and biology and resulting advances in biology, medicine and the life sciences.

Innovations in chemical biology recognized by Nobel prizes

Chemical biologists have skills that are interdisciplinary in nature. While their work may lie within areas traditionally associated with biology or biological systems, the contribution of chemistry to problems are transformative. This is illustrated by the many contributions of life scientists that have led to Nobel Prizes in Chemistry some of which are illustrated here. The Nobel prize in 1980 was awarded to Walter Gilbert and Frederick Sanger for methods to sequence bases in nucleic acids and to Paul Berg for his work on the chemistry of nucleic methods. This was followed by the 1993 Nobel Prize for development of methods within DNA-based chemistry to Kary Mullis for his invention of the polymerase chain reaction (PCR) and Michael Smith for his fundamental contribution to the establishment of oligonucleotide–based, site-directed mutagenesis and its development for protein studies. Venkatraman Ramakrishnan, Tom Steitz and Ada Yonath developed chemical approaches to crystal formation to solve the structure of the ribosome and its function (Nobel Prize 2009). Robert Lefkowitz and Brian Kobilka elucidated the structure of the beta-adrenergic receptor, a G protein-coupled receptor, by

stabilizing a structure sufficiently for crystallization. Their work also provided insight into how G protein-coupled receptors function (Nobel Prize 2012). In 2018 the Nobel prize was awarded to Frances H. Arnold for demonstrating the directed evolution of enzymes (Joo et al., 1999) and George P. Smith and Sir Gregory P. Winter for the phage display of peptides and antibodies. The 2021 Nobel prize was given to Emmanuelle Charpentier and Jennifer Doudna that used CRISPR for gene editing which represent an example of an innovative and impactful application of chemistry to alter biological function. The 2022 Nobel Prize for the development of Click chemistry discovered independently by Morten Meldal and Barry Sharpless and bioorthogonal chemistry developed by Carolyn Bertozzi. These reactions have expanded the toolbox used to describe chemical reactivity in cells as well as reactions not previously identified in nature. The Frontiers publishing structure provides an opportunity for chemical biologists to publish their research in an Open Access journal using a uniquely constructed peer review process (Suib 2014) that addresses the importance of novel chemistry in studies at the chemistry/biology interface.

Innovations in chemical biology illustrated by the application of recent technical advances

Synthetic chemistry remains an important pillar of chemical biology whether the goal is to make new molecules or to develop new organic or inorganic syntheses or both. Chemists will continue to develop both simple and sophisticated methods to overcome the natural reactivities and selectivities of chemistry. This can be accomplished by expanding the repertoire of available chemical methods such as "umpolung" or "enzymatic" or "cellular" synthesis regardless of whether the target is organic, inorganic, chiral or achiral. Within natural product chemistry the goal can be the identification of newly discovered small molecules, preparation of naturally existing mineralized materials of organisms that forms shells or huge monsters of molecules such as the toxin palitoxin or the therapeutic paclitaxel. Palitoxin is a polyhydroxylated and partially unsaturated natural product with a long carbon chain. Its unique properties include lipid-soluble and water-soluble parts. The naturally occurring molecule has 64 chiral centers and 8 double bonds and hence has over 10^{21} stereoisomers. This complex molecule has been synthesized *via* a "bottom up" synthesis, a monumental task that demonstrates the level of sophistication achieved by organic synthetic chemists led by Yoshito Kishi and coworkers (Uenishi et al., 1987).

Natural products have been explored for their unique- and beneficial-properties and have now become therapeutic agents in medicine. This is illustrated by paclitaxel, available under the brand name Taxol, which is a well-known natural-product used for treatment of cancer. It was initially isolated from the bark of the Pacific yew tree (*Taxus brevifolia*) grown in the Amazon forest. Harvesting of the bark killed the yew tree making the yew an unsustainable source of paclitaxel. Semisynthetic approaches developed by Pierre Potier and Robert A. Holton as well as plant cell fermentation technology made commercial synthesis practical. This was not a trivial undertaking. The molecule consists of a tetracyclic 17-atom skeleton with eleven stereocenters. The mode of action and detailed bioorganic chemistry has been investigated by Wender (Wender et al., 2012) and many others, leading to the detailed understanding of this compound and its cellular interactions.

In addition to naturally occurring compounds like paclitaxel, man-made compounds such as Cisplatin have made dramatic improvements in cancer treatment. Cisplatin is synthetic inorganic compound which Barnett Rosenberg showed to have a profound effect on cell development. Cisplatin together with its simple inorganic coordination compounds such as oxaliplatin are among the most highly used anticancer compounds more than 40 years after cisplatin's discovery. Medicine has benefited from the several generations of pharmaceutically useful Pt-based anticancer compounds as well as an understanding of the structures of cisplatin-DNA intermediates, its mode of interaction with DNA and interactions in cellular systems (Johnstone et al., 2016). More recently new formulations of cisplatin and oxaliplatin have been submitted to clinical trials. These new preparations improve the action of these drugs and/or decrease their toxicity. Hence these drugs continue to be useful for treatment of cancer patients.

Combinatorial methods have been developed to enhance product development in large areas of chemical space. These methods quickly expand the discovery of one compound to the identification of thousands of different compounds. Assays of single compounds have been adapted to permit work with libraries of compounds through new synthetic and analytical techniques that accommodate combinatorial approaches. In addition, investigators have made use of robots to enhance data testing throughput. Together, combinatorial approaches have improved productivity and method development.

Comprehensive analysis of the structure, function, evolution, mapping, and editing of biological systems can be done by "omics" methods, referring to methods that typically use advanced high-throughput analytical approaches designed to handle complex mixtures of cell-derived biomolecules. Omics methods provide quantitative and qualitative information about a biological system, whether it is a cell or an organism and include several fields in analytical chemistry based on separation techniques including chromatographic methods as well as methods of detection of large numbers of compounds. This often involves various highly sensitive, and often quantitative mass spectroscopic methods, applied in various areas of life-sciences, such as genomics, proteomics, transcriptomics, metabolomics, lipidomics and metallomics. The development

and application of omic approaches has not only provided a vehicle to identify areas of chemical space specific to a particular biological system, but to provide enormous amounts of data characterizing the biological system (Scalese et al., 2022) and reinforcing the need for new methods to manage large data sets.

Many examples of the diverse nature of Chemical Biology can be drawn from studies of complex biomolecules such as large protein complexes, nucleic acids, and lipid structures and the construction of networks of interconnected metabolic processes. An example representing the amazing selectivity and power of biological conversions is the reaction catalyzed by squalene epoxidase, one of the first enzymes in the cholesterol biosynthesis. Squalene ($C_{30}H_{50}$) is a triterpene and the main component of skin surface polyunsaturated lipids. Squalene is oxidized by squalene epoxidase to 2,3-oxidosqualene (squalene epoxide) through a reaction that forms only one of 256 (2^8) possible stereoisomers. This remarkable reaction, either enzyme catalyzed or free in solution, is consistent with squalene epoxide adopting a pre-organized conformation prior to cyclization. Its preference for a single conformation affects both the molecule's properties and its reactivity (Woodward and Bloch, 1953). This example illustrates how some naturally occurring reactions can be understood by the chemical and physical properties of the compounds involved.

Developments exploring the genetic code have led to emerging strategies of genetic code reprogramming and expansion of the genetic code from a limited number of naturally occurring amino acids to the synthesis of proteins incorporating unnatural amino acids. The ability to genetically encode an expanded set of building blocks with new chemical and physical properties is transforming protein research and enabling novel approaches to probe, image, and control protein function. Furthermore, the site-specific incorporation of unnatural amino acids into proteins is no longer limited to isolated cells or unicellular organisms but has been expanded to include multicellular animals, such as the nematode *Caenorhabditis elegans*. Jason W. Chin and coworkers has "synthesized" an *E. coli* in which the 64-codons used to produce new proteins in cells has been replaced by a 61-codon genome in this new *E. Coli*. This involved recoding 18,214 codons to produce an organism that uses 59 codons to encode 20 amino acids and enabled the deletion of a previously essential transfer RNA (Fredens et al., 2019).

The development of the vaccines against SARS-19 is one of the recent scientific victories and an example of application of the principles central to Chemical Biology. Scientific advances and collaborations across the globe and political boundaries document the concentrated effort and ability of scientists to solve a shared scientific problem. Vaccines were developed in record time. This required complex steps beginning with conception of a viable methodological approach, the need to overcome social and legal hurdles and finally large-scale production and distribution methods to make the vaccine available to the public. It is estimated that more than 30,000 individuals were needed to move through these steps. The campaign to put shots in the arms of the general public is and will remain a testament to the human effort addressing a single biological problem for many years to come.

Who studies chemical biology?

The practitioners of Chemical Biology are life scientists who embrace interdisciplinary research and techniques. They are not limited by the constraints of a target biological system but seek to expand and overcome those limitations by exploring new and diverse territories within science. Chemical Biologists embrace complex systems and seek to develop new experimental methods that range from complex spectroscopies to study single cells at the nanoscale to large systems that require manipulation of big data and various -omic approaches. The Chemical Biologist will have a background in one of the core areas of chemistry and use that background to approach problems that also require non-trivial chemical, mathematical, computational, or engineering tools to address important scientific and societal questions.

The future of chemical biology

The quest for new science and solutions to current problems is often limited by the nature of current and known materials. The chemical biologist will therefore seek to develop new materials with new properties whether these be of a synthetic, semi-synthetic or biologic nature, and based on small or large molecules. Indeed, materials could span the chemical space of organic, inorganic, biological or polymeric types of molecular units and have properties that are smart and able to carry out self-selection of a particular function. New areas within material science include not only synthetic materials but materials based on biologics that are exploring new chemical space such as, for example, RNA Origami and DNA Origami, where investigators have made materials with specific properties on both the micro- and nano-scales. Indeed, such advances include preparation of analytical tools of minute sizes but able to carry out complex functions such as "laboratory on a chip", some of which are further amenable to using materials that will be possible to take in the field for inexpensive and rapid measurements. This quest for seeking to make and develop new materials will continue and will provide solutions to problems that have not yet been identified, promote an understanding of difficult biological systems, and solve long standing problems and controversies in science.

The quest for development of new quantitative methods for detection will similarly evolve as new materials and new spectroscopic and microscopic methods become available. This include areas in analytical chemistry ranging from simple quantitative measurements with newly developed and

synthesized fluorophores or chromophores, to simple and complex sensors ranging from single cell spectroscopy and imaging. Recently theranostics, a new field where diagnostic methods are directly combined with therapeutic compounds, has emerged. Theranostics makes possible both the identification of biomarkers and, at the same time, the treatment of targeted diseases.

Undoubtedly continued advances at the interface of chemistry and other areas in the life sciences will continue to lead to development of new disciplines. It is not unreasonable to expect that innovative developments in chemical biology together with nanoscience and artificial intelligence will produce advances that benefit mankind.

Summary

In summary, the area of Chemical Biology embraces both innovative man-made and natural systems with a biological foundation. The journal *Frontiers in Chemical Biology* will publish contributions on the development and understanding of these systems, thereby contributing to progress in interdisciplinary sciences at interfaces between several areas of life sciences. The journal will highlight studies where advances in chemistry provides innovative solutions to biological problems. *Frontiers in Chemical Biology* will do this through an open option publishing platform and a unique peer reviewing system (Suib 2014) that guarantees constructive and productive efforts to move forward scientific knowledge at the interface of chemistry and biology.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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