Q&A

Voices of chemical biology

We asked a collection of chemical biologists: "What would you say have been the most important historical contributions of chemical biology to broader areas of science"?

In the past decade, chemical biology significantly affected drug discovery. Chemical biology has unquestionably offered small molecules and tools that can be used to identify novel targets with exciting therapeutic potential. By using combinations of a new wave of chemically modified biologics, chemical biologists have opportunities to produce new classes of 'chemically tractable' targets and novel types of therapeutic scaffolds. In addition, chemical biology has provided new technologies and tools for drug discovery, including visualization, drug delivery and diagnostics approaches.

Hualiang Jiang
Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, China

At the most fundamental level, chemical biology has enabled key insights into the structure and function of numerous biomolecules (nucleic acids, peptides, proteins, metabolites, carbohydrates, etc.) by providing synthetic access to defined structures for biological studies. More broadly, chemical biologists have invented ways to recapitulate, modify and re-engineer molecules and biological systems to learn about their properties in ways that scientists from other fields cannot.

Linda C Hsieh-Wilson
California Institute of Technology, Pasadena, California, USA

The discovery of phytohormones—small molecules that regulate plant growth and development in response to environment cues—and the recent elucidation of their modes of action have contributed new, fundamental insights in plant biology. When used in the agricultural setting, these chemicals have shaped modern food production and have influenced the population growth trends we have seen in the last century.

Paulo Arruda
UNICAMP, Campinas, Brazil

It would be hard to overstate the impact of chemical biology on the history of neuroscience. Many of the most important neuronal macromolecules were discovered and characterized as the targets of small molecules. The mu opioid receptor was discovered as the target of naloxone in the 1970s, and the cannabinoid receptors were discovered as the target of synthetic cannabinoids in the 1990s. And the list goes on—various opioid receptors, AMPA receptors, kainate receptors and NMDA receptors were all discovered using small-molecule probes.

Randall T Peterson
Massachusetts General Hospital, Charlestown, Massachusetts, USA

Historically, I think that the sequencing and synthesis of DNA can be considered as enormous advances that together have changed the face of modern biology and would not have been possible without chemical biology—we often think of chemical biology as a 'newer' field, but to me these advances are quintessential chemical biology! Many other advances come to mind from the physical chemistry domain, including huge opportunities for studying the structures and dynamics of biomolecules in order to understand the logic of complex molecular structures and function.

Barbara Imperiali
Massachusetts Institute of Technology, Cambridge, Massachusetts, USA

Historically, I think that the 'bump-hole' concept is one of the most important contributions of chemical biology. While all small molecules have off-target effects in cells—thus complicating the interpretation of 'chemical genetics' experiments—the bump-hole idea allowed the development of systems in which only a single engineered enzyme is affected by a small molecule. A lot of biology has been elucidated in this way.

Thomas Kodadek
The Scripps Research Institute, Jupiter, Florida, USA

The traditional thinking was and often still is, especially in pharmaceutical research, that what small molecules mostly do is to inhibit the activity of enzymes. What I found extremely fascinating and paradigm shifting was the new idea that small molecules can promote and stabilize the interaction between proteins, resulting in new biological functions.

Erich E Wanker
Max Delbrück Center for Molecular Medicine, Berlin, Germany

Bioorthogonal chemistries have impacted diverse areas of molecular, cell and organismal biology. These transformations proceed selectively in living systems and other complex environments, and thus they have been used extensively used to probe biomolecule structure and function, inventory enzymatic activities and even visualize drug targets in live organisms. New and creative applications—spanning multiple disciplines—will continue to emerge as the chemistries improve and grow in number.

Jennifer A Prescher
University of California, Irvine, Irvine, California, USA

One important contribution of the field that is not well appreciated by the general science community is that the phenotypic consequences of modulating proteins are different for genetic and pharmacological interventions. Thus, while genetic methods are extremely powerful, they are ultimately complementary to pharmacological methods for understanding protein function and therapeutic utility.

Brent R Stockwell
Columbia University, New York, New York, USA

The development and application of fluorescent calcium indicators, using first small molecules and then fluorescent proteins, has had monumental impacts in cell biology and neuroscience and demonstrates two important aspects of the field. First, thinking about how local changes in concentrations of small molecules can regulate signaling is fundamentally a chemistry question. Secondly, synthesizing small molecules and engineering proteins to measure or perturb biological systems are two of the common techniques deployed by chemical biologists today to address biological problems.

Bryan C Dickinson
University of Chicago, Chicago, Illinois, USA

Much of our mechanistic knowledge behind cellular processes has been gained by recreating a system *in vitro* or by engineering a cell or a model organism such as yeast, nematodes or mice. One may argue that probing a hypothesis in a model system may, in numerous instances, lead to an understanding that serves the model but has little to do with the real human disease. Having the chemical toolset to probe and validate such models in their real settings is, in my opinion, a historical contribution of chemical biology to biological and biomedical sciences.

Gabriela Chiosis
Memorial Sloan Kettering Cancer Center, New York, New York, USA

Chemical biology has contributed many important advances in our ability to measure and perturb biological functions. One of the earliest contributions from the field (and a still vibrant one) is the 'chemical inducer of dimerization' (CID) systems. Over the last 20 years, there have been thousands of manuscripts published using this general chemical approach to controlling protein localization. In addition to the staggering amount of new biology uncovered across nearly every discipline, this area of study has also attracted clever individuals who have continued to adapt, refine and advance the original concept.

Jason E Gestwicki
University of California, San Francisco, San Francisco, California, USA

Chemical biology has provided useful small-molecule tools for probing basic biological processes. In parallel, one major development is that researchers can now purchase almost any interesting small molecule, even those under development as drugs. This has permitted many biology labs to access key small-molecule tools without the need for in-house synthesis. It's likely that many factors drove this trend, but it's clear that chemical biology has had an important role in making well-validated small-molecule tools more widely available for the broader scientific community.

Timothy J Mitchison
Harvard Medical School, Boston, Massachusetts, USA

Academic research in chemical biology often identifies new small molecules that can serve as starting points for drug development, and this development can really only be done by partnering with industry. Thus, chemical biology as a field serves as a bridge between academia and industry and enables research funding that supports academic research to 'go further' if the small-molecule leads are picked up by industry. This synergy between academic chemical biology and industry has the potential to increase public support for academic research in general.

Rebecca A Butcher
University of Florida, Gainesville, Florida, USA

Although dating from before the existence of the term 'chemical biology', the most important historical contributions of chemical biology may be the discoveries of low-molecular-weight organic compounds that have biological activities, such as hormones, pheromones and antibiotics. These compounds have served as natural bioprobes to unravel complex mechanisms in living cells and organisms as well as to provide insights into stereospecific recognition.

Yasuo Ohnishi
University of Tokyo, Tokyo, Japan

What are the most important historical contributions of chemical biology?

Two scientific areas where chemical biology has had an impact include the discovery of how siRNAs and other small RNAs regulate gene expression, which has provided crucial insight into epigenetics. Also, the discovery of how small molecules may reprogram the fate of stem cells is of historic importance and a milestone in the larger endeavor of controlling stem cell decision-making and applying these insights to therapy.

Lene B Oddershede
Niels Bohr Institute, Copenhagen, Denmark

Chemical biology has been central to the scientific basis for innovative drug discovery and for understanding human nutrition. It is clear that any basic insight does advance science in general, and this is often sufficient general motivation for scientific endeavors. However, there is also a fully justified societal pull (in addition to a scientific push), and chemical biology has the inherent ability (and therefore the requirement) to contribute to the betterment of human life, in particular by inspiring and fueling the development of novel, better medicines and improving human nutrition.

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

Chemical biology, especially through chemical genetics and optogenetics, has provided tools that permit biologists to probe live cellular circuitry with a degree of specificity that was simply unattainable less than a decade ago. For example, approaches such as 'designer receptors exclusively activated by designer drugs' (DREADDs) for GPCRs and 'pharmacologically selective actuator molecules' (PSAM/PSEM) for ligand-gated ion channels have paired chemistry and protein engineering to yield tools with orthogonal pharmacological selectivity and wide applicability. More broadly, the rise of chemical biology exemplifies the way science should be heading, in that the traditional silos associated with reductionist approaches or hard-core discipline-specific academic departments are naturally giving way to more nimble multidisciplinary research.

Arthur Christopoulos
Monash University, Parkville, Australia

The most important historical contributions of chemical biology have been in DNA sequencing and chemical DNA synthesis resulting in elucidation of the genetic code. Many contributions have been made to modern molecular medicine as part of medicinal chemistry, including the semisynthesis of penicillins and cephalosporins. More recently, research on biopharmaceuticals, such as erythropoietin and insulin, and in vaccine development have demonstrated the field's important contributions to biotechnology.

Sabine Flitsch
The University of Manchester, Manchester, UK

An early illustration of the power of chemical biology was the identification of the mammalian target of rapamycin (mTOR). This work demonstrated the role that chemical approaches could play in target identification and validation, but it also identified rapamycin, along with related synthetic analogs, as a small-molecule probe for exploring molecular aspects of the mTOR signaling pathway and as a research tool.

Seung Bum Park
Seoul National University, Seoul, Korea

Two biomedical examples that jump out in my mind include the discovery of penicillin and related antibiotics that launched the modern use of small-molecule therapeutics, and modern medical imaging, where unique features of elements across the periodic table have enabled noninvasive detection of injury and progression of disease through radioactivity, as with [^{18}F] deoxyfluoroglucose for imaging cancer and neurodegeneration and ^{99m}Tc-Cardiolite for scanning heart function, or spin, as with f^7 Gd^{III}-Magnevist for assessing injury and tumor growth.

Christopher J Chang
University of California, Berkeley and HHMI, Berkeley, California, USA