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Training future chemical biologists

Chemical biology is not a new concept. For nearly two centuries, innovations in chemistry and biology have been intimately connected. In 1828, for example, Frederick Wöhler ushered in the field of chemical biology through his pioneering synthesis of urea "without the use of kidneys [from] either man or dog" (*1*). We celebrate the Wöhler synthesis of urea as the first total synthesis of a natural product and as the first demonstration that chemical principles govern living organisms. This observation nailed the coffin shut on the theory that living organisms require a "vital force". Although Wöhler perhaps did not call himself a chemical biologist, his goal would be familiar to today's chemical biologists—immediate biological insight through chemistry.

In the current era of chemical biology, a large variety of powerful tools are available to explore the chemistry–biology interface—a unique and exciting opportunity. For the first time in history, we have a complete map of the human genome. Furthermore, from this vast information source, we can pluck out a single gene for detailed study using the polymerase chain reaction. Drawing on more than 50 years of modern synthetic chemistry, we can synthesize almost any organic molecule imaginable. With techniques as robust as these available at every bench in almost every laboratory, we are quite possibly living in the golden age of chemical biology, with abundant tools and seemingly endless possibilities for exploring biology (see Table 1).

Cross-talk between chemistry and biology pushes the frontiers of both fields. The recent completion of the human genome sequencing project, arguably the most important event in two centuries of biology, could only have occurred with help from tour-de-force chemistry, including oligonucleotide synthesis (e.g., >99% yields for phosphoramidite coupling reactions!) and capillary electrophoresis. In the field of chemistry, the need for small-molecule probes of protein function in living cells has instigated a different approach to organic synthesis with the goal of generating diverse products (*8*). The next generation of chemical biologists, now entering graduate school, inherits this legacy of achievement and is challenged to put it to good use.

Are you a chemical biologist?

The answer is "Yes!" if your research applies chemical techniques and leads to immediate insight into how living organisms work. This definition is purposefully inclusive, because many different methods offer uniquely powerful tools for dissecting molecular mechanisms in biology.

UCI's chemical biology program

Here, at the University of California, Irvine (UCI), we have initiated a program to train a new breed of chemical biologists to develop techniques that can be used to tackle problems traditionally found in departments widely dispersed across a university. Accordingly, we have recruited students with diverse undergraduate backgrounds—from genetics to pharmaceutical chemistry. Despite their varied undergraduate research experiences, students in our program are united by a passion to study living organisms by applying chemical tools and tactics from organic, physical, or inorganic chemistry. This year (2001–2002), nine students are charter enrollees in the program, which will lead to a Ph.D. in chemistry.

Table 1

Chemical biology tackles all characteristics of living organisms

Characteric of life	Example of the chemical basis	Chemical biology example from the recent literature
Motility	Hydrolysis of ATP to power motor proteins	Kinesin inhibitors (2)
Heredity	DNA	Small-molecule transcription factors (3)
Metabolism	Citric acid cycle	In vitro models of metabolism (4)
Growth	Biopolymerization	Artificial polyketide synthases (5)
Death	Apoptosis pathways	Mechanism-based antitumor drugs (6)
Sensing the environment	Receptors	Molecular recognition by protein mimetics (7)

Students enter the program during the summer to begin coursework and rotations. Two courses are offered in the summer quarter—Advanced Organic Chemistry and Chemical Biology. These courses are designed to prepare students from varied backgrounds for the challenging graduate coursework they will encounter in the fall.

Students immediately begin the first of three 7-week rotations in laboratories of their choice to explore atomic force microscopy imaging, phage display, organic synthesis of protein mimetics, or other state-of-the-art topics in chemical biology. Rotations are not usually required in chemistry Ph.D. programs, but the multidisciplinary nature of chemical biology research makes them attractive. Ideally, students will gain exposure to a broad range of methods and scientific approaches during their seven-week rotations. Realistically, we expect students to run a few experiments, learn a few procedures, and most importantly make valuable contacts in other laboratories on campus. Later in their graduate careers and beyond, when students encounter new experiments requiring unfamiliar practices, they will know resources are available to help guide them.

Coursework continues in the fall and mixes conventional graduate-level chemistry courses with cutting-edge instruction in bioorganic chemistry and chemical biology. Thorough, expert-level knowledge is an essential requirement for any Ph.D. program, so we have preserved the requirement to complete three traditional "core" courses in organic, physical, or inorganic chemistry. For their electives, students are encouraged to take courses outside the Department of Chemistry; graduate-level molecular biology, for example, is a natural fit for a well-rounded chemical biology education. Two graduate-level courses in bioorganic chemistry and chemical biology cover advanced topics from the current literature. Our goal is to equip students with a deep understanding of the important problems in chemical biology and enough practical knowledge to devise original experiments. At least three original research proposals in chemical biology are required, and students receive extensive mentoring on developing scientific creativity.

Social interactions

Fostering a collegial environment at all levels of education is critical to a successful multidisciplinary research environment. We host weekly events for faculty and students to meet informally over refreshments. Our Friday Chemical Biology Social Club is modeled on similar programs at biotechnology companies, whose future innovations also depend on cross-pollination of ideas between disciplines. A large blackboard is strategically located on a nearby wall, and enthusiastic conversations often progress to chemical jam sessions with chemical structures and biological pathways thrown onto the board. We invite faculty and students from related departments to join us at these events to foster informal interactions with students from chemical biology.

Although our chemical biology program has welcomed its first entrants only this year, we expect graduates to earn the same enthusiasm for their talents and potential that other chemistry Ph.D. graduates from UCI enjoy. With specialization in core chemical principles and diverse knowledge that cuts across multiple fields, these graduates will be outstanding scientists at biotechnology, pharmaceutical, and medical device companies. We are developing a program for companies to visit UCI to interview graduates from the chemical biology program, and we welcome inquiries from future industrial partners. Numerous assistant professorships are available at the chemistry–biology interface for students pursuing careers in academia, with well over 100 academic openings nationally advertised last year alone.

The horizons opened for chemical research in the post-genomic era are comparable in magnitude to those available to physicists in the first half of the 20th century. However, the boundless opportunities in chemical biology are tempered by the challenges of educating students to think broadly and to master the wide range of techniques necessary for successful chemical biology research. Like the field itself, our program at UCI is not revolutionary, but evolutionary. It leverages current developments in the science to maximize the scientific potential of the next generation of chemical biologists.

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