ACS chemical biology

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Chemical Biology at Berkeley

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Image courtesy of Michael Barnes, UC Berkeley

CBGP graduate student Stavroula Hatzios (left) working with undergraduate Zsofia Botyanski

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Chemical Biology has transformed the curriculum and student composition of the Department of Chemistry at the University of California, Berkeley (UC Berkeley). The rapid growth in this area has been fueled by the steadily increasing number of young scientists who seek to apply chemical reasoning, synthetic techniques, and quantitative analysis to the study of biomolecules and the cellular contexts in which they reside. To a significant extent, these interests have been inspired by the growth of the biotechnology industry, and over the years several members of Berkeley's Chemistry Advisory Board have suggested that individuals with both chemical and biological experience will be in increasing demand. As further evidence for this need, many Bay Area companies have been providing generous financial backing to support these interdisciplinary training efforts in our department. Equally important has been the growth of chemical biology research throughout the academic community, which has offered an expanded set of opportunities for advanced study and future academic employment for students who emerge with this type of pedigree.

As the popularity of this scientific area grew, however, it quickly became clear that new programs would be needed to train students broadly in chemistry and biology without compromising scientific rigor. To answer this call, UC Berkeley has integrated new training opportunities and instructional approaches into both the graduate and undergraduate chemistry curricula. What has emerged is a vibrant chemical biology community that has invigorated the Berkeley Chemistry Program and initiated numerous collaborations among a diverse set of research groups.

The Berkeley Chemical Biology Graduate Program. This effort began with the development of a Chemical Biology Graduate Program (CBGP), which was designed to expand the set of research opportunities that are available for students with these interdisciplinary interests. The participants are selected from the graduate admissions pools of four departments: molecular and cell biology (MCB); chemistry; chemical engineering; and bioengineering. At this time the current students are from MCB and chemistry. The CBGP does not offer a degree in chemical biology but is designed to enhance the program of the student's home department. Students from MCB, for example, meet both the requirements of CBGP and of MCB. Students in chemistry who join the CBGP still take their Ph.D. qualifying exams in the same way as other chemistry students.

A key aspect of this program has been the incorporation of research rotations for all participants. Through a series of three 10-week rotations, the CBGP students gain hands-on experience that can solidify their ideas about the type of research that is personally the most rewarding. The students are strongly encouraged to explore a broad set of options before ultimately selecting a thesis laboratory for the remainder of their stay at Berkeley. As a result of this opportunity, many students have selected a laboratory that they might not have even considered under other circumstances.

In 2001, a pilot rotation program began for three students in the Chemistry Graduate Program. The department covered a sig-

nificant portion of the student stipends and administrative costs during this time, but help from an anonymous private donor was crucial. With this support, the program was able to grow over the next few years to its present level of 10–12 students per class. In 2004, a training grant was obtained from the National Institutes of Health to cover a significant portion of the costs, although a number of biotech companies continue to provide essential financial support for the program. At present, >38 faculty members in the departments of chemistry, MCB, chemical engineering, and bioengineering participate in the CBGP.

It is worth noting that the format of the CBGP, which bridges so many departments, needed to accommodate different scientific cultures from its beginning. For example, the concept of laboratory rotations, while generally the rule in most biologically focused departments, is quite foreign to most chemistry departments. This requires more flexibility when it comes to accepting graduate students into the groups, as some join through the regular program in the fall and the CBGP students officially join in the spring. This complication is more than compensated for, however, by the cross-fertilization that has occurred between the research programs of the participating groups. The 10-week rotations expose the incoming CBGP students to a wide array of experimental approaches, from cell culture to structural biology, single-molecule biophysics, and chemical synthesis. This often accelerates the progress they make after they have selected their thesis laboratory, and thus they do not start appreciably "behind" the students in the regular program. In addition, the rotations provide an excellent means to learn what other graduate students on campus are doing, and to find resources that could come in handy later in their Ph.D. research. Many of the CBGP students also keep in touch with the faculty in whose laboratories they have rotated, providing a great source of collaboration and scientific discussion throughout their Ph.D. research.

As an additional way to foster these interactions, the CBGP has several activities that all students share in common. At the end of each rotation cycle, the students present posters detailing the work that they have accomplished. This session is open to all of the participating departments and is well attended by students and faculty alike. It is consistently a highlight of the program, and in addition to the free lunch (always a draw), it provides a great way to talk with students and faculty in different CBGP laboratories, as well as scientists from local industry.

Second, all of the students take one graduate-level chemical biology course together. This requirement ensures that the students share at least one point of reference in common and is designed to present the core set of tools that chemists are applying to the understanding of the biological sciences. The first section of the course examines methods for biomolecule modification, techniques for the *de novo* synthesis of peptides and oligonucleotides, common strategies for protein expression and purification, and the growing list of *in vivo* labeling techniques that have become available. Following this section, basic principles of enzyme function and natural product biosynthesis are discussed with the same level of detailed mechanistic analysis that is used by organic chemists. This portion of the class also provides a convenient opportunity to discuss the mechanism of action for many common pharmaceuticals. The course concludes with discussions on a series of contemporary topics chosen to demonstrate chemical biology in action. Lecture subjects in this portion include diversity-oriented synthesis, biological studies using fluorescence and resonance energy transfer, techniques for drug and gene delivery, and chemical studies of ion channel function. Although it is impossible to cover the full range of topics that the students will encounter, it is hoped that this thorough grounding in the use of chemical techniques will serve them well as they apply it to their own research interests.

Students in the CBGP also participate in two annual events that allow them to meet other chemical biology students in the Bay Area, including those from UC San Francisco, UC Santa Cruz, and Stanford. The Chemical Biology Annual Retreat occurs on a weekend, and the students in the program (not faculty) present their work in a series of talks and posters. It is a great event for networking and learning about the broad range of research taking place in the Bay Area. Beginning last year, a Chemical Biology Career Day was also held, in which scientists in academia, industry, government, and law shared their paths to rewarding careers (see accompanying article).

Where will the Berkeley CBGP graduate students end up after they finish? It is too early to tell for most, as the first six students have just completed their Ph.D. research in the last couple of years. However, it is already clear that they will follow many diverse paths, from clinical medicine to industry and academia, bringing with them a deeper appreciation for the new and exciting research now underway in the burgeoning field of chemical biology.

The Berkeley Undergraduate Chemical Biology Major. As the CBGP was taking root, it was noticed that the undergraduate enrollment in the College of Chemistry had been declining slowly over the years. However, a number of the faculty members had observed that some of the best students on campus were taking our advanced chemistry courses, even though their majors were in other disciplines. It was suggested that a new hybrid major could recapture these students by augmenting our chemical training curriculum with a significantly stronger background in the biological sciences.

This idea met with immediate enthusiasm among many of the Berkeley chemistry faculty. However, several careful deci-

sions needed to be made about the curriculum of the new undergraduate major. The most important of these involved the way in which physical chemistry would be incorporated. Historically, all Berkeley chemistry majors have taken a semester of quantum mechanics and a semester of statistical mechanics and thermodynamics. These courses are generally taught by using a rigorous mathematical treatment, and thus require four semesters of math and two semesters of physics as the prerequisites. Although we agreed that these foundation courses were absolutely essential for the proper training of a "typical" chemistry major, there was much debate about whether these requirements should be reduced to accommodate more biological courses. In the end, it was decided that rigorous quantitative training is a hallmark of the molecular view that chemists bring to the biological sciences, and that this identity should carry over into the new major. We therefore elected to maintain both semesters of physical chemistry as well as the full set of math and physics requirements. However, it was realized that the different interests of the chemistry and chemical biology students would significantly influence the context of physical chemistry that would be appropriate, and thus two parallel tracks of the physical chemistry courses were created. In a similar fashion, transition metal reactivity and coordination chemistry is offered to the chemical biology majors as a specialized bioinorganic chemistry course. Although the level of difficulty and material content of the classes are the same as that of their chemistry counterparts, the ability to select the perspective of their training has been a popular feature of the program among the undergraduate students.

Another key development for the program was the creation of a new chemical biology core course for the undergraduates. Although the topics discussed in this class are similar to those in many biochemistry courses (including biomolecule structure, enzyme mechanisms, energy and information flow, and metabolism), the class is taught with a larger dose of organic chemistry, quantitative thermodynamics, and kinetics than is often encountered at the entry level. The emphasis on structure and mechanism provides a way to understand the logic of biochemical pathways. Many examples of natural products and medicinal compounds are explored in the context of biological systems, highlighting the impact that chemical approaches have had on our understanding and treatment of disease. Conformational analysis and molecular strain are used to rationalize protein secondary structure and the differences between the preferred conformations of RNA and DNA. Many of these topics are explained by using computer visualization software in the classroom setting. Also, many of the tools that chemists have applied to the understanding of biology (such as stereochemical analysis, isotope tagging, molecular dynamics, unnatural amino acid incorporation, and biomolecule labeling) are introduced in this course. Many of these students continue in the program by enrolling in the graduate level chemical biology course described above, and this year a new undergraduate-level course has been added to examine metabolism, biosynthesis, and natural product chemistry in more detail.

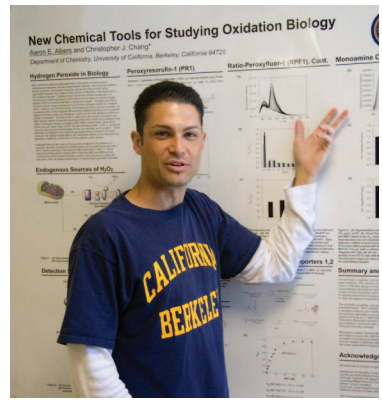

Image courtesy of Michael Barnes, UC Berkeley

CBGP student Aaron Albers presents his research at one of the three poster sessions held each year.

As with the CBGP, a key to the success of this program has been our collaboration with Berkeley's MCB department. After taking the chemical biology course, all of the undergraduates are required to take an upper-division molecular biology lecture course and an intensive molecular biology laboratory. These courses are only offered by the MCB department, so much flexibility on the part of our MCB colleagues has been needed, particularly with respect to adding new laboratory sections. In many instances, chemical biology graduate students have served as teaching assistants for these courses. In the early stages, our chemical biology majors are also required to take an introductory survey course that covers the basic principles of biology. Finally, many of the chemical biology students carry out undergraduate research in MCB laboratories.

In 2003, the major was initiated as an *ad hoc* Independent Study Program within the College of Chemistry. Within 1 year, >50 students had signed up for this program under the approval of the Dean's Office. This undeniable level of interest prompted the formal drafting of the major requirements, and in 2006 the chemical biology undergraduate major was formally approved by the Berkeley Academic Senate. It is the first new major to be introduced in the College of Chemistry since 1946.

After the new major was introduced, the enrollment in the department of chemistry increased faster than anyone had predicted. Applications of incoming freshman to the department of chemistry have nearly doubled, and student transfers have increased as well. As of June 2007, 272 chemical biology majors were enrolled in our department, in addition to 223 chemistry majors. The steady-state enrollment for the program is predicted to be ~75 chemical biology students per class.

This rapid increase in enrollment has not occurred without its challenges, however. It

TABLE 1. The Berkeley Bachelor of Science in Chemical Biology Curriculum[a]

Core Degree Requirements:	
Chem 4A/B (2 semesters)	General Chemistry and Quantitative Analysis
Chem C96	Introduction to Research and Study in the College of Chemistry
Chem 112A/B (2 semesters)	Organic Chemistry
Chem 135	Chemical Biology
Chem 103	Inorganic Chemistry in Living Systems
Chem 120A	Physical Chemistry: Principles of Quantum Theory
Chem 120B	Physical Chemistry: Statistical Mechanics and Thermodynamics
Chem 105	Instrumental Methods in Analytical Chemistry
MCB 110	Molecular Biology of Prokaryotic and Eukaryotic Cells and Their Viruses
MCB 110L	General Biochemistry and Molecular Biology Laboratory
Allied Subject Requirements:	
Bio 1A	General Biology Lecture and Laboratory
Math 1A/B (2 semesters)	Introductory Calculus
Math 53	Multivariable Calculus
Math 54	Linear Algebra and Differential Equations
Physics 7A/B (2 semesters)	Physics for Scientists and Engineers

[a]In addition, seven additional units are selected from upper division courses in MCB, Chemistry, Chemical Engineering, Bioengineering, or other allied departments. The students must also complete the General Education Requirements for all Berkeley undergraduates.

has created a sharply increased demand on faculty teaching loads and academic advising staff during difficult budgetary times. It has also created a significant need for additional instructional laboratory facilities, including those that are configured to carry out biological experiments. Most significant, however, has been the dramatic increase in the number of students who are interested in pursuing undergraduate research. While this is seen as an essential part of the program (particularly for those who intend to continue their studies in graduate school), many of the research laboratories have taken on a larger number of undergraduate students than they normally would. Fortunately, the matching success of the GCBP has brought in a number of talented graduate students who have helped to mentor them.

This spring, the second class of Berkeley graduates received their B.S. degrees in chemical biology. Although we do not yet have the full breakdown of their career paths, several popular trends have been observed. A large fraction of the students has elected to continue their training by enrolling in chemistry or biology graduate programs at universities across the country. Others have joined medical school programs or have chosen to pursue M.D./Ph.D. combinations. Many of the graduates are now in pharmacy school, and the bulk of the remaining fraction has found employment in the chemical and biotech industries.

Final Thoughts. As progress in the biological sciences is increasingly driven by a molecular level of understanding, integrated approaches are needed to provide rigorous training in both chemistry and biology. Berkeley has responded by offering classroom and laboratory opportunities for both graduate- and undergraduate-level students, resulting in a dramatic increase in the student population of our department. The talent and enthusiasm of the students enrolled in these programs speaks volumes about the bright future that lies ahead for research at this interface.

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