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Symbiosis: Chemical Biology at Wisconsin

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Chemical biology has been percolating at the University of Wisconsin (UW)–Madison for most of the university's history (www.chemicalbiology.wisc.edu; *1*–*4*). UW–Madison played a predominant role in early research on vitamins—those small molecules that are essential in trace amounts for human life. There, Harry Steenbock developed the irradiation process for the production of vitamin D and thereby eliminated the scourge of rickets (*5*, *6*). Vitamin A was discovered at Wisconsin, as were the vitamin B complex and the hormonal form of vitamin D. Karl Paul Link isolated the potent anticoagulant dicoumarol there and then synthesized warfarin, an analogue that is still a common chemotherapeutic agent. Microbial fermentation methods developed at UW–Madison enabled the large-scale biosynthesis of penicillin and other antibiotics. H. Gobind Khorana carried out the first chemical synthesis of a gene there (*7*), and W. S. Johnson and Eugene van Tamelen devised synthetic routes to steroids inspired by the biosynthesis of this critical class of natural products (*8*). The use of natural protease inhibitors to devise highly effective inhibitors of aspartyl proteases was an insight that arose at Wisconsin and was used to design potent HIV protease inhibitors (*9*). These and other triumphs demonstrate an early symbiosis of chemistry and biology, which fostered the training of eminent interdisciplinary scientists such as Carl Djerassi and Ralph Hirschmann.

Seeking to coalesce the well-established success in research at the interface between chemistry and biology, Dan Rich sought one of the initial Chemistry–Biology Interface (CBI) Training Grants from the National Institutes of Health (NIH) in 1993. His vision was to provide graduate students with a multitude of opportunities for interdisciplinary training in chemistry and biology. The process of preparing the grant application launched the UW–Madison program in chemical biology (www.chemicalbiology.wisc.edu). The now long-standing NIH training grant remains a core component of graduate training in chemical biology at the university.

Since the inception of the training program, UW–Madison's commitment to graduate-student training in chemical biology has increased. For example, the university has made the recruitment of faculty members with research interests in chemical biology a priority. As a result, graduate students have a wide variety of research options from which to choose. In addition, a powerful infrastructure for conducting chemical biology research has been built. Third, courses in chemical biology have been developed that employ innovative teaching methods. These courses are designed not only to introduce students to concepts in chemical biology but also to build their skills in critical thinking, creative problem selection, and communication. Lastly, students affiliated with

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UW–Madison CBI trainees (L to R) Jared Mays, Christopher Marvin, Joseph Binder, Rachael Carpenter, Emily English, Matthew Shoulders, Paola Mera, Kelly Gorres, Kimberley Peterson, and Nicholas George.

the training program have an opportunity to gain research experience in industry. Such experiences allow graduate students to make truly informed career decisions.

The aforementioned components were designed to provide graduate students with an education that goes beyond teaching them to design and implement experiments. The Wisconsin approach includes helping students develop the skills to formulate exciting research questions, design appropriate experiments, critically evaluate results, and explain to others why their conclusions are important. It is with this backdrop that the program components are discussed.

RESEARCH OPPORTUNITIES

In 1998, UW–Madison launched an innovative program—the Cluster Hiring Initiative. This bold effort was designed to foster collaborative research, education, and outreach by creating new interdisciplinary areas of knowledge that cross the boundaries of existing academic departments. As an indicator of the UW–Madison's commitment to chemical biology, it is the focus of one of the selected Cluster Hiring Initiatives (www.clusters.wisc.edu/clusters/show/8), selected by the Provost with input from faculty. A central aspect of this initiative is the recruitment of faculty members with interdisciplinary research interests. With the new faculty members hired under the initiative added to existing faculty, the university now has >36 research groups with chemical biology research interests. Thus, graduate students have an opportunity to engage with a wide variety of chemical biology faculty members at the cutting edge of the field. Because chemical biology research groups not only are located in the core departments of chemistry, pharmaceutical sciences, and biochemistry but also are interspersed throughout the university, from bacteriology to pharmacology to chemical and biological engineering. This spectrum of research opportunities allows incoming students to choose a research adviser from a variety of departments. Because chemical biology students are located in many different departments, extensive cross-fertilization of ideas, approaches, and expertise occurs.

RESEARCH INFRASTRUCTURE

UW–Madison has recognized the importance of building the proper infrastructure for conducting research in chemical biology. Graduate students have ready access to state-of-the-art equipment with personnel to help them implement experiments in areas that are new to them and their research group. This infrastructure is especially important to graduate students in chemical biology, who often need access to a wide variety of experimental methods and instrumentation. Some of UW–Madison facilities of interest to chemical biologists are the Keck Laboratory for Biological Imaging (KLBI), the Biophysics Instrumentation Facility (BIF), and the Keck Center for Chemical Genomics (KCCG).

Imaging methods are invaluable for monitoring protein or small-molecule localization and function. Indeed, chemical biologists continue to make major contributions to this area. Moreover, many chemical biologists benefit from applying modern imaging methods. The KLBI provides the necessary facilities and expertise to the campus. Similarly, the BIF offers instruments for evaluating the strength and stability of biomolecular interactions that require a wide variety of methods. Both centers are staffed by highly experienced scientists who advise students and faculty on implementing experiments.

The KCCG is especially valuable for chemical biologists, because it provides equipment for researchers to synthesize and screen libraries of small molecules. The center is composed of a Chemical Genomics Research Facility and a Compound Screening Facility (CSF). The former has equipment for library generation (liquid handlers and microwave ovens that accelerate library synthesis) and instrumentation used to develop and implement screens (plate readers, surface plasmon resonance imaging, *etc.*). The CSF is integrated with the Comprehensive Cancer Center, providing a conduit for chemical biologists to mix with scientists from different disciplines. The facility contains compound libraries, screening robotics, data-analysis tools, plate readers, and high-throughput microscopy; chemical biologists and biologists are able to identify compounds with biological activity that could serve in drug development or as research tools.

An Interdisciplinary National Cooperative Drug Discovery Group works closely with the KCCG. This UW–Madison consortium of natural-products researchers is using natural products as blueprints to develop new medicines to treat colon, breast, cervical, and pancreatic cancer. The campus-wide group, led by Ben Shen, is producing and testing analogues of natural compounds from microorganisms. These engineered "natural products" provide an alternative

Box 1. Comment from the 2006 Evaluations for the Chemical Biology Course

"This was, by far, the most interesting class I have ever taken—undergraduate or otherwise. With few exceptions, I never noticed the amount of time that had elapsed during lecture until we were dismissed. The topics discussed were very intriguing, the papers used to augment the learning process were applicable and represented leaders in the field, and the instructors were very knowledgeable and interested in engaging the students. This class was an excellent example of a graduate-level course with just the right pace and had a degree of difficulty (for material covered) that served to appropriately stretch the student's mind. Finally, the proposals were a good addition to the class requirements. Few classes ever truly challenge the student to perform in this capacity—while this was not the first proposal I've written, it was the first necessary for a normal class, as opposed to senior-level research. Furthermore, the requirement that the hypothesis utilize chemical-biology-related techniques to answer present, novel questions helped me to grapple with the field effectively."

to the libraries produced by chemical synthesis.

EDUCATION

The chemical biology curriculum at UW–Madison includes two core courses that have been tailored to interdisciplinary researchers—chemical biology and a chemical biology seminar. These courses have unique features devised to promote independent thinking and creativity. In addition, each course has aspects that help to hone graduate-student skills in written and oral communication.

Chemical Biology Course. The beginning of the chemical biology course is taught from a perspective of how to merge chemical and biological concepts to explore biological systems. The course is organized around the flow of information in biological systems (DNA to RNA to protein) and emphasizes how to use chemical approaches to intervene in each step to elucidate and control that flow. A major goal is to empower scientists: to give chemists relevant novel targets and to offer biologists useful new tools and approaches. Examples of topics include creating small molecules that act to inhibit or enhance transcription and using genetic methods to synthesize proteins containing non-natural residues. An introduction to the chemical concepts underlying catalysis is given, and chemical approaches to controlling signaling pathways are discussed. In addition to using specific examples, the course focuses on common features among different approaches. For example, many aspects of chemical biology rely on modularity: proteins have modular units, and molecules composed of modular units can be used to alter protein function, localization, degradation, and so forth. When students are shown that approaches that address very different biological questions can be based on similar fundamental concepts, they can begin to recognize how to devise new strategies to solve the biological questions that interest them.

Student participation is a key component of this course. Because the student participants have heterogeneous backgrounds (*i.e.*, some come from biology, others from chemistry), the lively in-class discussion allows students to appreciate different scientific perspectives. Perhaps the most valuable (and fun!) aspect of this course, however, is student participation in peer review through in-class study sections. Each student writes an original research proposal, which is reviewed anonymously in an NIH-style study section composed of a subset of other students in the course. The study sections, in which a faculty member acts as the chair and scientific-review administrator, offer students the unique opportunity to experience the review process from the perspectives of both an applicant and a reviewer. Students typically find that serving as a reviewer is challenging, and the faculty chairs provide feedback at the meetings on their reviews (*e.g.*, do the criticisms focus on the central issues of the grant?). The students' feedback reveals that through this exercise, they have developed a deeper appreciation of the importance of clarity in writing (see Box 1). In addition, they also build their communication skills in the study-section meetings; in these venues, the students must present their ideas to a group with heterogeneous scientific backgrounds. The skills that students gain from this experience are critical for success, whether they later choose a career in academia, government, or industry.

Chemical Biology Advanced Seminar. The participants in the chemical biology seminar are typically advanced graduate students who already have completed the course in chemical biology. In the seminar, students discuss key publications from the past year. The format is designed to encourage an active dialogue. Students are given (or choose) a specific paper to present. A few days before the class meets, the presenter sends three to five discussion questions to other members of the class so that they can consider them as they read the assigned paper. During the course period, the student presenter provides the group with background information that summarizes the key findings and puts them into context. The students then break up into small groups to talk about the discussion questions. During the last 10–15 min, the entire class comes together again to share the ideas that were raised in the small groups. What makes this course interesting and stimulating is that it prompts the discussion of larger issues: the importance of the paper and the questions it seeks to address, the benefits or drawbacks of the approaches used, and the potential future

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directions of the research field under discussion. Thus, this seminar allows students to practice their formal presentation skills and to develop their ability to think critically about science.

CAREER CHOICES

Chemical biology students benefit from their varied research and training experiences when they select a career. The CBI trainees, who typically have three consecutive one-year appointments under the training grant, participate in industrial internships. The internships, usually ~12 weeks long, give students an opportunity to gain research experience in a new environment. Many students elect to pursue their internships in the pharmaceutical or biotechnology industries; others carry out research in a government laboratory (*e.g.*, NIH or Los Alamos). Students are uniformly positive about their experiences, and they draw on them in making postgraduation career decisions. This type of training opportunity is available to all chemical biology students.

As described earlier, the CBI Training Grant (GM008505) from the National Institute of General Medical Sciences catalyzed graduate training in chemical biology at UW–Madison. Indeed, this grant, which has been running since 1993, helps fund the training of 10–12 outstanding chemical biology students every year. Moreover, several additional affiliated students receive funding from other sources. The training grant director (Laura Kiessling), the deputy director (Jon Thorson), and an advisory committee (five faculty trainers and one graduate-student trainee) develop and oversee the program in conjunction with the chemical biology trainer faculty. Trainees take the chemical biology course and a course on ethics for scientists and teachers, attend the chemical biology advanced seminar and the chemical biology colloquium, help recruit and welcome new students, participate in industrial research internships, receieve an annual allowance to travel to present their research at scientific conferences, and receive invitations to special and routine seminars by relevant scientists. The CBI committee considers appointments of incoming graduate students nominated by departments and of current graduate students early in their programs nominated by trainers and have made a substantial impact. Although the CBI training grant has been a catalyst for chemical biology graduate education at Wisconsin, the educational initiatives described are open to all graduate students at the university.

Current trends indicate that the boundries between traditional scientific disciplines will continue to blur (*10*). We anticipate that educational initiatives like those at Wisconsin and elsewhere (*11–17*) will continue to facilitate the evolving symbiosis between chemistry and biology.

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Correction: Symbiosis: Chemical Biology at Wisconsin

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Because of a production error, the following references were misformatted: 5, 7, 10–17. These errors do not affect the scientific integrity of the article. The electronic version was corrected and reposted to the web on October 20, 2006.

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Correction: Graduate Education in Chemical Biology at the University of Michigan

Tonia J. Buchholz, Bruce Palfey, Anna K. Mapp, and Gary D. Glick*

The name of author Tonia J. Buchholz was inadvertently misspelled. This error does not affect the scientific integrity of the article. The electronic version was corrected and reposted to the web on October 20, 2006.

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Jacquin C. Niles and Michael A. Marletta

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Correction: Design, Synthesis, and Biological Activity of a Potent Smac Mimetic That Sensitizes Cancer Cells to Apoptosis by Antagonizing IAPs

Kerry Zobel, Lan Wang, Eugene Varfolomeev, Matthew C. Franklin, Linda O. Elliott, Heidi J. A. Wallweber, David C. Okawa, John A. Flygare, Domagoj Vucic, Wayne J. Fairbrother, and Kurt Deshayes

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