ACS chemical biology

When Undergraduates Ask "Why," Chemical Biology Answers

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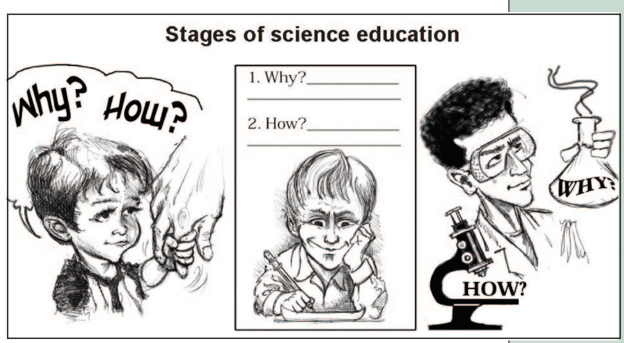
Universities face many challenges in educating the next generation of scientists, including how to implement inquiry-based teaching methods and how to prepare students for careers in chemical biology. New initiatives are demonstrating that the breadth and innovation inherent to chemical biology can be used to bring more student-led inquiry into the classroom and the teaching laboratory.

As any exasperated parent of a five-year-old can tell you, children are born with an innate desire to ask questions. "Why doesn't the ocean dry up?" "Where do plants go in the winter?" "What are germs, and why do they make us sick?" When students reach the undergraduate level, they often rediscover the childlike excitement of broad academic freedom. The prospect of choosing their own classes, majors, and electives forces students to consider their own interests and their own questions about the world. Recent programs aimed at reforming undergraduate science education have taken into account this inquisitive energy. Inquiry-based teaching has emerged as a pillar of well-publicized initiatives such as the National Resource Council's *BIO 2010* report (*1*), the National Academies' Summer Institutes on Undergraduate Education in Biology (www.academiessummerinstitute.org), and the Howard Hughes Medical Institute's (HHMI) Professors Program (www.hhmi.org/research/professors). By allowing undergraduates to follow open-ended research projects, often in groups with the help of a mentor, these programs let undergraduates experience firsthand the excitement of scientific research.

The questions of how to implement inquiry-based teaching dovetail with concerns on how to train the next generation of chemical biologists (*2*). Chemical biology poses unique problems for education because it requires breadth of knowledge as well as depth; even scientists with great in-depth understanding of their own fields can run up against obstacles when pursuing a lead in chemical biology. For instance, a cell biology postdoctoral fellow who never took an undergraduate statistics course might suddenly find himself awash in microarray data. Or a chemistry grad student might have spent years synthesizing a family of natural products only to be left to her own devices to demonstrate their relevance in biological assays. Training the next generation of chemical biologists thus requires an undergraduate education that values a wide exposure to a variety of interrelated fields, from cancer evolution to robotics or from immunology to image analysis. But how can undergraduates gain exposure to diverse subject matter without becoming jacks of all trades and masters of none?

Inquiry-based approaches are a natural way to broaden the experience of future chemical biologists without completely



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Box 1. Student Feedback.

The Chemical Biology for Sophomores! lecture and lab courses have been revised, updated, and tweaked each year since their launch in 2004. A key part of this development process is feedback from students. The following are excerpts from anonymous end-of-course student questionnaires from the first 2 years of the courses.

On the Lecture Course

"I enjoyed the fact that we focused mainly on primary literature with Prof. Schepartz guiding us on the scientific story behind the papers. This was a unique thing to experience, especially as a sophomore."

"I surprised myself when I ended up liking the class—as a biology major, I had just finished organic chemistry the semester before and was looking forward to never taking another chemistry class again. However, chemical biology showed me how the reactions I learned in organic chemistry could be used in fascinating ways to explore biology. I would recommend this course if you really enjoy biology and wish to see how extremely relevant chemistry can be to the field."

"Great chance for non-chemistry majors to really see the interdisciplinary connections."

On the Lab Course

"It gave me a sense of what research is like without a commitment to a lab . . . a great place to decide whether research is for you."

The Chemical Biology Laboratory "is infinitely more interesting than standard laboratory courses, in which specific lab techniques are performed not as means to an end, but as ends in and of themselves. [This lab] is unique in that it gives a student a reason for performing the techniques, namely, to solve an actual research problem."

"I learned that you never know where trying to answer a seemingly simple question may take you. Scientific research is unpredictable."

rewriting existing curricula. By structuring an early-level course to allow undergraduates to pursue problems where they lead (rather than in a predetermined direction), educators can encourage students to explore fields on the borders of their chosen majors. Thus, despite the limited span of, say, a year-long lecture and laboratory course, students can gain experience in a variety of fields in a fluid way. Keeping both lecture and laboratory courses unforced and often self-directed provides a refreshing and realistic view of science and gives the student an appreciation for the interdisciplinary nature of modern scientific research. Also, because chemical biology's most impressive work is still ongoing, the student comes away feeling that he or she has contributed substantively to chemical biology as a whole (and with the chance to publish their laboratory findings).

The Chemical Biology for Sophomores! lecture course and laboratory, first implemented at Yale University in 2004 and funded by an HHMI Professors Award to Alanna Schepartz (Yale University), exemplifies how chemical biology can make the most of inquiry-based teaching and *vice versa* (www.schepartzlab.yale.edu/chembiolsoph and www.hhmi.org/news/professor-schepartz.html). The lecture course offers detailed introductions to diverse topics. It uses current primary literature as the source text and casts the professor in the role of guide to explore the most dynamic and innovative sections of chemical biology. Similar survey formats may be more typical of graduate-level courses, but the science is not dumbed down or glossed over for sophomore-level undergraduates. Instead, the interdisciplinary nature of chemical biology allows for the teaching of basic science along with the cutting-edge applications. For instance, the course begins with Merrifield's original papers on solid-phase peptide synthesis (*3*, *4*) and immediately dives into case studies on applications of intein chemistry and direct labeling of proteins *in vivo* (*5–7*). During this first unit, students are exposed to basic biochemistry (the names and structures of the 20 amino acids, and methods of protein expression in bacteria) as well as basic bio-organic chemistry (the strategies and mechanisms of protecting group chemistry, amide bond formation, and bio-orthogonal reactions). In this way, the focus on chemical biology frees professors to explore truly exciting, present-day fields of study while still teaching nuts-and-bolts basics.

Other open-ended techniques were used to complement this lecture strategy to enhance the atmosphere of exploration. Students were encouraged to think out loud about key papers in discussions led by open-ended questions. Every 2–3 weeks, case studies were used to reinforce the basic science behind the applications while exposing the students to innovative chemical biology being performed by leaders of the field. Students were asked to compose a review article or original research proposal on a topic of their own choosing rather than take a final exam. Individual students found that they could manage such an assignment (normally expected only of graduate students) because they had the freedom to remain in their intellectual comfort zone while focusing on a question they were personally interested in. Altogether, these inquiry-based techniques have been successful because they take advantage of the unique scientific breadth and innovative characteristics of chemical biology.

The laboratory-based portion of Chemical Biology for Sophomores! also uses the field's strengths to advance inquiry among undergraduates. Graduate-student mentors lead small teams of undergraduates in semester-long research projects, from making buffers to writing up the results and everything in between. The projects are limited in scope and streamlined by the graduate students to fit into the allotted time frame but are not diluted in their import or rigor. For example, one project involved a phage display selection seeking to optimize miniature protein inhibitors of the oncoprotein hDM2 (*8*). The undergraduates performed techniques as diverse as Kunkel mutagenesis (*9*), phage preparation, biopanning, and fluorescence polarization, all while getting an up-close view of how molecular evolution methods work (or fail to work). These topics and techniques span diverse areas of molecular biology, virology, biochemistry, and biophysics but were integrated into a seamless scientific story by the overarching goal of developing novel hDM2 inhibitors (*10*). Other projects have involved CD and NMR spectroscopy, synthesis and screening of synthetic libraries, cell-culture experiments, and live-cell fluorescence imaging. A short science-writing workshop is included in the laboratory course, and at the end of the semester each sophomore writes a preliminary manuscript with background, methods, results, and discussion sections. In the above example, the project was completed by the mentor and the work was published (*11*), ultimately giving the students both a first publication and a career-altering experience.

Educating the next generation of scientists to take advantage of the increasingly interdisciplinary nature of research will require major shifts in strategy, including broader implementation of inquiry-based teaching methods. New programs such as Chemical Biology for Sophomores! are demonstrating that the breadth and innovation inherent to chemical biology can facilitate student-led inquiry in the classroom and the teaching laboratory. In return, undergraduates are demonstrating that, in parallel to in-depth study of a chosen major, they have the interest and ability to pursue a range of topics at the chemistry–biology interface.

REFERENCES

1. National Research Council Committee on Undergraduate Biology Education to Prepare Research Scientists for the 21st Century. *Bio 2010. Transforming Undergraduate Education for Future Research Biologists,* Washington, DC, 2003.
2. Godwin, H. A., and Davis, B. L. (2005) Teaching undergraduates at the interface of chemistry and biology: challenges and opportunities, *Nat. Chem. Biol. 1,* 176–179.
3. Merrifield, R. B. (1963) Solid phase peptide synthesis. I. The synthesis of a tetrapeptide. *J. Am. Chem. Soc. 85,* 2149–2154.
4. Merrifield, R. B. (1964) Solid phase peptide synthesis. II. The synthesis of bradykinin. *J. Am. Chem. Soc. 86,* 304–305.
5. Muralidharan, V., and Muir, T. W. (2006) Protein ligation: an enabling technology for the biophysical analysis of proteins, *Nat. Methods 3,* 429–438.
6. Prescher, J. A., and Bertozzi, C. R. (2005) Chemistry in living systems, *Nat. Chem. Biol. 1,* 13–21.
7. Chen, I., and Ting, A. Y. (2005) Site-specific labeling of proteins with small molecules in live cells, *Curr. Opin. Biotechnol. 16,* 35–40.
8. Momand, J., Wu, H. H., and Dasgupta, G. (2000) MDM2–master regulator of the p53 tumor suppressor protein, *Gene 242,* 15–29.
9. Kunkel, T. A. (1985) Rapid and efficient site-specific mutagenesis without phenotypic selection, *Proc. Natl. Acad. Sci. U.S.A. 82,* 488–492.
10. Chene, P. (2003) Inhibiting the p53-MDM2 interaction: an important target for cancer therapy, *Nat. Rev. Cancer 3,* 102–109.
11. Kritzer, J. A., Zutshi, R., Cheah, M., Ran, F. A., Webman, R., Wongjirad, T. M., and Schepartz, A. (2006) Miniature protein inhibitors of the p53-hDM2 interaction, *ChemBioChem 7,* 29–31.