Chemical biology: the promise, and confusion, of adolescence

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It takes time for any new scientific discipline to gain momentum, and chemical biology is no exception. But with the formation of new training programs and interdisciplinary departments, the changes are coming.

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In the beginning there was biochemistry. Its practitioners were well versed in the ways of molecules, and respectful of chemists. But then came the scourge of molecular biology.

After several decades of ascendancy, molecular biology is facing an increasingly powerful challenger in the form of chemical biology. "Molecular biology is so seductive and has taken over so much of biology; it has permeated all the way down to high schools," says Ron Estabrook of the University of Texas Southwestern Medical Center (UTSW; Dallas). "We want to get away from the descriptiveness of biology to the quantitation of chemistry. We want to bring back a type of thinking that molecular biology doesn't encompass."

For UTSW that effort involves creating a Chemical Biology graduate training program, and hiring more chemists and chemical biologists. Both changes were requested by Steven McKnight as conditions for accepting the chairmanship of the UTSW Biochemistry Department. McKnight says he is intent on building a department that is equally strong in biophysics, molecular biology, and chemistry.

UTSW is far from the only research center making moves towards chemical biology. Departments are changing names, forming graduate programs, and hiring new faculty. In many cases faculty are trying to create what they never had—a truly interdisciplinary training—and thus bootstrap a young field into prominence. "Five years from now," says McKnight, "a biochemistry department that doesn't have chemistry in it I think is going to be a weak department."

Chemical biology: many things to many people

If chemistry used to be integral to a biochemistry department, it rarely is today. "To be brutally honest, there are very few departments that are old-school biochemistry departments," says Gerald Koudelka of the State University of New York (SUNY) at Buffalo. "Many of them are very far away from what I would consider a biochemistry department." McKnight sees his changes as an embrace of the past. "This is nothing fancy," he says. "I think this is getting back to the roots."

But for others chemical biology is not just the return of enzyme purification and intermediary metabolism, so what is it? "Everybody's definition will be different," says Estabrook. "The first thing is a rigor of thinking that takes into account the key role of functional groups, and the key role of quantitation." For other researchers, the focus is the use of small molecule inhibitors that can be titrated in and out at will, and used to study processes such as angiogenesis that are hard to address using genetics. "Chemical biology is not a totally novel creation, but the emphasis on synthesis is what sets it apart, especially complex synthesis," says Tom Scanlan of the University of California, San Francisco (UCSF). Notably these chemical tools can be used to study an entire pathway, or even multiple pathways, rather than taking the traditional approach of focusing on a single protein.

The name game

In adopting these tools, more chemists have moved towards biology than biologists towards chemistry. Thus the ultimate embrace of chemical biology—the addition of 'chemical biology' to a department's name—has come from chemistry departments such as those at Harvard (in 1995) and Cornell (ongoing). The Scripps Research Institute in La Jolla, California, created a new Skaggs Institute of Chemical Biology in 1996, which continues a commitment dating back at least to 1991, when the institute's director, Richard Lerner, hoped that Scripps would be seen as "the Bell Labs of chemical biology."

Changing a name is not always the best or simplest solution, however. In the University of California (UC) system, for example, Scanlan says a name change requires UC regents' approval, and funding approval by the state legislature.

And then there is the issue of territory. "Molecular biology can play within a biology department. Chemical biology has to play in between," says Gerald Joyce of Scripps. "Scripps is all mixed together, so there's no threat." Like Scripps, UCSF is crowded into one or a few clustered buildings, so department naming is less of an issue. As UCSF plans its move to reclaimed land near the San Francisco bay, it is rearranging itself into 'affinity' groups, one of which is chemical biology. These groups will be assembled without regard to departmental affiliation.

Departments still control hiring decisions, but at the University of Wisconsin at Madison even that process has been distributed. Laura Kiessling of the chemistry department explains that "we haven't switched the department name more because we don't want all of [chemical biology] to be localized in chemistry." Instead, Kiessling and fellow faculty member Jo Handelsman put together one of several interdisciplinary hiring programs at the university. The chemical biology faculty hired under the Kiessling/Handelsman proposal take up appointments in any one of a number of departments, including biochemistry and chemical engineering. "At Madison it's not coming solely from the chemists, it's coming from a campus-wide initiative," says Kiessling. "That to me is exciting, because it suggests that other disciplines are recognizing how important an understanding of chemistry can be."

Bringing in new talent

In the chemical biology hiring drives at several universities, the criteria for a good chemical biologist are about as clear as the definition of chemical biology. For UCSF's Scanlan, chemistry comes first. "I look to see that they [the job applicants] are truly chemists—which means a Ph.D. in a chemistry department—and then they are expected to get up to speed in biology in a postdoc," he says. "Usually we have to make a judgement call on the potential rather than the publication record in biology."

"I personally like to see that they can synthesize molecules, because I think that is where the good things are coming from," he says. "When people are creating new ligands and inhibitors, interesting things happen."

The desire to build a chemical biology group is not enough if the qualified applicants are not out there. "Without question there's a shortage," says Scanlan. "We see that when we're hiring. It's very difficult to get the right person."

In Europe there are other challenges. According to Don Hilvert, who recently moved from Scripps to the Federal Institute of Technology (ETH) in Zurich, Switzerland, the typical German university has only one or two organic chemistry professors, who are expected to operate in the mainstream of organic synthesis. "Chemical biology is less well developed in Europe than in the US, with perhaps the exception of England, but that's changing," says Hilvert. At the ETH, he says, there is greater latitude for explorations in chemical biology. And in France chemical biology is receiving a lift with the establishment of the European Institute of Chemistry and Biology (IECB) in Pessac near Bordeaux. The IECB will eventually house up to 200 working scientists, with a large effort in structural biology and biophysics, and other groups focused on natural product and combinatorial library synthesis.

Training the ground troops

One obvious solution to the shortage of chemical biology faculty candidates is education. In such a young field, it is not surprising that education mechanisms are only now falling into place. The first crop of chemical biologists have seized upon any available help to get a grasp of two very different fields. "There's a lot of self-education going on, and that's why a more formal training would really accelerate the process," says Craig Crews (Yale University, New Haven, Connecticut).

Training grants from the National Institutes of Health (NIH) have encouraged the growth of interdisciplinary graduate programs, with chemical biology being a significant beneficiary. Newly formed programs include those at Duke (started in 1994), Philadelphia State University in Pennsylvania (started in 1996), UTSW (started in 1997), and UCSF and SUNY, Buffalo (both starting in 2000). Generally, training programs are not affiliated with any single department, so the territorial issues encountered in faculty hiring are moot. Recruiting students is a mixed bag: Estabrook at UTSW says that biology students are reluctant to do chemistry, so it will be important to spread the gospel in undergraduate courses, but Matthew Shair of Harvard University (Cambridge, Massachusetts) says there is no such problem in chemistry departments. "There is a higher proportion [of chemistry graduate students] every year interested in the chemical biology aspects," he says. "People are coming in saying, 'I want to learn about making molecules, but then I want to do something interesting with those molecules'."

The distinguishing characteristics of the chemical biology programs vary, with some programs incorporating little more than a required biology course with a chemistry degree. Others add custom-designed courses, seminar series, and the requirement for laboratory rotations in both sponsoring departments.

Exactly what works best is not yet clear. "I think the rules are still being written," says Shair. "But you need real interdisciplinary training. That doesn't mean being trained in biology in a vacuum and then being trained in chemistry in a vacuum. It's a different type of research." Shair is, for example, developing a course to address the emerging field of diversity synthesis—making large libraries of complex and diverse chemicals.

Chemical biology students may have to take more courses in the early years of their degrees, but compensation should come in the form of jobs in both academia and, especially, industry. Biotechnology companies have been steadily moving away from gene research and protein therapeutics and into chemistry and small molecule drugs. That change is in turn influencing academia, especially at UTSW. "During my five years at [the biotech

company] Tularik I got used to working with chemists, and just loved it," says McKnight. "Being in a biochemistry department without chemists there was something critical missing."

Research interests in academia and industry are likely to remain distinct, however, as industry is focused on drugs, whereas academics are worried more about testing hypotheses, often using chemicals that are clearly unsuited for use as medications, and on time-scales that are financially untenable in industry.

Motivations and opportunities

Any new field needs money, and chemical biology has benefited from the emphasis of funding bodies on interdisciplinary research. Grants for chemical approaches to cancer research from the National Cancer Institute have helped fund the Institute of Chemistry and Cell Biology (ICCB) at Harvard Medical School (Boston, Massachusetts), the Combinatorial Chemistry Center at the University of Pittsburgh, and programs at Scripps and the Torrey Pines Research Institute (La Jolla, California). Standard funding sources are also adapting to chemical biology. "There are no new [NIH] study sections for chemical biology," says Joyce, "but people are willing to take in a little more hard-core chemistry with their biology."

Successes with natural products, such as the use of leptomycin to isolate a nuclear export receptor and of capsaicin to isolate a pain receptor, have raised the profile of chemical biology. But the science that is driving the expansion of chemical biology perhaps most directly is combinatorial chemistry, which provides access to a vast supply of novel chemicals. Making sure that those chemicals are diverse enough and large enough to be biologically interesting is one of the challenges for chemists. "From target-oriented synthesis to diversity-oriented synthesis there isn't always a smooth connection — the reactions have to be exquisitely general," says Shair. "It's a fantastic opportunity for organic synthesis development."

But the chemical challenge discourages some. "It's one thing to be able to make a 100,000-compound library; it's another thing to get it to be useful for biological research," says Leroy Hood, the Chairman of the Department of Molecular Biotechnology at the University of Washington, Seattle. Hood's department is combining biology and engineering to focus on genomics and proteomics; a similar fusion of interests is planned for a new Molecular Engineering building at the University of California at Berkeley. Hood is also involved with a new Institute for Quantitative Systems Biology at Seattle, which will address the behavior of complex biological systems. Initially he will observe how these systems react to genetic perturbations, but eventually he hopes to hopes to use chemicals as probes. "Combinatorial chemistry," he says, "is a powerful way to give us shapes to interrogate the biology."

The difficulties are acknowledged by the chemists. "Molecular biology was accessible to everyone," says Shair. "Chemical biology is not as accessible; the reagents are not accessible. The chemistry is still very hard, whereas making mutants is not so hard. There is still a lot to be worked out." Shair hopes that a few centers will be able to generalize the process, so that it can be exported to less chemically oriented centers such as those in Seattle and Berkeley. The initial work may come from those with an abundance of both chemistry and money, such as Harvard's ICCB and its sister institution the Harvard Center for Genomics and Proteomics (CGP), and the new Novartis Institute for Functional Genomics (La Jolla, California). The Novartis institute is directed by Peter Schultz and has been funded by Novartis (Basel, Switzerland) to the tune of US$250 million.

Once the export process is under way, genomics may be the field that needs chemical biology the most. "I think chemical biology plays right into genomics," says Joyce. "With genomics you identify genes, but ultimately you have to tweak them and turn them on and off." Figuring out what all those genes are doing will take a lot of work, but some clever chemistry will make the process go a whole lot faster.