Intellectual Ferment

James Keglev

CHEMISTRY WAS THE FOCUS OF MY ACADEMIC INTERESTS WHEN I arrived as a freshman on the campus of the University of California, Berkeley. But unlike countless undergraduates everywhere, it wasn't synthetic organic chemistry that turned my thoughts in new directions. Instead, it was a fascination with biology and the chance to work in the lab of the legendary Daniel Koshland that drew me to biochemistry. Ever since, my research has been shaped by a single view: to attack major problems in biology, it is essential to understand what molecules are doing and how they interact with each other.

Every field has a different definition of what it takes to be a good scientist and these competing definitions can be vexing when you're interested in working at the interface of multiple disciplines. At the risk of oversimplification, I would say that for many years, biologists were focused on discovering how things work and less interested in the underlying processes. Chemists, on the other hand, skipped past the question of how something worked because they were focused on figuring out how to manipulate a process or make it better. I'm happy to say that these disciplinary and philosophical distinctions have become increasingly blurry: biologists are manipulating systems and chemists delight in discovering biological phenomena.

For me, it has always come down to something that my scientist colleagues can have a hard time talking about: intuition. Do you have an instinctive feel for a subject? Does it speak to you? That intuition or instinct—whatever word you use to describe it—is not so much about solving problems as it is about asking the right questions. If you have "biological intuition"—whether you are a chemist or physicist—you will have a sense of what makes a profoundly important question worthy of your time and energy. Figuring that out is the big challenge for all of us in biomedical research because we have an almost infinite number to address.

Labs that mix biochemists, engineers, physicists, and mathematicians together with biologists generate a kind of intellectual ferment that is productive and exciting. I see it in my UC Berkeley lab all the time, at the Janelia Farm Research Campus as it approaches the five-year mark, and with greater frequency at universities throughout the country.

This issue of the *HHMI Bulletin* takes special notice of the interactions between biology and chemistry—a fitting subject as we near the end of 2011 and the International Year of Chemistry. We're taking a look at the complex and exciting connections between chemistry and biology from both "sides" of the disciplinary divide as well as what's changed for chemists interested in biological questions and vice versa. As Kevan Shokat of the University of California, San Francisco, rightly observes, some problems can't be addressed unless you harness both the tools of biology and those of chemistry. Instead of "Better Living through Chemistry"—Dupont's famous 1960s advertising slogan—this new breed of scientists might propose something along the lines of "Better Biology with Chemistry." Or in a variation on the Robert Frost poem, "Lower Fences Make Better Neighbors."

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If you really want to understand the function of complex biological systems that underpin disease, you want to use every imaginable tool at your disposal—that means genetics, cell biology, chemical engineering, computer science, and biophysics, to name just a few—because you can't get there by being purely descriptive. In my own work, I am interested in the molecular mechanism of complex reactions that involve close to 100 polypeptides doing the right thing at the right time. The problem is, how do those 100 proteins talk to each other in a live cell in real time?

It's solving problems like this, at the level of the living cell, that makes the confluence of biology and chemistry so important. And we have no better illustration of it than the discoveries honored by this year's Lasker Award for Basic Medical Research. You can figure out how proteins fold from the standpoint of expected atomic interactions or you can understand what actually occurs in living cells amid the complex regulatory processes that need to happen along the way. That is what Arthur L. Horwich, an HHMI investigator at the Yale School of Medicine, and Franz-Ulrich Hartl of the Max Planck Institute of Biochemistry, succeeded in doing with such elegance.