

## Biomolecular Crowdsourcing

A GENERATION OF WEB-SAVVY ENTREPRENEURS HAS FOUND A relatively cheap and effective approach to solving complex problems and soliciting ideas: toss out a challenge into a vibrant digital community and watch what happens. Professionals and amateurs compete on an equal footing to provide often surprising solutions. HHMI investigator David Baker sees it on a daily basis with Rosetta@home, a distributed network dedicated to solving big questions in protein folding.

This phenomenon of crowdsourcing—a term that journalist Jeff Howe lays claim to coining—has some interesting parallels with old-fashioned bucket biochemistry (my kind of science). Each requires a vast input and powerful filters to yield a pure nugget of information. In biochemistry—which often requires real buckets of biological material, such as liters of HeLa cells—the nugget is a few nanograms of scarce proteins that researchers need to begin the real work of understanding the machinery of life.

Fishing is one of my passions, but some of my most successful fishing expeditions have been scientific. Starting during my years as a postdoc with Jim Watson at the Cold Spring Harbor Laboratory and subsequently at the University of California, Berkeley, my colleagues and I went fishing for a very specific molecular target: transcription factors—key regulatory proteins that control the flow of biological information in cells. We used short segments of DNA as bait, hunting for a match among the tens of thousands of proteins in cells. We started with viruses and then found the first transcription factor in human cells, something we called specificity protein 1, or Sp1.

We've learned that transcription factors work by interacting with short regions of DNA once denigrated as “junk” that in fact control the activity of all our genes. You can think of transcription factors as specialized proteins that recognize DNA sequence “punctuation marks”—start and stop signals recognized by the enzymes that read and transcribe genes. The transcribed “messenger” RNAs go on to generate important products like hemoglobin, the iron-rich protein that carries oxygen in red blood cells. Not surprisingly, when gene regulation goes wrong, disease occurs: diabetes, cancer, inflammation, and heart disease among them.

Like collaborations in cyberspace that rely on many anonymous contributors, bucket biochemistry has inherent limits. For example, by measuring transcriptional events in extracts derived from mixtures of cell types, we can detect only average events, not the reactions taking place in individual cells or at a single gene locus. In short, biochemists like me have been missing the rapid, dynamic, and mysterious real-time events taking place in individual cells at specific genes. But now developments in fluorescence microscopy make it possible to witness transcription as it unfolds in real time, molecule by molecule, and in some cases even in living cells.

A convergence of serendipity—involving a sabbatical detour in Paris in 2005, a collaborative project with a Berkeley colleague, and a subsequent stint as a visiting scientist at HHMI's Janelia Farm



“A convergence of serendipity has led my research in unexpected and illuminating new directions.”

ROBERT TJIAN

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Imaging tools have long played an important role in cell biology, but the fuzzy world glimpsed through the lens of a microscope always seemed too qualitative for my taste. Then, during a sabbatical at the École Normale Supérieure in Paris, I had the good fortune to occupy a lab bench next to Xavier Darzacq, a new faculty member who had just completed postdoctoral training in Robert Singer's laboratory at the Albert Einstein College of Medicine. The two scientists and their colleagues have contributed to major advances in our capacity to visualize actively transcribing RNA in live cells and to track the movements of RNA polymerase—the enzyme responsible for producing RNA during transcription—through the development of new molecular techniques, high-resolution microscopes, and sophisticated computational tools.

Back at Berkeley, physicist Steve Chu and I brought our labs together to build a new kind of microscope—one that uses multiple-color lasers to observe and measure complex events at the single molecule level. These collaborations developed into an international consortium that includes Singer, Darzacq, Chu, and many other scientists working at the frontiers of molecular and cell biology, biophysics, and mathematics. Our small collaborative project team also benefits mightily from interactions with Janelians Eric Betzig, Harald Hess, and Mats Gustafsson, who have done so much to advance light microscopy that we're now able to peer into cells with exquisite precision. It's been a literal eye opener for me. I'd describe it as biomolecular crowdsourcing—of a very different type—in a venue that allows us to cross national, disciplinary, and subject-matter boundaries to think about big interesting questions.