

An Elegant Molecular Dance

Images reveal how telomerase is created.

XIAOWEI ZHUANG ONCE SCORNE D BIOLOGY FOR ITS LACK OF ELEGANCE.

She'd been drawn to physics for its ability to explain the world with fundamental concepts since before she'd entered grade school, when her father, a physicist, set a cup on a table and asked her to speculate about the forces that held it there. Gravity, supporting force from the table, air pressure—those things made sense. But she saw little, she says, simple or beautiful about biology. ¶ Zhuang has since changed

her mind. "I have no doubt now that biology is the discipline where I want to make my contributions." As she studied physics as an undergraduate in China and a graduate student at the University of California, Berkeley, she came to realize that much of its appeal lay in the fact that the physical world was, relatively speaking, fairly well understood. "That was attractive as a student," she notes, "but when it came time to be an independent researcher, it was more interesting to begin to think about things that were less explored." Today Zhuang, an HHMI investigator at Harvard University, relies on her lab team's collective expertise in the physical and life sciences to try to explain some of biology's seeming complexity.

Her team's strategy is to spy on biological machines in action, watching as individual molecules fold, interact with one another, and do their work. They use sensitive optical imaging techniques to collect extraordinarily detailed pictures of this activity—watching, for example, as a single molecule of RNA folds into its functional shape or a tiny polio virus invades a mammalian cell. Combining those images with findings from their experiments in molecular biology and biochemistry, the scientists are revealing how the structural dynamics and movements

of molecules drive biological processes. A related technique developed in Zhuang's lab, called stochastic optical reconstruction microscopy, or STORM, can generate images of cells and other biological specimens with molecular-scale resolution.

Zhuang focuses on biomolecules of obvious medical relevance, and part of the research in her lab investigates viral infection. It's a system for which the lab's ability to track individual molecules and particles is especially germane, Zhuang says, since as few as one in a hundred to a thousand of the viruses that swarm a potential host cell may lead to infection. Thus, the behavior of a single virus may be more pertinent than the behavior of the group. By following individual influenza and polio viruses on their journeys into cells, the group has already unveiled several pathways and molecules that enable infection.

One of the lab's most recent successes, however, is developing a precise portrait of the molecular dance that creates telomerase, a complex of molecules that protects the

ends of chromosomes during DNA replication. Michael Stone, a postdoctoral fellow in Zhuang's lab, led the study published in the March 22, 2007, issue of *Nature*. The enzyme is essential for rapidly dividing cells, such as those in a developing embryo, but is usually shut off in healthy adult human cells. Upregulating the enzyme's activity allows adult cells to achieve a dangerous immortality. The enzyme is inappropriately active in the vast majority of human cancers, making it a potential target for new cancer therapies.

To preserve the tips of chromosomes, telomerase uses a protein enzyme called telomerase reverse transcriptase, or TERT, and a short stretch of RNA that serves as the enzyme's instruction sheet. The two components, however, can't seem to interact properly with each other on their own; helper proteins are needed to promote their assembly into a functional complex.

To find out how one helper protein called p65 helps choreograph the movements that bring together TERT and telomerase RNA, Zhuang and her collaborator, Kathleen Collins, a telomerase biochemist at UC Berkeley, used a technique known as fluorescence resonance energy transfer (FRET). Researchers label the molecule at precise locations with two dyes that emit distinct colors of

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Xiaowei Zhuang pairs sensitive optical imaging techniques with molecular biology experiments to reveal with precision how molecule movement drives biological processes.

light. One of these dyes can transfer energy to the other; how much is transferred depends on how close together the two dyes are.

Zhuang and her colleagues attached FRET labels to telomerase RNA and, by monitoring changes in the energy transfer between the labels, observed step-by-step changes in the assembling complex. Their data showed that p65 kicks off the process by binding to the RNA, flexing it so that its

TERT binding sites are close together. TERT can then latch on, snapping the RNA into its final, functional form. “It’s like a jigsaw puzzle,” Zhuang says. “When you put in one piece, it helps another find its proper place.”

With experiments like these, Zhuang says biophysicists and biologists are steadily moving their field toward the kind of fundamental and quantitative ways of explaining the world that first attracted her to science.

She acknowledges, however, that biology’s underlying elegance will differ from that found in physics. “We don’t necessarily want to strip away all the complexity of biology, to say ‘here are the bare bones and now it’s simple,’” she says. “But a different way of viewing that complexity may emerge, to allow us to understand the connections and interplay between biology’s many components.” ■ —JENNIFER MICHALOWSKI