Elvis, Nixon, and Stuart Schreiber

Getting chemists and biologists together is just one of the many goals of the ambitious ringmaster | **By Karen Hopkin**

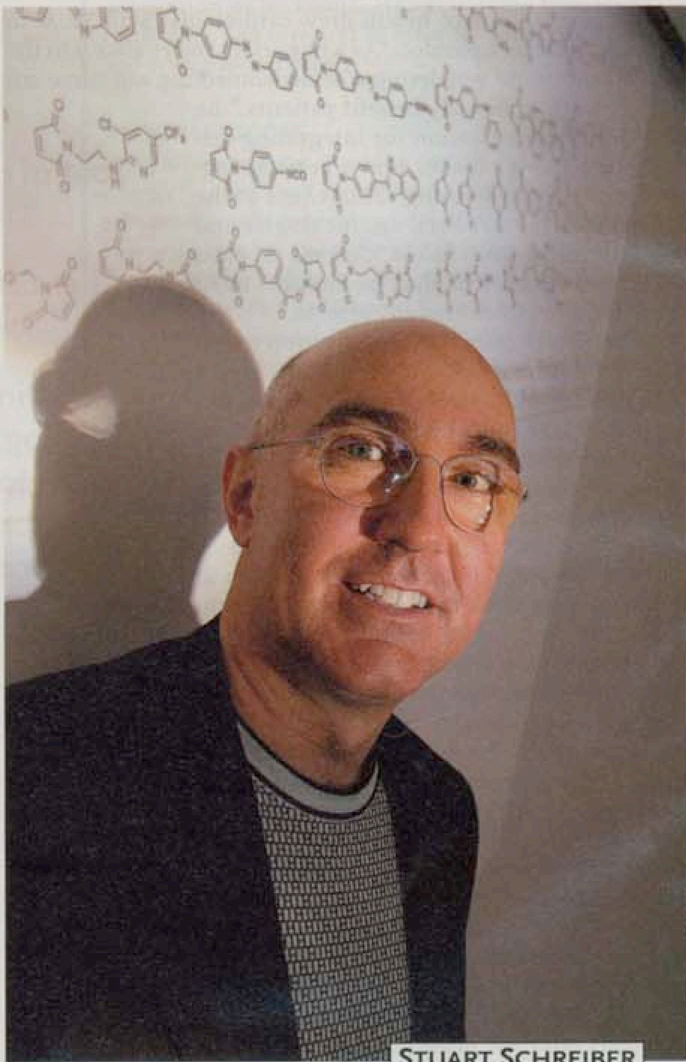
On the floor of the lounge that serves Stuart Schreiber's lab lie a pair of rugs that declare, "Welcome to Schreiberia." But Schreiber grimaces at the suggestion that his lab might be likened to an empire. "It's just an inappropriate descriptor," he says, shaking his head and all but tut-tutting.

According to Schreiber—a Harvard University professor, a member of the Broad Institute, and a Howard Hughes Medical Institute investigator—no single word can characterize the sprawling collection of trainees, collaborators, staffers, and institutions with which he is currently affiliated. On the Harvard campus, Schreiber heads a traditional academic lab, populated by 50 or so graduate students, postdocs, and physician-scientists. Across the river on the medical school campus, he oversees the operation of the Harvard Institute of Chemistry and Cell Biology (ICCB). There, staff scientists synthesize and screen the compounds that form the backbone of Schreiber's work in chemical genetics: the use of small molecules to modulate protein function.

FROM SMALL MOLECULES TO BROAD And then there's Broad. Last June, Schreiber joined forces with Eric Lander, then director of MIT's Whitehead Center for Genome Research, to become one of four founding members of the Eli and Edythe L. Broad Institute (pronounced "Brode") of Harvard and MIT. Established with $100 million, pledged over 10 years, from Los Angeles businessman Eli Broad and wife Edythe, and a commitment of $200 million from Harvard and MIT, the institute is dedicated to developing what Lander calls "a new toolkit for genomic medicine."

Schreiber was not always academically oriented; his high-school course load included classes on automotive repair and "bachelor wardrobe planning" (the boys' version of home economics). Yet, he completed his PhD in three years and landed a faculty position at Yale University straight out of graduate school. There he made his first foray into chemical biology by synthesizing cockroach pheromones—a study that earned him *Esquire* magazine's Dubious Achievement Award for "creating a dating service for cockroaches."

The pheromone worked for the roaches but left Schreiber vaguely unsatisfied. From a chemical standpoint, the project was a success, but it didn't reveal anything new about biology. That sort of success would wait until Schreiber returned to Harvard, where he identified a protein that binds to the powerful immunosuppressant FK506. The discovery led to the unraveling of a signaling cascade that allows white blood cells to recognize foreign tissue. And it gave Schreiber a taste of how small molecules could be used to probe biological systems, allowing him to assemble wiring diagrams of the cell's circuitry. Investigators in his lab have since used small molecules to delineate nutrient-signaling pathways in yeast and to characterize proteins that regulate gene expression by chemically modifying the histone proteins around which DNA wraps.



Courtesy of Stuart Schreiber

STUART SCHREIBER

The approach is analogous to classical genetics, whereby researchers attempt to explore the activity of a gene by knocking it out or making mutations. Using chemical genetics, Schreiber and his team do the same thing, only they use small molecules to interrogate protein function directly. Lander sees it as another means of "asking the cell to tell you, in an unbiased fashion, what's going on."

From Lander's perspective, Schreiber brings to the Broad ideas, energy, and his prowess as a chemist. "Stuart's a visionary. And he's an Olympic gymnast when it comes to chemical reactions," says Lander, who once synthesized a

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molecule with seven chiral centers during a 48-hour "nanosabbatical" in Schreiber's lab.

In addition to tying together chemistry and biology, Schreiber says that small molecules can also bring biology closer to medicine. Although he's not in the business of developing drugs, Schreiber says that learning which compounds can perturb a disease-related pathway "will enable people who want to make medicines to prioritize their efforts."

That link to human health drew cardiologist Stan Shaw to Schreiber's lab as a postdoc. "As a physician, you're always in the back of your mind wondering whether something will come out of your work to directly benefit patients," he says. Schreiber's passion for integrating disparate disciplines makes him a perfect ringmaster for leading young researchers at the Broad, says Jay Bradner, an oncologist and postdoctoral research fellow. "Stuart's led such a collaborative lifestyle that for him this must seem like a totally natural thing to do."

Witness Schreiber's weekly group meetings: one covers biology, another chemistry, a third technology. "That's where all the science happens," says Paul Clemons, a Broad fellow and former Schreiber student. "Most of the things we do are either conceived or vetted at one or more of these meetings."

Schreiber is a regular attendee. "Stuart goes to every meeting, unless he's out of town at another meeting," says Bridget Wagner, another Schreiber grad-cum-Broad fellow. His participation reveals that Schreiber has a foot firmly planted in each world. "On Tuesday, he talks about histone function, on Wednesday it's organic syntheses, on Thursday, bioinformatics. It's very impressive," says Shaw. "What he thinks about on his own time, I can't say," adds Clemons, "but he has a voracious appetite for science. He reads journal articles like they're going out of style."

PROJECT KORNBERG One particularly provocative article prompted Schreiber to launch a somewhat sociological study. In the late 1980s, Arthur Kornberg wrote an essay in which he lamented what he saw as a cultural rift between chemists and biologists. Schreiber and his team hope to bridge that gap in an experiment they've dubbed Project Kornberg.

Their goal: to establish a partnership in which chemists and biologists put their heads together from the get-go. Steeped in this crosstalk, the chemists will synthesize a set of small molecules that will address problems of interest to biologists. The biologists then will develop a set of assays that will provide chemists with information about the properties of their compounds. In their PowerPoint presentations, project participants represent this alliance using the iconic image of Nixon shaking hands with Elvis, although they continue to debate which figure symbolizes which discipline.

Project Kornberg was born on New Year's day, when Schreiber jotted down on his 2004 to-do list, "Increase impact of chemistry on biology and medicine." Yet nobody blames the eggnog. "He was probably drunk on the excitement of science," laughs Annaliese Franz, the senior postdoc heading up the chemistry contingency of Project Kornberg.

"At first the chemists were skeptical," she admits. "But the new students and postdocs are really getting excited. They can see how this will change the way people think about their projects." Instead of spending years synthesizing thousands of compounds, chemists might make 100 that will go through a series of screens. The resulting information will then guide the type of molecules they'll produce in subsequent, larger libraries. Previously the chemists might hand over their compounds and not find out what became of them until a year or two after they graduated, notes Wagner. By next January, Franz and the chemists plan to generate 10,000 compounds, which Wagner and the biologists will run through a dozen different screens.

Working on the project has already taught Franz how to make her libraries more useful to biologists, by making enough compound to go around. A tenth of a milligram wasn't cutting it. So now the chemists are aiming to produce between 1 and 5 mg of every molecule, an amount that Franz says "blows biologists' minds." She describes her revelation in the form of a MasterCard TV commercial: Cost of reagents: $100. Chemists' time: $200. Knowing that a biologist will want to screen your compound: priceless.

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In the end, the project will produce a multidimensional matrix of data that will help researchers see how chemical space intersects with biological space, in other words, what chemical properties make a molecule biologically active. Ultimately, the goal is to generate modulators, both activator and repressors, for each individual function of every single human protein. "That's it," says Schreiber. "If you've got that, you're pretty much done." Maybe 500 to 5,000 such compounds already exist. If 500,000 compounds are needed to cover all protein functions, and you already have 5,000, you're one percent of the way there, says Schreiber. "That's the equivalent of year three of the Human Genome Project."

For Schreiber, whose life's work has revolved around synthesis and integration, things are really starting to come together. On the chemistry-biology-medicine front, his postdocs and fellows are using chemical genetics to study cancer and metabolic disease. And, his separate locations will soon be physically united; In January, the ICCB team will join the Broad people in an interim space near MIT. Then everyone will move to the new Broad building at 7 Cambridge Center, currently the Whitehead parking lot.

In the meantime, juggling these endeavors and disciplines and locations keeps Schreiber plenty busy. As of mid-August, he had not yet been out to his summer house in Gloucester, a quaint, not-yet-touristy New England fishing town. Instead, Schreiber is spending his nonmeeting hours editing manuscripts in his office as tropical fish swim lazily across his 23-inch flat-screen computer monitor.

Schreiber recently stepped down as chair of his department, so at least that gives him a bit more time. "It's been joyous," he says wistfully. But who knows what he's really thinking. Perhaps he's imagining a quiet dinner in a cottage near the ocean. Or perhaps he's envisioning the day when half a million molecules will allow chemists and biologists to talk to cells and get some answers. ⊗

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