

## Shane Crotty Has a Hot Paper and a New Biography, Too

Science may speak with the authority of age, but it often moves on the shoulders of youth. Shane Crotty, a 26-year-old HHMI predoctoral fellow at the University of California, San Francisco (UCSF), has been moving quickly. He just had a paper published in *Nature Medicine* on the discovery of a new mechanism that overwhelms RNA viruses, and his biography of noted biologist David Baltimore is about to be published. Says Crotty, “It’s all very cool.”

It also was, he concedes, all very unpredictable. As the son of an Air Force officer, Crotty loved to “hang out in nature,” yet it was the rhythms and atmosphere of the outdoors as much as its biology that interested him. While growing up in 11 different places from Guam to New Mexico did nurture his appreciation for natural diversity, it did not create an irresistible attraction to fluorescent lighting and microscopes. Indeed, he might have become a writer had not a persistent high school chemistry teacher insisted that Crotty apply for the National Science Foundation’s Young Scholars Program.

“I blew it off at first,” Crotty recalls, preferring the challenges of his creative-writing elective. In what would be the first of several turning points in his young life, however, Crotty not only applied to and qualified for the program, he also landed a job studying color vision in sharks in a laboratory on Catalina Island, off the coast of southern California. “I didn’t accomplish anything,” he recalls, “but I did learn what that life was like.” And, he says, smiling at the more spartan research space of a UCSF graduate student, “the lab on the island was gorgeous.”

The chance to do research right away lured him to the Massachusetts Institute of Technology in 1992. Armed with his now twin passions—writing and biology—he enrolled as a double major. For

some late adolescents, the pairing might have fueled a high-octane self-absorption. For the gregarious Crotty, it only propelled his curiosity about life writ both large and small. And what life loomed larger than that of Nobel laureate David Baltimore, the current president of the California Institute of Technology, who was vindicated in a decade-long drama concerning allegations of scientific fraud? “I was taking a biography class and was told to write a 25-page assignment on a serious topic,” Crotty recalls. “Since the core of Western literature has always been conflict, I settled on the careers of E.O. Wilson [the evolutionary biologist at Harvard University] and David Baltimore.” Both were accessible from Crotty’s Boston base, but Wilson was on sabbatical, so it was Baltimore who got the call—or, more correctly, the e-mail.

Crotty’s scant knowledge of his chosen subject did not deter him. The interview with Baltimore went well, and using the wealth of information in MIT’s archives for background, Crotty’s 25-page paper tripled in size. It then doubled again when, after nine more interviews, Crotty had enough primary material to make it

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his thesis. Good fortune and good strategy then converged. Crotty chose Alan Lightman, author of *Einstein’s Dream*, as his thesis adviser. “Lightman had been the only person at MIT to give me a B, so I figured I had something to learn from him,” Crotty says. In the end, that something included how to secure a publishing contract.

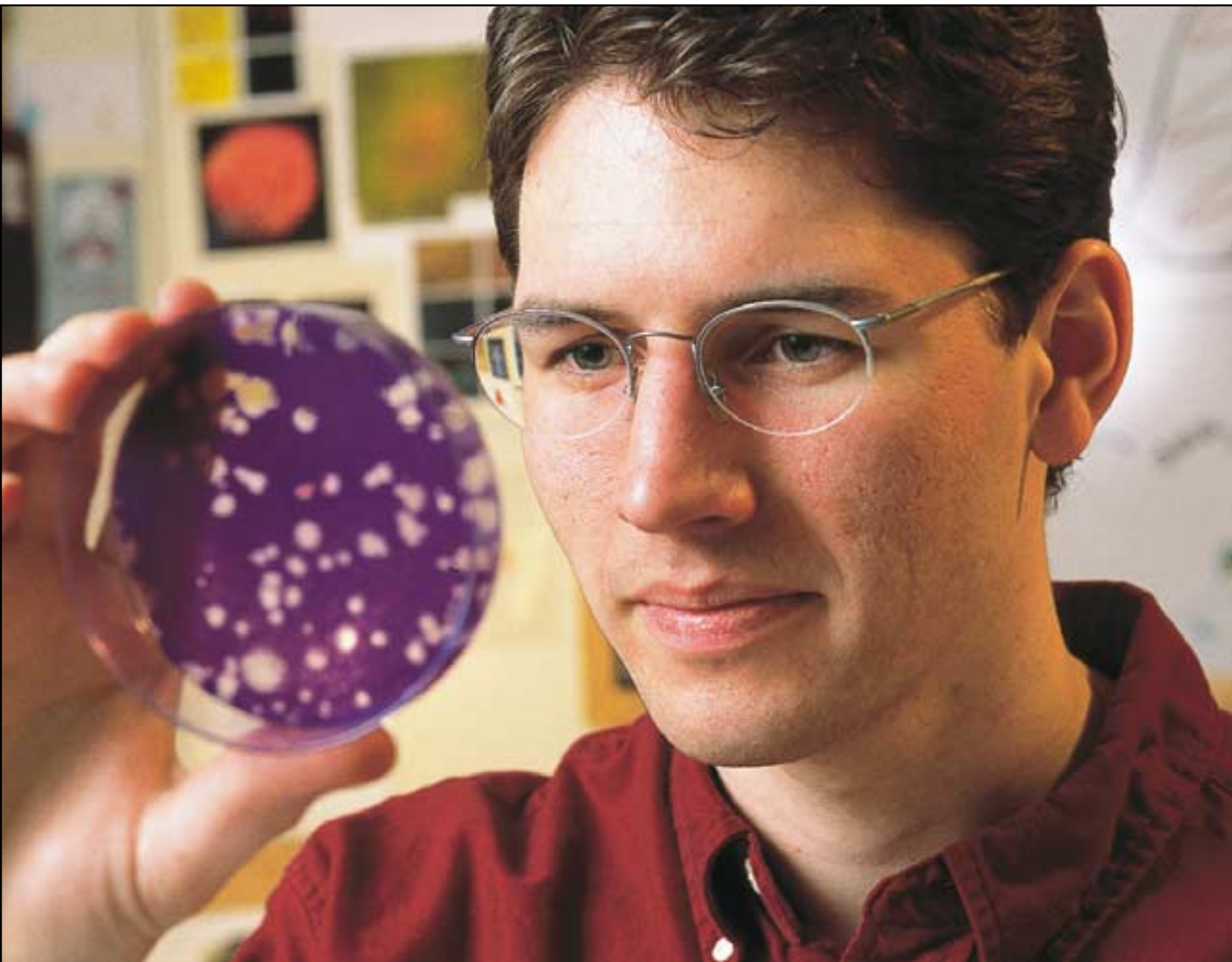
The chance to probe Baltimore’s life and mind did not stir Crotty to become

active himself in applying basic science to public health crises such as the AIDS pandemic. Instead, he found that he enjoyed the more reductionist, less stressful side of biology. Somewhat to his surprise, he also had discovered that he liked to teach. So when the opportunity arose to capture, coordinate, write and wrestle into shape the information for an online biology teaching course, a “hyper-textbook,” Crotty was its driving force. In this, too, he played the role of science writer, honing the same skills for explaining everything from vaccines to viruses that would later win him the praises of book reviewers.

Looking back, the Kurt Vonnegut and Tom Wolfe fan admits that his emerging profile cast no clinical shadows. “I knew I wanted to be an academic scientist,” Crotty says. “And when I came to UCSF in 1996, I thought I wanted to study protein evolution.” Perhaps he would have stayed this course had not a virology course taught by HHMI investigator Donald Ganem and former Baltimore postdoc Raul Andino intervened. “I was polishing the book at that point and wanted to make sure what I was saying about viruses was correct,” Crotty says.

That mundane task soon yielded to an epiphany: “I realized that I liked viruses. They are incredibly clever and they break the standard rules of biology.” As he learned more about their strange parasitic behavior, the tricks they use to invade a host cell and take over its reproductive machinery and the novel health problems they pose, Crotty also realized something else. Outwitting such clever adversaries was an appealing scientific problem in its own right, but the chance to prevent disease offered satisfaction of a different sort. “I decided I would need something to get me out of bed in the morning.”

Hepatitis C sufferers may one day be glad he made that choice. For as part of a collaboration with Andino and Pennsylvania State University researcher Craig Cameron, Crotty helped determine how ribavirin, a drug used to treat the disease, works—and why it sometimes doesn’t. “Until now,” Crotty says, “we didn’t have a good idea why only one-third of patients responded to treatment.” One theory suggested that



BARBARA RIESS

*Shane Crotty is pursuing his twin passions—writing and virology.*

ribavirin killed RNA viruses, those that use RNA as their genetic material, by blocking enzyme synthesis. “But this wasn’t convincing. We knew that ribavirin impeded nucleotide enzymes without any antiviral effect.” Crotty and his colleagues also knew, however, that a ribavirin nucleotide so closely resembles a viral nucleotide that it can trick the virus into mistakenly inserting ribavirin into newly formed copies of its RNA genome.

What happened next was a surprise. As Crotty added more and more drug to

viral cultures in petri dishes, more and more viral mutations occurred. Normally, viruses use their ability to mutate as a way to survive. Ribavirin turned this tactic on its head, forcing the viruses to mutate so often that they would self-destruct. Called error catastrophe, the mechanism is not new, but it had never before been demonstrated in an available drug. Not surprisingly, two pharmaceutical companies are already using the results to develop a more effective form of ribavirin, which also is used to treat severe respiratory syncytial virus infections in newborns. Equally important, the findings might help researchers discover

drugs that use mutagenesis as a strategy to destroy other RNA viruses.

The importance of the work is not lost on Crotty, who, lifting samples from his array of petri dishes, proudly traces the viral death march. This was cool stuff, he admits. “But,” he adds, “I have so much more to learn, particularly about immunology.” The next stop on that quest is the laboratory of viral immunology expert Rafi Ahmed at Emory University. “You know, we don’t really know how to make good vaccines,” Crotty says. If past is prelude, Crotty may help close the gap, smiling all the way. **H**

*Jeff Miller*