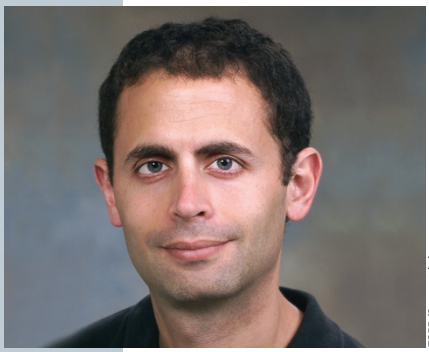
THE AUTHOR FILE

Benjamin F. Cravatt

Building an approach to quantify chinks in a protein's armor.

Biochemist Benjamin Cravatt loves the author J.R.R. Tolkien, experimental and computational problem-solving, and linking chemistry and biology. As the chair of the department of chemical physiology at The Scripps Research Institute (TSRI) in La Jolla, California, he seeks to understand the physiological role of enzymes and develops techniques to study them. In his most recent work, he sought to quantitatively characterize the locations that render a protein vulnerable.



TSRI/Cravatt lab

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As Cravatt explains, "thousands of arrows could hit the dragon Smaug and do zero damage." He is referring to the fire-breathing dragon in the novel *The Hobbit*. Evil and tough, Smaug was clad in iron scales. He protected his underbelly with diamonds and gems. But the hobbit Bilbo Baggins detected a missing scale near the monster's heart. And a single arrow to that vulnerable spot brought the dragon down, says Cravatt. In his work on proteins, "we are attempting to find these places of heightened sensitivity—relevant for both signaling and pathology."

Cravatt harnesses mass spectrometry to find and count sites where proteins are modified by chemically reactive molecules called electrophiles. Inflammation leads to these molecules, which stick to proteins and change their function. Electrophiles can also serve as signals that help cells cope with stressors. "Like many productive signals, however, in excess they can hurt the cell," he says.

Cysteine, one of the types of amino acid in proteins, is vulnerable to electrophilic modification. Cravatt created a probe that binds to cysteine only if it is not already besieged by an electrophile. Mass spectrometry can then detect the difference between unblocked cysteines and those under attack.

Although other labs have inventoried electrophile-protein interactions, their quantitative evaluation has proven elusive, says Cravatt. The challenge here was to quantify thousands of reactions between cysteines and electrophiles in parallel and in 'native', unpurified and complex systems.

Cravatt's approach expands a method he previously developed called activity-based protein profiling. In this case, profiling the reactivity of electrophiles against more than 1,000 cysteines required a combination of experimental and computational approaches.

To advance work in the lab, Cravatt also applies an athletic method. "I get many of my best ideas while running, which is my alone time," he says. "I usually run in the middle of the day to clear my head."

Cravatt is "just tireless," says Harvard University biochemist Alan Saghatelian, who has known Cravatt for 15 years. He worked next to Cravatt's lab and later joined it as a post-doctoral fellow. "No matter how tough the problem, Ben will push as hard on the thousandth day of the project as he did on the first." And Cravatt attracts people with the same attitude. "Being part of his group reminds me of the 2013 Red Sox without the beards," Saghatelian says, referring in jest to the heavily bearded and driven baseball team that won the World Series last year.

Cravatt completed his PhD at TSRI and landed a faculty post without a post-doctoral fellowship. He has received numerous awards for his work. Helping him get his start, he says, was his molecular characterization of the endocannabinoid-metabolizing enzyme FAAH. His mentor at the time, Richard Lerner, then TSRI president, saw this discovery as the launching point for Cravatt's lab. "Very few mentors would have been this generous," Cravatt says.

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His numerous collaborations with pharma and biotech firms begin with mutual research interest on a specific topic, and participation in the science by both sides. Cravatt believes that interactions with pharma solely as financiers are less likely to succeed. "Also, one cannot force these relationships," he says. "Genuine scientific interest must come from both groups for success."

To him, integrating chemistry and biology means using the principles and methods of chemistry—synthetic, analytical and computational—to solve life sciences problems, especially those in which biological techniques fail, he says.

Cravatt believes that chemical biologists must embrace how complex biological systems are. "While this complexity may mean that we never understand every single molecular component or reaction mechanism in a cell or organism, we can still learn a tremendous amount about life processes and how to treat their dysfunction."

Vivien Marx

Wang, C. *et al.* A chemoproteomic platform to quantitatively map targets of lipid-derived electrophiles. *Nat. Methods* **11**, 78–84 (2014).