RETROSPECTIVE

Roger Y. Tsien (1952–2016)

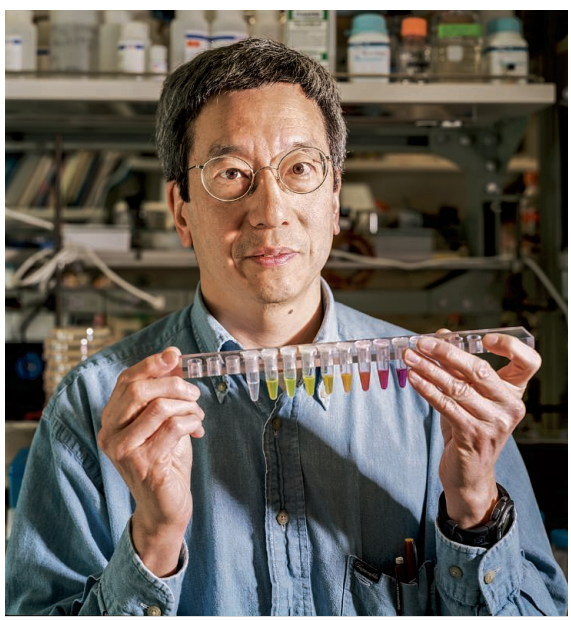
An exceptionally creative scientist shed light (of many colors) on biological mysteries

By **Stephen J. Lippard**

The world of biological chemistry lost one of its most creative pioneers when Roger Y. Tsien died on 24 August 2016 at the age of 64 while biking on a challenging trail in Eugene, Oregon, where he and his wife Wendy had their home. Tsien, who shared the 2008 Nobel Prize in Chemistry, was a professor in the Departments of Pharmacology and of Chemistry and Biochemistry at the University of California, San Diego (UCSD). Born in New York City and raised in Livingston, New Jersey, Roger had special talents that were manifested early—he won the Westinghouse Science Talent Search at age 16 for his original research project, "Bridging in Transition Metal Thiocyanate Complexes." After graduating summa cum laude from Harvard College with a bachelor's degree in chemistry and physics, he studied at Cambridge University, receiving a Ph.D. in physiology in 1977 before joining the faculties of the University of California (UC), Berkeley, and, 7 years later, UCSD, where he spent most of his career. His thesis on the design and use of organic tools in cellular physiology set him on a course to investigate the chemistry of the brain.

I first met Roger in the late 1960s when he appeared at my office in the Chemistry Department of Columbia University as a high school senior trying to decide between Columbia and Harvard. It was immediately obvious that he was a very special person—bright, inquisitive, personable and, above all, determined. His choice of Harvard, I learned recently from Wendy, may have been influenced by his passion for combining science with music. Roger often walked wearing earbuds, deep in thought. He was also an avid photographer, a hobby that paralleled one of his principal scientific interests—using light to image biological function. Art and music were a huge part of his life. We reconnected in 1998, when I took a sabbatical in his lab at UCSD to steer my own research program toward "metalloneurochemistry." Roger's work on imaging calcium in biology provided powerful tools and tactics that I needed to learn. I was delighted that he found it "compelling" to host someone who had reached out to him when he was in high school to offer advice on how best to fulfill his own career ambition to use chemistry to reveal biology.

The Tsien lab at UCSD was a spectacular place. As a toolmaker, Roger was unparalleled, producing molecule after molecule that provided the means to unveil many mysterious intricacies of cellular processes. An early success was Fura-2, a fluorescent sensor for imaging Ca^{2+} in cells. Roger's seminal paper describing this and closely related Ca^{2+} sensors has been cited over 20,000 times. Additional Roger Tsien creations for probing calcium biology included chelators, like BAPTA, that bind to and prohibit the ion from performing its functions; acetoxymethyl esters that enable fluorescent sensors to enter cells in cases where a membrane is impenetrable; and so-called "caged" compounds, synthetic constructs that turn on illumination after photochemical cleavage of a bond to release the active species. This tool allows control of the timing, location, and signal intensity of a probe.



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Roger had an encyclopedic knowledge of the literature, which enabled him to design synthetic routes to molecules with minimal sequential steps. After my sabbatical at UCSD, my lab at the Massachusetts Institute of Technology embarked on a program to image mobile zinc in the central nervous system. When our first construct (Zinpyr-2), prepared in a multistep synthesis, responded well to zinc in the test tube, I called Roger to enlist his assistance to image zinc in live cells. He was very excited to learn about this result (I could imagine him waving his hands in characteristic fashion as he spoke to me on the phone) because, for a very different reason, he had independently prepared a closely related compound that behaved similarly, in a single step! We published the results together and, needless to say, his Zinpyr-1 became the "go-to" molecule for imaging mobile zinc in the early days of our explorations.

Roger's work on calcium signaling was worthy of the Nobel Prize, and many were surprised when the announcement came from Stockholm that he received it for work on green fluorescent proteins (GFPs). These amazing proteins, discovered by Osamu Shimomura in the jellyfish *Aequorea victoria*, give off a green fluorescence upon irradiation with blue to ultraviolet light and could be genetically encoded into animals to explore biological phenomena, as demonstrated by Martin Chalfie. Roger, who referred to GFP as "dim, fickle, and spectrally impure" modified one of the amino acids at a key position in GFP to produce enhanced GFP, which shone more brightly, and then engaged in an extensive program to mutate amino acids across the 11-stranded β barrel of the protein to produce versions that fluoresced in colors across the rainbow. Shimomura, Chalfie, and Tsien shared the Nobel Prize for their work.

Toward the end of his all too short life, Roger became interested in contributing to medicine and devised a means to color-code nerve cells to enable surgeons to avoid cutting them during operations—fluorescence-guided surgery. He came up with ideas, and devised ways to test them, for investigating where long-term memories are stored in the brain. Early detection of cancer was also of interest, and he viewed cancer-illuminating probes (one is currently in clinical trials) as more important than nerve-highlighters.

One can only wonder what creative inventions were taken from us by the untimely loss of Roger Tsien, a true giant of chemistry and biology. He is survived by Wendy; two brothers, Richard and Louis; and stepson, Max Rink. We miss him greatly. ■

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