THE AUTHOR FILE

Samie Jaffrey

RNA sensors lend proteins both specific and bright signals.

Like neon signs that flash to a nighttime driver on a long-haul trip, fluorescent sensors light up a cell's dark landscape. Green fluorescent protein (GFP) lights up proteins, but RNA—so important for protein manufacture—lacked a neon sign until 2011 when Jaffrey and his team developed Spinach, an RNA-based fluorescent probe. Now he and his team show how Spinach can visually reveal not just small metabolites, but also a targeted protein in live bacteria. "The fluorescent proteins are often named after fruits, so we name our fluorescent RNAs after vegetables," says Jaffrey who is on the faculty at Cornell University's Weill Medical College.

Cornell University Weill Medical College

Spinach is an aptamer with a particular sequence, to which a fluorophore can bind and then switch on. It is common to engineer proteins as sensors, he says, but "it is always kind of amazing that an RNA can be engineered so readily to have user-defined functions."

In creating this sensor, Jaffrey purchased and synthesized hundreds of small molecules. But they either had background fluorescence or killed cells. He realized he needed to synthesize a switchable molecule and digging through the literature discovered that GFP's fluorophore only lights up when it is bound to GFP. Transferring that idea to RNA world, he showed that Spinach can handle the same job as GFP and switch on a fluorophore.

In future applications, these sensors could show spikes and dips in protein levels when a cell becomes diseased. Its readout could also help optimize a pharmaceutical process with bacteria producing recombinant proteins, he says.

RNA's habit of misfolding is one of many reasons why sensors fail. Getting past the hurdles in tool development is like the math puzzles that Jaffrey enjoys. "You sometimes have to think out of the box," he says. He teaches a course called 'critical analysis' to help others learn how to focus their energies as experiments inevitably serve up decision forks.

Dogged pursuit characterizes Jaffrey's approach both now and in the past. He created a way to detect S-nitrosylated proteins, which was a dramatic advance, says his graduate advisor neuroscientist Solomon Snyder at Johns Hopkins University. Snyder originally thought Jaffrey's approach to the challenge was flawed. "He disregarded my counsel and soon came up with his classic procedure," says Snyder.

Jaffrey grew up near the US National Institutes of Health campus and always liked science and engineering. He took part in computer science programming competitions against other junior high school students. The seed of his interest in design principles and quantitative measures was planted during his undergraduate years in biology at the Massachusetts Institute of Technology.

Jaffrey did his MD-PhD and postdoc at Johns Hopkins University. He set out to be a physician but shifted to medically relevant protein chemistry and chemical biology. Snyder says he is not only talented and "fiercely independent" but also someone who "loves all science, reveling in the creative act of discovery with no regard to credit." In collaborative studies wherein Jaffrey did 90% of the work, he insisted a labmate be the study's first author.

Jaffrey was "an inveterate night owl," says Snyder, who adjusted his schedule to be able to meet with Jaffrey in the evening before he did his typical 18 hours of research. "I worried that he would never be able to handle the medical student clinical routine of 7 a.m. to 6 p.m. to which he would return after completing his thesis research," he says. "Samie managed just fine; he can accommodate to any challenge."

"You sometimes have to think out of the box."

Now in New York City, Jaffrey says he thrives on the city's energy with many young people in art, theater and fashion striving to create what no one has yet seen. "I think being in an environment where people are pushing the limits in other areas, it inspires you to try to be similarly creative when you are designing new tools and approaches," he says.

Jaffrey's going-away gift in the Snyder laboratory was a collection of tickets to New York Yankees versus Baltimore Orioles baseball games. Although Jaffrey adores the Yankees, he roots for the underdog, the Baltimore Orioles, who break fans' hearts with their performance. But they are making a comeback, he says, noting a parallel to science. He likes papers in which simple and elegant approaches lead to major discoveries despite a small budget, he says. "It's like rooting for the underdog."

Vivien Marx

Song, W., Strack, R.L. & Jaffrey, S.R. Imaging bacterial protein expression using genetically encoded RNA sensors. *Nat. Methods* **10**, 873–875 (2013).