THE AUTHOR FILE

Yamuna Krishnan

A probe for a journey into bubbles and why it's good to be both inventor and discoverer.

Blowing bubbles is a way to think out loud and it captures the childlike wonder she cultivates in her research, says University of Chicago chemist Yamuna Krishnan. Bubbles look like lysosomes, a recycling unit in the cell and a structure she has been studying and finding ways to image. The only way to quantify calcium inside a lysosome, and learn how it triggers cellular signaling, is to get inside this acidic bubble and deliver a readout under various conditions. That's hard.

Traditional probes are pH sensitive and one cannot see whether a fluorescence signal is due to a change in pH or calcium. But CalipHluor can. That's Krishnan's new DNA-based fluorescent reporter, a nanodevice. It's a calcium sensor and a pH sensor, and it's equipped with small molecules and fluorescent dyes. Because DNA is the device's basic construction unit, the lysosome readily takes it in. Sensors typically tell an experimenter "I'm here," says Krishnan, but not what is taking place at that location. CalipHluor can target a location and report activity. "Now you've been able to give detection chemistry an address inside the cell," she says. A big challenge was deconvoluting the two factors, pH and calcium, that contribute to the signal readout. The team built a detailed, dynamic map of the lysosome, on the basis of how the probe's affinity changes as pH changes. This path to addressing "is it acid or is it calcium" emerged in discussion with her two graduate students, Kasturi Chakraborty and Anand Saminathan. "Had you taken any one of us out of the room, we would not have been able to get this calcium heat map," says Krishnan. CalipHluor can help scientists explore how signaling begins, a process called calcium-induced calcium release. The lysosome contains micromolar concentrations of calcium. It travels near the endoplasmic reticulum (ER), a veritable bank of calcium. As it passes the ER, the lysosome acts a little like "smelling salts," says Krishnan, and releases some calcium, which leads the ER to massively release calcium. Signaling begins.

To date, labs have only been able to quantify calcium leaking out of the lysosome and lacked good ways to learn, for example, how calcium gets into the lysosome. That's important to study given that lysosomal misregulation is implicated in a number of neurodegenerative diseases. Krishnan and her team used CalipHluor to get a quantitative readout on how a Parkinson's disease risk gene affects the way calcium is imported into the lysosome.

Yamuna Krishnan

After Krishnan received her PhD in organic chemistry at the Indian Institute of Science in Bangalore, she completed a postdoctoral fellowship with Shankar Balasubramanian at the University of Cambridge. She joined the faculty and earned tenure at the Bangalore National Centre for Biological Sciences (NCBS) and switched to the University of Chicago in 2014. During her eight years at NCBS, Krishnan was surrounded by biologists. As she strove to develop solutions for them, she explored how to make something they would use. To do so, "you have to literally be in a biologist's head," she says. Krishnan built sensors, a pH sensor among them, and worked out how to use DNA as construction material and to see how well cells fared after taking in DNA-based sensors. The experiments worked. "Chemists are actually inventors, most biologists are discoverers," she says. "I think it's important people should try and do both." She has recently developed a device to sense pH and chloride. Taken together, the probe family presents a way to quantitatively capture what a cell is doing, she says. "The numbers will basically be a readout of the metabolic status of your cells," she says. The probes could be used to 'chemotype' a patient's cells, such as to get a quantitative, personalized readout related to how someone is faring on a drug, or potential drug, to treat a neurodegenerative condition. This potential has led her to launch a company, Esya, which is Sanskrit for medically probing or examining something or someone.

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As a postdoc, Krishnan showed enormous drive and creative energy, and kept everyone on their toes, "including me," says Balasubramanian. "I'm so proud of the great progress and success she has shown in her independent research," he says. He's happy to see she's now also on a mission to exploit her creativity and fundamental science to make a difference in the world. "She is without doubt a scientist to continue to watch out for over the next decade," he says. In her spare time, Krishnan enjoys pilates and yoga, which is a way to speak positively to oneself. "Don't give up and you'll try tomorrow," she says of yoga's message to many areas of her life, including science. Cooking is another favorite pastime. "I make a mean chicken curry," she says, laughing about how her pastimes advance female stereotypes. In the lab, she encourages positive incentives. Good results are celebrated, for example, with a meal, she says. "I think we need to celebrate our little successes." ❐

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Published online: 10 December 2018
https://doi.org/10.1038/s41592-018-0263-0

References

Narayanaswamy, H. et al. A pH-correctable, DNA-based fluorescent reporter for organellar calcium. *Nat. Methods* https://doi.org/10.1038/s41592-018-0232-7 (2019).