THE AUTHOR FILE

Min Zhuang

Swimming to a new way of decoding messages at the cell membrane.

From her life science building at ShanghaiTech University, where she joined the faculty in 2014, biochemist Min Zhuang sees the logos of well-known pharmaceutical companies glowing in the evening sky. “They all have their R&D centers located in this area,” she says. Zhangjiang Hi-Tech Park, the nearby technology and biopharma hub, is one place where her students could apply their newly formed skills. In her lab, she melds biochemistry, proteomics and, of late, cell biology to follow the pastimes of membrane proteins and the proteins they interact with, such as in signaling events or when a ligand docks to a membrane protein.

Many proteins react quite transiently with one another, says Zhuang, which makes detection hard. And the interaction might not be their first; perhaps, “actually, they know each other,” she says. She wanted a better way to study these encounters. “Let’s find out who knows who.”

“Imagine the Great Wall is the cell surface membrane,” says Zhuang. Membrane proteins are like sentries along the Great Wall. A messenger arrives with information such as, “enemy is coming.” The sentry passes the message on. “We want to find out who contacted this ‘soldier’ on the Great Wall and delivered the message?” Framed in cellular terms, this is a protein–protein interaction that can be studied with her new tagging approach PUP-IT, or pupylation-based interaction tagging.

PUP-IT applies a bacterial protein called prokaryotic ubiquitin-like protein, or Pup, and its conjugating system. The gene that encodes Pup ligase, *pafA*, is genetically fused to a bait protein with a short amino acid linker. When interaction with a protein occurs, Pup gets attached to the ‘prey’. This marked prey can be identified with mass spectrometry, revealing ‘who’ is interacting with the bait protein. Zhuang has used PUP-IT to look at a pathway involved in T cell activation, and also for following an extracellular cytokine.

Another tagger, APEX, is faster, says Zhuang. Other methods are better at taking a “snapshot” of brief cellular events. Both APEX and the method BioID involve

Min Zhuang (Photo: W. Zhang)

the external addition of small molecules, which starts a controlled reaction when these are added to the cell culture media, where they diffuse into cells, labeling them. For experiments requiring precise reaction control, these methods might be best, she says. But for work with live neurons or other cells, with tissues or organisms such as *Caenorhabditis elegans*, or for animal experiments, her system might be better at avoiding cell harm or stress. With PUP-IT, the tag is genetically encoded, which also opens up the possibility of genetically inducible experimental designs.

Sequence alignment revealed that *pafA* is highly conserved across many bacterial species, indicating that the Pup system is perhaps one of several possible conjugation systems. Using PUP-IT, Zhuang plans to keep exploring E3 ubiquitin ligases, or E3s. She is interested in an E3 subfamily that has transmembrane regions; they might be anchored on the surface of a cell or organelle. Little is known about the substrates that regulate E3, but PUP-IT might help change that.

“Min is a passionate, bold, and creative scientist,” says Jim Wells, her postdoctoral fellowship advisor at the University of California at San Francisco (UCSF). She pioneered the development of NEDDylator, a first-generation proximity tagger based on the ubiquitin system, to find partners of proteins and small molecules. Expanding this work to pupylation is “remarkable and very useful,” he says.

After graduating from Nanjing University, Zhuang left China to do her PhD research in the lab of Howard Hughes Medical Institute investigator Brenda Schulman, a structural biologist at St. Jude Children’s Research Hospital. There, Zhuang used X-ray crystallography to study protein structure. When she left China for St. Jude’s 15 years ago, she had experienced little of the wider research community. It was her very first flight. Nowadays, students in China are exposed to much international research. Visitors give talks at ShanghaiTech, and her students take part in summer schools and exchange programs at several US universities. One of her students is set to leave for graduate school at Washington University. Zhuang had encouraged her to apply. Among the ShanghaiTech faculty are a number of returnees. “We share our life experience in the US,” she says. Her student will be better prepared for her US chapter than she herself was, says Zhuang.

“We learned together and we learned from each other.”

As a postdoctoral fellow in Wells’s lab, she applied techniques from cell biology to chemistry. “We learned together and we learned from each other,” she says. She took that trans-disciplinary approach when she returned to China. But she could not, however, bring the hiking and other outdoor sports she enjoyed in California. “There’s nothing around that can be called a mountain,” she says. In San Francisco, she envied surfers and swimmers. At the time she didn’t know how to swim. These days Zhuang is taking a swimming class. Soon she will be able to try aquatic sports that “can open up a different door to myself,” she says. □

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Reference

Liu, Q. et al. A proximity-tagging system to identify membrane protein–protein interactions. *Nat. Methods* <https://doi.org/10.1038/s41592-018-0100-5> (2018).