Making sense of nonsense

Ryan Mehl is on a mission to make unnatural amino acids part of the natural order at the Unnatural Protein Facility.

When the first mass spectrometry, NMR and microscopy centers were launched at universities and institutes around the world, the impact these and similar facilities would have on scientific research was hard to predict. Though researchers still needed to understand when and how each technique might be suitably employed to advance their studies, dedicated center experts could more effectively advise and instruct researchers in the techniques, help troubleshoot problems that arose and, in some cases, collect data on behalf of the scientist. These experts often also used the facilities themselves to advance the techniques, further expanding the power and the generality of the approach. Ryan Mehl has created a welcome addition to these established centers in the first Unnatural Protein Facility (http://mehl.science.oregonstate.edu/), located at Oregon State University (OSU), with the goal of putting proteins modified with spectroscopic probes, crosslinking groups, post-translational modifications and many other amino acid variations in the hands of scientists across the world.

Mehl recalls that when he arrived for his postdoctoral position with Peter Schultz at The Scripps Research Institute, the first paper describing the incorporation of an unnatural amino acid using a nonsense codon in *E. coli* had just been published and much of the lab's focus was on expanding the technology. Coming from a background in mechanistic enzymology, Mehl was interested in developing the method but even more curious as to how proteins labeled with unnatural amino acids could be broadly used to advance research. Of course, he wasn't the only one interested in these potential applications: Schultz estimates that his lab "has given these tools to a huge number of labs—two requests a week for years." Many vectors have also been deposited in Addgene, a nonprofit plasmid repository, to facilitate uptake.

Though this material transfer can work well for labs that are already familiar with molecular biology techniques, Mehl thought the methodology could also be extremely valuable for scientists with more diverse backgrounds. From his perspective, "the tools give everyone that power of being able to make a chemically defined compound that they can then characterize in a very specific way." This technique thus allows scientists to address one of the major challenges Mehl sees in studying proteins: "We know that many protein modifications are present as heterogeneous mixtures with different physiological effects. It's very hard to decipher what's happening unless you can make the homogeneous proteins and study them individually." Although unnatural amino acid labeling can therefore provide constructs to answer research questions in unique ways, Mehl worried that the technology had become so advanced that new users could be shut out entirely. Instead, he envisioned a dedicated facility that could both serve and train the community, opening the technique up to a broader group.

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In January 2012, the Unnatural Protein Facility was officially established by the OSU Environmental Health Sciences Center funded by the NIEHS. The facility directly serves users in three ways: First, it provides advice about experimental design to scientists trying to get the technology up and running in their own labs. Second, the facility will also construct optimized plasmids meant to remove obstacles in protein production, or even express a batch of labeled protein for preliminary experiments or to validate that the construct is viable. Indeed, Mehl suggests that seeing the desired band on a gel can go a long way towards building confidence in a project, including for obtaining funding for further studies. Finally, scientists can also visit the facility for hands-on training and troubleshooting. P. Shing Ho, a professor of biochemistry and molecular biology at Colorado State University studying halogenated proteins, thought it was important to send one of his students to the facility. In addition to understanding "the methods and strategies that are directly associated with his thesis project," Ho suspected that "once the student understood the power and the limitations of the technique, he could better design his experiments to take maximum advantage of unnatural amino acids.

In addition to direct interactions with the community, the facility is curating a repository of methodologies that will allow users to make good choices about which amino acids might be most appropriate for a particular application or whether improved strategies have replaced old methods. Mehl also intends for the center to continue to make improvements in the technology, both to make it simpler and more robust and to explore further extensions of the technique. Jason Chin, one of Mehl's colleagues from the Schultz lab and now head of the Centre for Chemical and Synthetic Biology at the Medical Research Council Laboratory of Molecular Biology in Cambridge, UK, similarly suspects that "as experience grows within the facility, this may feed back into general improvements in the approach."

Ho describes the expertise provided by the Unnatural Protein Facility as invaluable, saying "it would be difficult, if not impossible, for us to pursue the studies using unnatural amino acids without the facility." Angela Gronenborn, a professor at the University of Pittsburgh studying labeled proteins by NMR, agrees that Mehl "has made the use of unnatural amino acids in proteins a reality for scientists like me." Weihong Qiu, an assistant professor in the physics department at OSU studying motor protein function, says he would have invested the time to establish the technique on his own, but the increased speed "allows us to think more creatively and to go after more challenging research problems." Chin agrees that "the ability to provide modified proteins will allow researchers to focus on the intellectual questions of what to do with a particular modification, and less on how to make their particular modified protein." By all accounts, the new Unnatural Protein Facility is helping protein modifications come more naturally. ■

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