

THE AUTHOR FILE

John Yates III

Digging deep into proteomes

As a biology undergraduate at the University of Maine in Orono, he was “instantly hooked” when he first saw a mass spectrometer, says John Yates III from The Scripps Research Institute. Seeing how the instrument identified molecules “was just pretty cool.” At a time when computers filled entire rooms, he was also enamored with the instrument’s data-processing abilities.

For his graduate studies, Yates decided to apply mass spectrometry to proteins. After contacting Don Hunt at the University of Virginia about possibilities, he received a handwritten invitation in reply, launching Yates’s proteomics career, which has included the development of widely used tools and methods.

Yates and his colleagues have now adapted classic enzyme biochemistry for a method that digs deeper into proteomes, as the method’s name, DigDeAPr, implies.

The work is mainly the brainchild of postdoctoral fellow Bryan Fonslow, Yates says. Together they had been exploring how to optimize protein digestion, in which proteins are broken down into peptides to be analyzed in the mass spectrometer. But digestion enzymes work inefficiently when protein abundance falls below a critical level, and low-abundance proteins can escape analysis.

The new approach lets researchers whittle away at the more abundant proteins in a sample to bring signals from lower-abundance proteins to the fore. After being digested into peptides, the high-abundance proteins are filtered out, allowing the researchers to focus on undigested low-abundance proteins. Yates hopes his method can now help other scientists. “I think people will be able to take this and innovate on top of it and make it better,” he says. “I’ve become very intrigued with the concept of innovation,” he adds. His reading list of late includes Jon Gertner’s *The Idea Factory*, which is a history of Bell Laboratories, and Steven Johnson’s *Where Good Ideas Come From: The Natural History of Innovation*.

Because innovation calls for trying new approaches, he gives his mentees “a lot of slack in the lab.” But as he mentors, he balances the slack by averting research projects that could take too long to complete.



The Scripps Research Institute

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Yates has mentored over 70 scientists with a creative and collaborative style. “Perhaps the most important thing I learned from John was the value of building a multidisciplinary team in your own lab,” says former postdoc Michael Washburn, who now directs the proteomics center at the Stowers Institute for Medical Research. Yates encouraged Washburn and another postdoc, Dirk Wolters, to collaborate on a project started in his lab, which ultimately led to the development of multidimensional protein identification technology (MudPIT). The method advanced the way proteins in complex mixtures are identified, using a combination of multidimensional liquid chromatography and mass spectrometry.

Even as a graduate student, Yates saw the potential for mass spectrometry-enabled proteome analysis, but “you couldn’t interpret the data fast enough by hand.” Addressing that challenge, he and his team also developed the widely used software tool SEQUEST for mass spectrometry data analysis. Together, MudPIT and SEQUEST “unleashed the potential of tandem mass spectrometry.”

When he first used these tools on protein mixtures, mass spectrometers were not quite up to the task, he says. “We tried to do whatever we needed to do in order to solve our problems,” he says. “But we also bugged the manufacturers to improve their technologies to meet the need of this particular area.”

Over a decade ago, a manufacturer presented Yates with a peek at a mass spectrometer almost ready for the market. “The first question out of my mouth was: ‘Can you make it scan faster?’” he says. The instrument manufacturer took the question in stride, beginning an exchange that continues today. Yates greets new instruments with ever-new ideas for experiments, which come to him in the lab and while he’s running. After completing several half-marathons, he is considering a full marathon.

To foster a collaborative lab environment, he explicitly picks postdocs from many backgrounds, from molecular biology and analytical chemistry to theoretical physics. “There isn’t an experiment that you might want to do that somebody in the lab doesn’t know how to do,” he says. The lab atmosphere is also about consideration for others. “If somebody is careless with the mass spectrometer, that affects everybody,” he says. “Everybody has to take care of that ecosystem.”

Vivien Marx

Fonslow, B.R. *et al.* Digestion and depletion of abundant proteins improves proteomic coverage. *Nat. Methods* **10**, 54–56 (2013).

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