A chemistry pioneer works to improve a flawed test for a common cancer

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Kelleher says top-down proteomics provides a more comprehensive understanding of human proteins than bottom-up proteomics, which is both imprecise and incomplete. Credit: Northwestern University

DNA sequencing used to cost thousands of dollars. Now, you can pay $99 for a genetic screening, all without leaving your house.

"The genome was a wild frontier in the 90s, but ten years later, it

wasn't," says chemistry professor Neil Kelleher. "And that's because the technology caught up to the challenge of precise molecular readout."

Kelleher believes the world's achievements in genomics—specifically, mapping the human genome—can be a guide for the study of proteins, known as proteomics.

"The Human Genome Project was an incredible feat of gene mapping and sequencing," he says. "We're poised to do the same thing for proteins. We have to catalog the 1 billion proteins in the human body in order to build businesses, develop drugs, and detect cancer and other diseases with much greater efficiency."

Kelleher believes the establishment—and successful completion—of what he calls the "Human Proteome Project" would revolutionize our understanding of health and disease.

A better test for prostate cancer

The current PSA test demonstrates the need for precise mapping of our proteins, Kelleher says. The prostate-specific antigen—or PSA—test, is a blood test for prostate cancer. PSA is a protein produced by cells of the prostate gland.

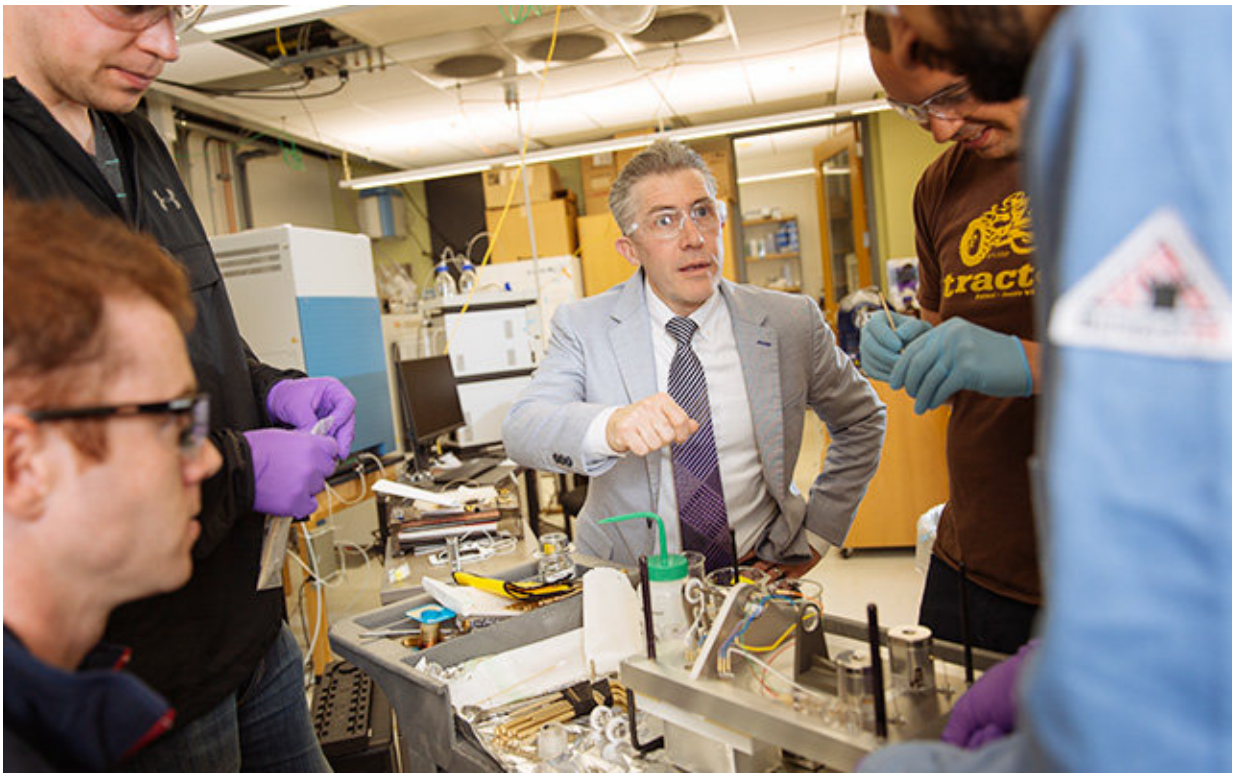
"This test isn't really great as a screen, and it has led to imprecision in diagnosis and early detection of cancer," Kelleher says. "Why is that? We believe it's because it's imprecise with regard to protein molecules."

PSA consists of over 100 unique protein molecules, and each must be measured precisely in order to fully understand the antigen. Conventional techniques have never managed that complexity, but Kelleher's lab has developed technology that could dramatically improve protein analysis, resulting in a more accurate test.

Top-down detection

"Our technique is called top-down proteomics," Kelleher says. "It's the analysis of proteins with complete molecular composition."

The difference between conventional technology, called bottom-up proteomics, and Kelleher's "top-down" method, is stark.



Kelleher with his team. Credit: Northwestern University

"Imagine trying to do a puzzle where you don't have the picture on the box of what it's supposed to be, and you're missing over half the pieces, and there are pieces of other puzzles in the box too," Kelleher says.

"That's bottom-up proteomics, and that's what the world uses."

By looking at whole proteins, Kelleher and his team understand "the picture on the box" and then make sure they have all the pieces.

When applied to the protein PSA, bottom-up and top-down proteomics look very different. In bottom-up proteomics, Kelleher says, scientists use an enzyme to break apart the PSA protein forms produced by the human body. About 80 percent of these broken-apart "shreds," as Kelleher cells them, will be lost in this process.

Top-down proteomics, by contrast, keeps those millions of protein molecules intact and separate, enabling scientists to analyze each and every protein molecule with "complete molecular specificity."

Kelleher knows that a better PSA test—one that is informed by the top-down method—could help make a case for mapping the entire human proteome. "Then we can use top-down techniques to create the definitive catalog of all the proteoforms in the human body," he says.

Once equipped with that catalog, Kelleher says, researchers would be able examine the proteoforms that comprise PSA more closely, determining which specific proteins, when elevated or otherwise modified, are the true harbingers of prostate cancer.

"If we map the 100 different flavors of the PSA protein, and measure them in their entirety as cancer progresses, we will be able to use protein states to detect cancer earlier and with greater confidence," he says.

Proteomic potential

The Kelleher lab, called Northwestern Proteomics, sees great potential in proteomics for early detection of other cancers and much more.

"We are very interested in detecting protein leakage out of tumors," Kelleher says. "This is something the world tried using bottom-up proteomics, and it didn't really work. But now, we have the best technology in the world right here, and we're taking that difficult measurement challenge head-on."

Northwestern Proteomics is uniquely positioned for this work, and Kelleher has grand goals for PSA and beyond. His team is already using top-down proteomics to predict the success of organ transplantation, and Kelleher is confident that top-down techniques could revolutionize our understanding – and treatment – of brain ailments like Alzheimer's disease and amyotrophic lateral sclerosis (ALS).

"Proteomics is not limited to oncology and cancer," Kelleher. "Our work has applications across all types of human disease because they all converge on proteins."

Provided by Northwestern University

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