ADVERTISEMENT FEATURE

A PROTEOMIC TOOL TO SEPARATE CLINICAL SIGNALS FROM A SEA OF NOISE

Clinically relevant proteins can be difficult to distinguish against a background of more abundant molecules. THE SOMASCAN® ASSAY OFFERS A WAY TO DECIPHER PROTEOMIC HEALTH SIGNATURES.

Blood doesn't lie, but sometimes it whispers — and it takes sensitive molecular methods to hear what it has to say. This is one of the biggest problems that clinical researchers face when attempting to detect disease-associated proteins in blood samples, but a new generation of high-throughput proteomic assays is making it possible to conduct such analyses with greater breadth and sensitivity.

The pathology of most diseases can be traced back to the influence of a handful of proteins, and the ability to identify the relevant molecules in blood or other biological samples can guide the development of more accurate diagnostics and effective drugs. But that signal can be drowned out by vast noise levels. The concentrations of individual proteins can vary by more than 10 orders of magnitude in the blood, meaning that one molecule might be billions of times scarcer than another in the same sample.

Antoine Dufour, an inflammatory disease researcher at the University of Calgary, says that 99.9% of the protein in a typical blood sample is albumin — biologically important, but not a useful clinical indicator for most diseases. "It's about a million-fold more abundant than a cytokine or a drug target that you'd be interested in," says Dufour. He adds that the challenge can be even greater when working with other biological fluids, like tears, which offer useful physiological information but deliver fewer protein molecules than blood or serum, in abundance or diversity. By incorporating SomaLogic's SomaScan Assay into their experimental workflow, however, Dufour and other researchers in academia and industry are making headway in decoding proteomic signatures of disease.

ENHANCED PROTEOMIC SURVEYS

The primary tool in many proteomics labs is mass spectrometry (MS), which provides a powerful and sensitive platform for identifying and quantifying the molecular contents of a given sample. This method entails breaking molecules into smaller fragments, and then analysing and interpreting those pieces based on their unique mass and electrical charge. MS is a mature and well-established technology but is also limited in terms of how broad a net it can cast — it is difficult to profile rare and abundant proteins simultaneously, and the analysis of large numbers of samples can be very cumbersome.

The SomaScan Assay provides a powerful complement in this regard. This assay is built on a collection of chemically modified nucleic acid reagents called 'SOMAmers', each designed to bind tightly to a different protein target. After mixing a biological specimen with the SOMAmer library, the molecules that form complexes with proteins present in the sample can subsequently be isolated and analysed to determine which proteins are present, and in what amounts.

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Critically, this gives researchers the ability to profile far larger numbers of proteins than MS alone, with sufficient sensitivity and dynamic range to capture proteins at both ends of the abundance spectrum. The current generation of the SomaScan Assay can track approximately 7,000 different targets — nearly one-third of the full human proteome and, according to Dufour, roughly 10 times what can be obtained with an MS experiment. "As an initial screen, it's a game-changer in terms of numbers," he says. But there are other advantages as well. Cole Zimmerman, head of life sciences sales at SomaLogic, says samples can be analysed faster, while also generating consistent and reproducible measurements. "This means researchers can have higher confidence in their data," he says.

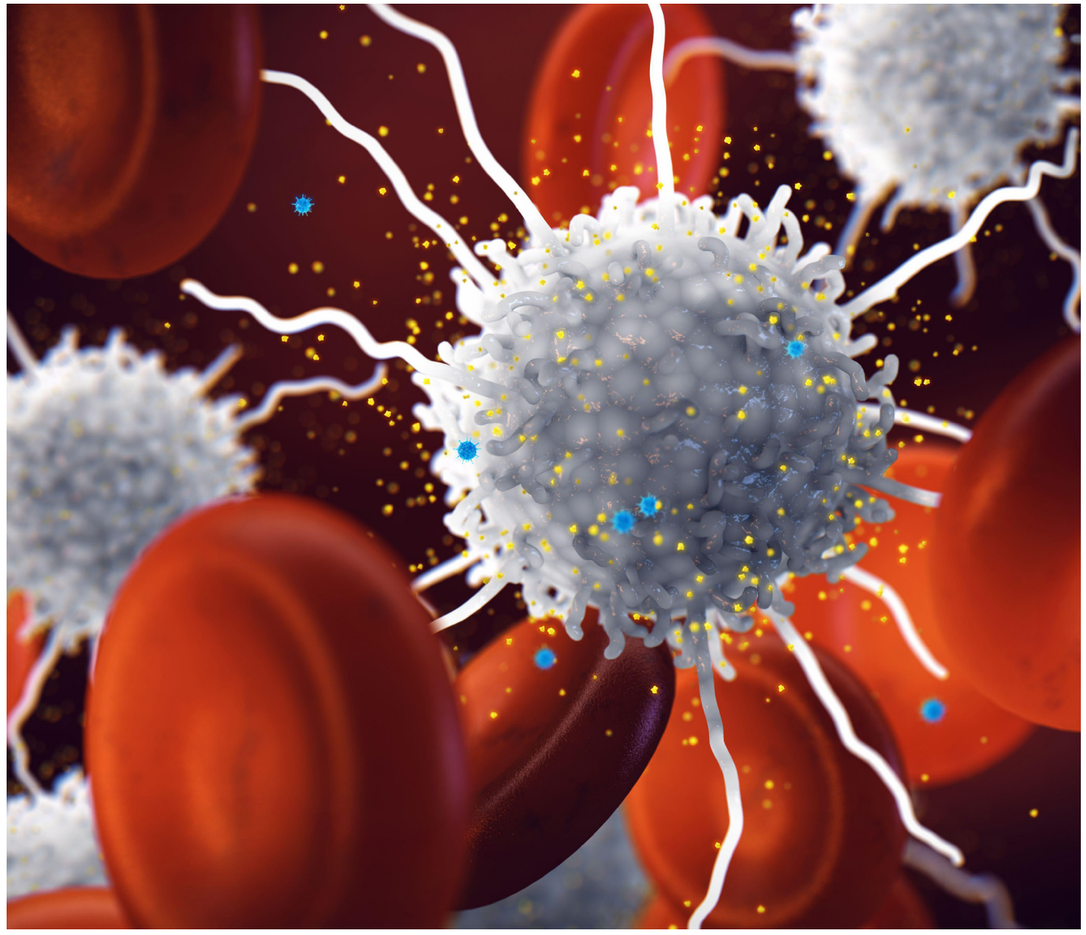
SUBTLE SIGNATURES

By starting with a SomaScan analysis, researchers can quickly home in on subsets of proteins that potentially contribute to disease in a wide range of disorders. For example, Dufour is part of a collaboration that has been using the platform to characterize disease-related proteomic signatures from clinical samples collected from hundreds of patients with Crohn's disease, a debilitating autoimmune disease afflicting the large intestine. This work has already uncovered two promising drug targets, and Dufour says that for one of them, "there are already drugs on the market, but they've never been used for Crohn's." His team is now working with drug companies to pursue clinical testing based on this work, which has yet to be published.

Zimmerman highlights another exciting area of research, in which SomaScan assays are being used to facilitate interpretation of genomic data. For decades, researchers have conducted large-scale genomic surveys in search of disease-associated mutations. Many of the identified genetic variants are not causal, but the discovery of protein-level biomarkers that are modified by these variants can give researchers greater confidence about clinical significance. "Users are leveraging enormous amounts of existing genomic information by adding proteomic information to it, and generating additional value," says Zimmerman. In a study from early 2022, for example, researchers used this approach to identify hundreds of previously unrecognized gene-protein combinations associated with cardiovascular disease in Black adults (Katz D, *et al. Circulation* **145**, 2022).

By conducting such proteomic surveys in ever-larger populations, scientists can uncover subtle but clinically important signals about disease biology that would be easy to overlook in small cohorts. To this end, in March 2022, SomaLogic announced it would be partnering with the European Prospective Investigation into Cancer and Nutrition (EPIC) study, which is monitoring the long-term risk of cancer in more than half a million participants. As part of this collaboration, the company will use the SomaScan Assay to perform 210 million protein measurements in tens of thousands of samples collected over the course of 15 years; the resulting data could reveal valuable new biomarkers that serve as a red flag for heightened cancer risk.

The SomaScan Assay is still just one part of the proteomic toolbox, however, and MS is the matching piece of the puzzle. The assay cannot determine whether proteins have undergone some form of chemical modification — a common process that can profoundly alter the function or activation state of a protein. MS is very well suited for both applications, making it a powerful tool for diving deeper into protein signatures revealed by SomaScan. "I don't see them as competitive," says Zimmerman. "The two techniques can work together to solve problems." ■



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▲ **Macrophages release cytokines in response to viral infections — these secreted proteins can be detected in blood serum using the SomaScan Assay.**

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