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New Australian Cancer Research Facility to Profile 70K Tumor Proteomes Over Next Seven Years

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NEW YORK (GenomeWeb) – The newly established Australian Cancer Research Foundation International Centre for the Proteome of Cancer (ProCan) has announced plans to generate proteomic profiles of roughly 70,000 cancer tumor samples over the next seven years.

Funded by $10 million in seed money from the Australian Cancer Research Foundation, Sydney-based ProCan is working with Sciex to acquire a suite of mass spec instruments to build what Phil Robinson, co-head of the center, called an "industrialized proteomics" lab.

The center has purchased six Sciex TripleTOF 6600 mass specs that it plans to use for Swath-based analysis of tumor samples, Robinson told GenomeWeb. The aim of the new facility, he said, is to move beyond the traditional, lower-throughput proteomics research he and his colleagues have typically focused on in the past and toward a more standardized, reproducible, and high-throughput workflow.

"We have been using traditional shotgun proteomics for years," Robinson said, noting that his work has largely focused on phosphoproteomics and protein-signaling studies. "And the better the instruments have gotten, the more and more phosphosites we can see."

However, Robinson said that in recent years, inspired in part by the launch of Sciex's Swath data independent-acquisition mass spec workflow, his focus has turned from pursuing increased proteome coverage and more toward devising workflows that allow for larger-scale proteomic studies.

In that spirit, Robinson said he told the ACRF that, were ProCan awarded the $10 million in funds the foundation was offering, he planned to "buy a room full of [Sciex] TripleTOF 6600s and do the proteomes of cancer."

"The idea was, what if we build a whole lab based on industrialized proteomics, if we had a room full of those machines that just churned away like a factory," he said.

"It's going from traditional proteomics research where we want to get one more protein, one more phosphorylation site, to thinking about how can we get stability, how can we get sample prep, how can we get cancer researchers to give us thousands and thousands of tumors that are incredibly well annotated where we know the patient records, we know what their drug treatments were, what their outcomes were, what their genomic data is," Robinson said. "What if we can marry all that together?"

In this, the effort is somewhat similar to other ongoing cancer proteomics research projects, such as the National Cancer Institute's Clinical Proteomic Tumor Analysis Consortium

program, which is similarly using mass spec to profile large numbers of well-characterized tumor samples and combine this proteomic data with genomic information. The CPTAC initiative, however, is spread across a number of different labs, each using different workflows. It also aims to characterize significantly fewer samples than the roughly 70,000 ProCan has set as its goal.

More similar in terms of scale is the effort by University of Texas MD Anderson Cancer Center researcher Gordon Mills who has characterized on the order of 100,000 tumor samples with data from around 10,000 samples available in The Cancer Proteome Atlas, a database developed by Mills and his colleagues. That data was generated using the antibody-based technique reverse-phase protein arrays, though, which typically measures on the order of hundreds of proteins, as opposed to the thousands measured by mass spec.

The TripleTOF 6600 instruments running Swath are ideal for the ProCan project, Robinson said, due to the relative ease of the workflow and the quantitative reproducibility of the data. While traditional shotgun mass spec approaches typically allow researchers to go deeper into a given proteome, Swath and other DIA methods have proved popular due to their higher reproducibility, which makes them particularly useful for comparing protein expression over large numbers of samples. (Though researchers are making strides on this front with conventional shotgun approaches, as well.)

Robinson said that with current Swath techniques, he and his colleagues can identify on the order of 5,000 proteins in a typical run. "And once we reach around that 4,000, 5,000 protein mark, we are talking about real proteome-level analysis," he said. "It isn't every protein in there, but it is a heck of a lot that we can do a lot with."

Also key to the center's proteomics workflow is use of Pressure Bioscience's (PBI) pressure cycling technology to maximize proteome coverage, particularly when dealing with the sort of small tissue amounts often common with clinical tumor samples. Robinson cited work out of the lab of Swiss Federal Institute of Technology Zurich researcher Ruedi Aebersold demonstrating the usefulness of PBI's pressure cycling technology in improving the coverage of Swath-based mass spec analysis.

PBI's PCT systems use controlled cycles of pressure to break down samples, allowing for improved extraction of molecules such as proteins. In the case of proteomic workflows, this can improve the depth and reproducibility of mass spec coverage.

This, Robinson noted, is important in that clinical sample size has in the past limited use of mass spec-based proteomics in clinical research.

"Patient tumor samples can be pretty tiny and very heterogeneous," he said, adding that use of PCT in sample prep allows the researchers to analyze tissue samples as small as those provided by needle biopsies.

"So you can use incredibly small amounts of tissue, reliably digest them in a couple of hours, and get large amounts of information [via Swath]," Robinson said.

Sciex and PBI last month signed an exclusive comarketing agreement, under which PBI will promote its PCT systems with Sciex's Swath-based proteomics workflows as well as its TripleTOF, QTRAP, and triple quadrupole mass spec systems.

Robinson and his colleagues at the center, Co-Head Roger Reddel in particular, have been working with leading cancer researchers around Australia to line up the patient samples for their analyses. Currently, Robinson said, they have enough samples to keep them busy for the next seven years.

The specific research questions asked will be up to their clinical collaborators, Robinsons said, but, he added, he is particularly interested in identifying particular proteins that could suggest new treatment approaches.

"In any disease you have several hundred proteins that are elevated in their expression and several hundred others that are lowered, and we will be matching those against [known] drugable proteins," he said. "And by matching drugs that are clinically available to tumor subtypes that already haven't responded to classic treatments we are hoping to give clinicians [new] treatment options. To me that is one of the really important outcomes."

One of the first cancer types the center will tackle is ovarian cancer. Robinson and his colleagues hope to identify markers that can be used for subtyping non-responders to existing therapies for the disease.

The researchers also plan to do validation work on potential markers they find, using labeling techniques combined with quantitation on the TripleTOF 6600.

Robinson said that while the center currently has capacity to profile around 10,000 tumors per year, they would like to add further capacity and are currently looking for another $20 million to expand the facility.

For Sciex, the center represents an opportunity to demonstrate its ability to put together a complete workflow for large-scale proteomics work, said Mark Cafazzo, director of the academic and clinical research business at Sciex.

"The whole vision of ProCan is really the first physical manifestation of a number of trends we have seen in the proteomics world over the last several years bubbling up and coming together," he said. "The challenges in reproducibility from sample to sample, and in data completeness, I think, are the biggest issues to overcoming the biological variability that researchers find when they are trying to do the sort of quantitative biology that often is involved in the clinical proteomics world."

Sciex was also involved in development of a similarly ambitious proteomics facility at the University of Manchester, which plans this year to open its Stoller Biomarker Discovery Centre supported by £17 million ($27 million) in funding largely from the UK's Medical Research Council.

According to Tony Whetton, the center's director, it will feature roughly a dozen Sciex mass specs, including several triple-quadrupoles and a number of TripleTOF 6600 machines.