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# Q&A: University of Toronto's Scott Tanner on the Use of Atomic Mass Spectrometry in Proteomics

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By [Adam Bonislowski](#)

Name: Scott Tanner

Position: Associate Professor in the Department of Chemistry at the University of Toronto; CEO of DVS Sciences

Background: Principal Research Scientist, MDS SCIEX; PhD Physical Chemistry, York University

Scott Tanner is an associate professor in the Department of Chemistry at the University of Toronto where he has developed a platform called mass cytometry that uses atomic mass spectrometry to simultaneously quantify as many as 100 protein biomarkers in individual cells.

He is also the president and CEO of DVS Sciences, a company created to commercialize the technology.

At the Association for Mass Spectrometry's third annual Applications to the Clinical Lab meeting in January, Tanner demonstrated how his team had used the device to measure multiple biomarkers in rare cell populations. He also has a paper forthcoming in *Science* presenting data obtained using the system.

He spoke to *ProteoMonitor* this week about mass cytometry and potential applications for atomic mass spectrometry in proteomics research more generally.

The following is an edited version of the interview.

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The mass cytometer is an alternative to traditional flow cytometry, right? What are the main differences between the two platforms?

Exactly. The only issue I'd take with that is I don't like to consider it an alternative to flow cytometry. I'd like to consider it complementary to flow cytometry. Flow cytometry is the method of choice if you're doing a few parameters – as many parameters as you're comfortable running and doing the compensation for. But if you're going to do more parameters than 4 or 8 or ten or twelve or however many you lose your confidence in, then mass spectrometry is the next solution. What it really is, is an atomic mass

spectrometry solution to the multi-parameter flow cytometry challenge. So it looks like a flow cytometer, but it's not a flow cytometer. But it's complementary to it.

I'd say there are three big differences. One is that the detector itself has significant resolution, so you don't need to do compensation. That means that you can look at many things [at once] because of [difference] number two, which is that there are many metals to look at. And then the third [difference] is that it's quantitative. There's a trend toward bringing quantitation into the bio-analytical world, but it's still in its infancy. We're trying to bring an analytical chemistry approach to doing that, and that's one of the strengths of atomic mass spectroscopy: absolute quantification.

Like flow cytometry, mass cytometry is aimed at studying rare cell populations, like cancer stem cells. Why did you decide to focus on that area?

Inherently, atomic mass spectrometry is incredibly sensitive. So one of the first realizations was that we would be able to detect antibody binding events at single-cell levels for proteins at low copy counts. Why do we want to do it? [We were] talking to [Ontario Cancer Institute researcher] John Dick, who is a leukemia stem-cell guru – the guy who first proposed that cancer was a stem cell-based disease.

And when we presented to him the concept of using elements for tagging in an immunoassay he said, 'That would be great, but I want to do it at the single-cell level so I can pick out the cancer stem cells.'

So that's the application: To look at the rare disease cells. And the pitch is that you can look at the rare disease cells before the disease actually exhibits itself, and so if you can [diagnose] this disease before it's actually a disease you can use less aggressive therapy. If you can identify that you have a stem cell which is cancerous and is going to generate a disease, then you can look at a therapy to eradicate the stem cell which doesn't involve chemotherapy or radiation therapy.

We don't do diagnosis at the moment, but I can see diagnostic opportunity. You can also use the multidimensional space to investigate the process of disease. 'How does that virus infect the cell? What's its propensity? What's its efficacy? What's the pathogenesis of that infection? What are the translational changes that induce a cell to become a cancerous cell?' We need to understand the biochemical basis of the disease so we can develop rational drugs for that disease.

In terms of diagnostics, how much need is there for being able to measure, say, 30 different biomarkers given that your panels under development typically aren't dealing with that many biomarkers and regulatory bodies like the US Food and Drug Administration aren't really there yet?

FDA certainly isn't there, but it's pretty clear that the pharmaceutical companies that are worried about approval and worried about getting into the clinic have recognized the need to measure more things at the same time. There's the famous expression – fail early, fail often – you want to do it before you get to the clinic.

And so they've recognized that measuring only one metabolite of an action doesn't tell you enough to give you assurance you're going to survive clinical phase I. So they're branching out.

I've talked to a few pharmas that are now requiring that they do assays in multidimensional space to get the information that they are eventually going to need as they go through the clinical trials. And in terms of what the researchers need, I think the issue really is the questions that need to be asked. We're at a point where people don't ask really hugely multidimensional questions because they've never had a multidimensional answer.

So we'd like them to move from where they're at – two dimensions – to many dimensions. And you do that

by looking at dimensions that you hadn't really anticipated as being critical to the path. Then you'll realize that there are many paths that are interactive and can be measured simultaneously to significant advantage, especially at the single-cell level where you're actually measuring them all at the same time in the same cell.

Beyond its applications to rare cell populations, could atomic mass spectrometry be useful for detecting low-abundance biomarkers in general?

Yeah, so there are two ways to use element-tagged immunoassays, which was our first invention 10 years ago. Initially we did it as a multicolor ELISA, and all we did was emulate an ELISA. It was a cell lysate analysis where you probed with element-tagged antibodies, and then you looked at the average biomarker distribution in an ensemble of cells – just like you do in an ELISA. The step we took after that was going to the single-cell level.

So there are really two assays. One of them is single cell, and one of them is bulk ensemble cell. The bulk ensemble cells can be done with conventional, standard ICP-MS instruments – it doesn't have to be the [mass] cytometry configuration. The mass cytometer is a very special enactment of ICP-MS. It's high sensitivity for single-cell work, and it's really fast. Conventional ICP-MS is much slower, much cheaper, and really good at doing quantification. It's good for a bulk ensemble assay.

Is there a reason why you don't see that much atomic mass spec used in protein biomarker research or diagnostic platforms? It seems like it could be a useful tool, particularly for low-abundance markers.

I think it's just a different mindset. It really just comes down to the fact that atomic spectroscopists and biologists just never talk. Because biologists really don't care about the atomic composition of matter, and atomic spectroscopists don't have the capability for doing molecular assays.

So there's no basis for them to talk, until you start to combine elements as labels in an immunoassay that can recognize a protein. Suddenly that makes us talk together, and it's just that that hasn't been promulgated enough in the audience.

Usually the people who are doing [atomic mass spec] are publishing literature in the atomic spectroscopy journals, not the biology journals. Or they're doing it, and they're not telling you because they're doing it at a pharma company. I think it's a familiarity thing. It's a matter of first of all getting people to understand that element tagged immunoassays are actually a pretty powerful technique, and then getting people to use it, and then getting people to report it. It's a growth thing.

It's a different mindset. Everyone comes into the biological world thinking either fluorescence for doing immunological assays or looking at *de novo* discovery mass spec. And they're not looking at using the mass spec as a detector of the probes that are put on an immunological stain.

Is this changing? Is atomic mass spec becoming a technique you're seeing more of in proteomics?

I would say there are more proteomics researchers aware of it but not to the point where they're a significant fraction of the proteomics community. The thing that really is getting the attention is the cytometric aspect of it. Because that's a group of people who really want to look at many things simultaneously and don't have a method, and this is really a transformation in the cytometry community. It's not really recognized yet as a transformation in the general cell lysate proteomics community.

Basically there are a few very powerful people who have taken it on: Mario Roederer at [the National

Institutes of Health] and Gary Nolan at Stanford are proponents, and as they are talking about the results, the word is spreading. We have a paper coming out in *Science* [in April], and I think that's going to really be a stepping stone. When that comes out that's going to be the catalyst for the next stage.

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