



New Era of Cytometry

As science advances, our understanding of complex biological systems enhances. We progress from understanding simple single processes to multistage inter-dependent complex processes. In a diseased state, minor changes to complex systems can have drastic effects on the overall state and health of the organism. We find ourselves in search of finding new ways to 'see' as much as possible – simultaneously - to separate the normal healthy processes and accurately define the diseased state; however, the limiting factor is most often technological. Over the years we have seen the emergence of technologies capable of a few simultaneous measurements within a biological system. A technique called 'flow cytometry' is the state-of-the-art for high throughput, single cell analysis up to about 10 simultaneous parameters. Now however, a new era of cytometry called 'mass cytometry' has begun right here in Toronto, and has revolutionized the field.

Professor Scott Tanner from the University Of Toronto's Department Of Chemistry leads the team that is defining the emerging field of mass cytometry. Their break-through research has led to the development of a new revolutionary analytical tool called CyTOF™ that is capable of high throughput simultaneous analysis of up to a hundred biomarkers in a single cell at an analytical rate of 1000 cells per second. As the President and CEO of DVS Sciences Inc, his team currently manufactures and sells the technology along with a new class of bioanalytical metal-containing polymer tags called MAXPAR™ antibody labeling reagents.

In this interview with **Sridhar Nadamuni**, Tanner explains the research, clinical, and business implications of his technology - the CyTOF™ Mass Cytometer.

The Collaboration

The origin of CyTOF™ stems from Tanner's collaboration in 2001 with John Dick (currently with University Health Network) and Mark Minden (Princess Margaret Hospital) . At that time, Tanner had already developed an expertise in ion optics for inductively coupled plasma mass spectrometry (ICP-MS) at MDS Sciex and he and his team began looking at applying the multiplex capability of ICP-MS to bioassays through element-tagging of antibodies. DVS Sciences Inc. was spun out of MDS Sciex in 2004 to apply atomic spectrometry using stable isotope tags (non-radioactive) linked to antibody probes in medical diagnostics.

Tanner and his ICP-MS colleagues left Sciex in 2005 for the University of Toronto to take on their new challenge of applying mass spectrometry as a detector for flow cytometry. That move was facilitated by John Dick, who assisted Tanner with an Applied Human Health Grant from Genome Canada. Since then, Tanner has leveraged \$16.8 million of non-dilutive funding.

Practical Applications

Tanner emphasizes that CyTOF™ mass cytometry answers the flow cytometry multi-parameter challenge by using specially designed multi-atom stable isotope tags instead of fluorescent labels that are conjugated to the antibodies using his novel MAXPAR™ labeling kits. Detection is accomplished by the high resolution, sensitivity, and speed of analysis of atomic Time-of-Flight Mass Spectrometry (TOFMS). The diversity of stable isotope tags available can facilitate the simultaneous detection of many proteins and gene transcripts in individual cells. The unique biomarker signature can enable identification of a diseased cell early enough for prompt, effective and specific thera-

peutic intervention. To date, the technology has shown to effectively analyze:

- Normal blood mononuclear cell surface markers
- Leukemia cell line (e.g., KG1a, HL-60, Jurkat and Ramos) surface markers
- Leukemia patient cell types
- Intracellular antigens, including phosphoproteins
- Live and dead cells

Commercial Aspects

In the past year, Tanner has moved the product closer to the marketplace, supplying Stanford University with two and the National Institutes of Health (USA) with one of these instruments, at \$600,000 each, which complement the initial installation purchased by the Ontario Institute of Cancer Research in 2008 .

In fact, Tanner says, "we have 100 hot prospects currently, with seven 'white' hot customers (in the next few months)" and he hopes to deliver 11 instruments in the next 12 months including one in Taiwan, one in Japan, two more in Canada, and seven more in the USA, "but not in Europe just yet". Not a tall order for someone who has kicked off with \$8 million from the Ontario Genomics Institute and matching grants from Ontario Institute for Cancer Research (OICR, \$2 million), Ontario Research Fund (\$3.75 million); The Health Technology Exchange (HTX, \$100,000); National Institutes of Health (NIH, USA, \$2 million). Aside from Agilent Life Technologies (California) chipping in with \$200,000 and another \$2 million from DVS sales, Tanner also credits Amgen Inc (California), the National Cancer Institute (USA), National Cancer Institute of Canada, Leukemia and Lymphoma Foundation (USA) and Princess Margaret Foundation with complementary grants.

He has plans to manufacture 100 instruments as he prepares to move into a research, development and manufacturing plant in Markham (ON) in late 2010. Tanner's goal is to build to \$120 million in annual sales in the next few years. He intends to recruit new talent—20 by December 2010 up to 140 by 2015, along with another 73 sales and support professionals worldwide. Tanner and his team have plans in place to provide both incremental improvements to the current commercial platform and to develop a derivative platform instrument. His aim is to supply CyTOF™ mass spectrometers and reagents to all the major labs with core facilities worldwide. ■



CyTOF™ Mass Cytometer



Dr. Scott Tanner, President, DVS Sciences Inc.
Associate Professor, University of Toronto

Scott Tanner is leading the research effort on the development and improvement of the mass cytometer and tagging technologies at the University of Toronto in the StemSpec group, and also the engineering and business development at DVS Sciences.

Scott received his PhD in physical chemistry from York University in Toronto, where he studied the chemistry and kinetics of ion-molecule reactions as they relate to the formation of soot in flames. He joined Sciex, then a small innovative private mass

spectrometry company, in 1980 and stayed for 25 years, eventually becoming Principal Scientist. By the early 1990's he had gained an international reputation for his understanding of the fundamentals of Inductively Coupled Plasma Mass Spectrometry, including both plasma processes and ion optics. With the commercial success of the ICP-MS products that he helped to develop and bring to the market through the PerkinElmer-Sciex Joint Venture, Scott had the great fortune to meet and entice Vladimir Baranov and Dmitry Bandura to join his elemental mass spectrometry research group. The team went on to develop and promote the Dynamic Reaction Cell® which remains, more than a decade later, at the pinnacle of quadrupole ICP-MS technology.

An opportunity to pursue the development of a mass spectrometer-based cytometer with his friends and colleagues Vladimir, Dmitry and Olga, in conjunction with generous support from John Dick at the University Health Network (a world renowned leukemia stem cell scientist), led Scott and colleagues to join the University of Toronto in March 2005. With an appointment as Associate Professor in the Institute of Biomaterials and Biomedical Engineering, Scott coordinated this \$8M, 3-year project to a successful conclusion. Transferring his faculty appointment to the Department of Chemistry in 2008, Scott continues to lead the \$3M, 2-year sequel project that will result in the commercial introduction of the technology in 2010.

The move from MDS Sciex to the University required the establishment of DVS Sciences Inc., initially a mass spectrometry consulting company. When it became evident that the **CyTOF™** and **MAXPAR™** technologies were both feasible and generating considerable excitement in the scientific community, DVS Sciences began its transformation into a research, development and manufacturing entity. Recognizing the challenges of entering the world market, and with many years experience with Joint Ventures behind him, Scott is looking to partner with an established market leader to bring the DVS products to the world.

Amongst his scientific awards, Scott notes the Manning Innovation Foundation Award of Distinction (together with Vladimir) in 2001 and the W.A.E. McBryde medal in 2003. In 2008 he joined the Editorial Board of the Journal of Analytical Atomic Spectrometry (Royal Society of Chemistry), and is the Chair of the Ontario Chapter of the Manning Innovation Foundation.