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As Shimadzu Begins Registering Mass Specs with FDA, Firm Appears Well Positioned for the Clinic

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Shimadzu said last week that it has registered several of its HPLC and LC-MS instruments as Class I medical devices with the US Food and Drug Administration, allowing them to be used in clinical settings.

The registration covers Shimadzu's LC-20 CL and LC-30 CL HPLCs; LC-MS-2020 CL single quadrupole mass spec; and LC-MS-8030 CL, LC-MS-8040 CL, and LC-MS-8050 CL triple quadrupole mass specs. Additionally, the company last year received FDA clearance of its Axima Assurance linear MALDI-TOF instrument for clinical use within BioMerieux's Vitek MS microbiology system.

Shimadzu has a relatively low US profile compared to other major mass spec vendors, with combined 2012 sales in North and South America accounting for only 10 percent ($150 million) of its analytical and measuring instruments business, which includes mass spec. Internally and through licensing and collaboration agreements, however, the company has put together what is arguably the industry's broadest portfolio of potential clinical proteomics tools.

For instance, while Agilent Technologies has over the last several years put significant work into establishing complete clinical workflows for multiple-reaction monitoring-based protein quantitation, the company offers little in terms of MALDI mass spec, which has of late established itself as a valuable platform for proteomics-based clinical microbiology and a potentially suitable technology for protein biomarker quantitation.

Thermo Fisher Scientific has, likewise, focused the bulk of its clinical proteomic attention on triple quad workflows, as have Waters and AB Sciex, despite these two firms also having MALDI instruments.

Bruker, on the other hand, has invested significantly in MALDI as a clinical proteomics platform, last year achieving FDA clearance for its MALDI-based clinical microbiology system the MALDI Biotyper and launching several collaborations to explore the technology's usefulness for clinical measurement of protein markers. But while the company last year launched several LC-triple quad instruments, it has not invested significantly in linking them to the sort of sample prep or automation tools required for a clinical workflow.

Shimadzu, meanwhile, is active in both the triple quad and MALDI spaces, and has, primarily through its relationship with protein prep firm Perfinity Biosciences, integrated into its systems the sort of sample prep and automation tools required for clinical work.

"We see increasing applications of LC and MS instrumentation for clinical applications ranging from microbiology and disease markers to inborn errors of metabolism and pain management," Scott Kuzdzal, the company's life science business manager, told *ProteoMonitor*.

In terms of clinical proteomics, the company views immunoenrichment mass spec as one of the key technologies, he said, noting that it has been collaborating with Perfinity on such workflows.

"That is a field where we've been looking to expand and increase our footprint," he said "We've been working with Perfinity to create platforms that are fully automated where the antibody pull-down can be achieved in solution."

Founded in 2004 by Purdue University researcher Fred Regnier, Perfinity has inked agreements with Shimadzu for a number of its products, most notably its mass spec sample prep platform, the Perfinity Workstation, which automates steps including immunoenrichment, clean-up, digestion, and desalting.

The technology is comparable, Kuzdzal said, to Thermo Fisher's mass spec immunoassay (MSIA) technology, which also uses antibodies to enrich target proteins prior to mass spec analyses. Also similar is SISCAPA Assay Technologies' SISCAPA technology, although that method enriches post-digestion, at the peptide rather than protein level. SAT has collaborated with firms including Agilent and Bruker on applying the approach on their instruments.

"So we have a very unique automated instrument and platform that can provide this immunoselectivity," Kuzdzal said. "And then the rest of the Perfinity workstation is designed to perform rapid digestion and clean these samples up rapidly for direct introduction into mass specs. So that has been one platform we've had great success in."

The company also this year began offering Novilytic Laboratories' Noviplex Cards for collecting plasma for LC-MS/MS analyses. Also founded by Regnier, Novilytic developed the cards as an alternative to blood draws, similar in principle to dried blood spots, which have of late drawn interest as a format for proteomic sample collection.

The card "allows you to take a drop of blood from a finger stick" and take it through sample prep and protein extraction on the card, significantly simplifying sample collection, storage, and processing, Kuzdzal said.

"So what it is moving toward is the incorporation of standards and antibody pull-downs directly on these cards," he said, "toward applicated cards that can process samples and clean up samples for the mass spec in just minutes, without the need for intensive laboratory equipment."

On the MALDI side of things, Kuzdzal noted that the company is interested in these platforms as possible clinical systems due to their "speed and ease of use." Much clinical proteomics work has focused on MRM-MS workflows, but these potential advantages of MALDI cited by Kuzdzal have led several researchers including SAT founder Leigh Anderson, Stanford University researcher Mark Stolowitz, and University of Victoria researcher Christoph Borchers to explore the method for targeted protein quantitation.

These researchers have primarily used Bruker instruments. However, a key element – FDA clearance – that has made Bruker's MALDI instrumentation intriguing from a clinical perspective also applies to Shimadzu.

In a 2013 interview with *ProteoMonitor* discussing MALDI's clinical potential, SAT's Anderson noted that the Bruker and Shimadzu MALDI instruments cleared by FDA as part of, respectively, Bruker's Biotyper and BioMérieux's Vitek MS clinical microbiology platforms, represented "a very attractive and interesting inventory."

"The idea that Bruker and BioMérieux [have gotten] these instruments FDA-cleared is really the first step down the road to getting something that could be a real *in vitro* diagnostic solution" for mass spec-based clinical proteomics.

Indeed, in the US, some hospital microbiology labs began using the MALDI platforms as their primary tool for bacterial identification even in advance of the devices receiving FDA clearance. Such use, as Anderson noted, suggests a path by which these instruments might enter the protein biomarker space, as well, moving from hospital microbiology departments to their clinical chemistry labs.

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