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Mass Spectrometry Makes Inroads Into The Clinical Lab

By Alina Kim, Sunayana Karra & Akash Kundu

THE USE OF MASS SPECTROMETRY IN IVD applications looks to be gaining momentum. In this article, Alina Kim, Sunayana Karra and Akash Kundu of Boston Biomedical Consultants report on new developments and innovations showcased at the American Association for Clinical Chemistry Annual (AACC) & Clinical Lab Expo (CLE) annual meeting that took place this summer. Players at the convention exhibited a range of Class I medical devices, research use only liquid chromatography tandem mass spectrometry (LC-MS/MS), matrix-assisted laser desorption/ionization (MALDI-TOF), inductively coupled plasma mass spectrometry (ICP-MS), sample preparation automation platforms, and software solutions.

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For years, mass spectrometry has been a key point of conversation during the annual AACC meetings but it was an especially hot topic in 2014. That year, both SCIEX and Thermo Fisher Scientific Inc., two top mass spec vendors, revealed products that were listed as Class I medical devices. Mass spec systems are typically not classified as medical devices and this is the first time SCIEX and Thermo Fisher were able to obtain this classification for their products.

Vendors that year also hosted five widely attended industry workshops with topics such as "How to Justify LC-MS/MS to Lab Administration" and "Automation and Integration of LC-MS/MS." Furthermore, the mass spec-related research abstracts centered on traditional core laboratory, immunoassay-based clinical segments, such as Drugs-of-Abuse Testing (DAT), Therapeutic Drug Monitoring (TDM), and Vitamin D, suggesting the intention of the mass spec vendors to draw test volume away from core laboratory analyzers onto their mass spec platforms.

The product launch cadence slowed down in 2015 and the companies chose to educate laboratory personnel with large in-booth theaters where company representatives gave presentations on the basics of mass spec technology and its utility in the clinical laboratory.

This year, at AACC 2016 which was held on July 31- Aug, while the number of displayed products along with the average size of companies' booths (and therefore the size of the in-booth theaters) had shrunk, there were still pockets of innovation and growth. Among these were mass spec technology for diagnosing cancer, ongoing improvements to clinical microbiology mass spec (including potential new applications), and the expanding role of automation in mass spec workflow.

Cancer

Historically, the use of mass spec methods has mainly been within clinical IVD, in the fields of microbiology, drugs-of-abuse testing/therapeutic drug monitoring, neo-natal screening, and select esoteric testing such as Vitamin D. At AACC this year, the applications of mass spec technology went beyond these key areas to include oncology, as demonstrated by established player Thermo Fisher and Agena Bioscience.

Headquartered in San Diego, California, Agena Bioscience was established in 2014 from the acquisition of Sequenom Inc. 's biosciences division by private equity firm Telegraph Hill Partners. Agena's technology platform is a MALDI-TOF mass spectrometry system for PCR-based nucleic acid, MassArray, which Sequenom

developed and marketed for years through its bioscience division.

Agena currently offers the MassARRAY Dx Analyzer 4 system in Europe, the US and the APAC region, including China. In the US and China, MassARRAY is still approved for research use only but the company is making moves into the clinical IVD arena.

In February this year, the company announced a partnership with China's DaRui Biotechnology to co-develop and commercialize targeted, multiplexed tests for oncology and inherited diseases, with DaRui tasked with conducting in-country clinical trials and submitting tests to the China Food and Drug Administration.

In April, the company announced the CE-IVD mark and subsequent European launch of two targeted somatic mutation profiling diagnostics panels, one for colon cancer and the other for non-small-cell lung cancer. The *MassARRAY Dx Lung Panel* analyzes 304 mutations spanning 10 oncogenes (EGFR, KRAS, BRAF, PIK3CA, NRAS, ALK, ERBB2, DDR2, MAP2K1, and RET). The *MassARRAY Dx Colon Panel* analyzes 211 mutations spanning four oncogenes (PIK3CA, KRAS, NRAS, BRAF). The panels utilize <40 ng of DNA from a number of sample sources including fresh, frozen or paraffin-embedded tissue. In addition to the two CE-IVD marked cancer panels, *MassARRAY Dx* also offers open-channel capabilities in a research use-only capacity for applications spanning pharmacogenetics, oncology, and inherited disease screening.

At AACC 2016, Thermo Fisher hosted an industry workshop titled "Monitoring Kinome Adaptations to Therapy using Quantitative High Resolution Mass Spectrometry" led by James Duncan, assistant professor at Fox Chase Cancer Center at Temple Health. Duncan discussed the use of multiplexed kinase inhibitor beads and quantitative mass spectrometry (MIB/MS) to monitor expression and activity changes in protein kinases (ie kinome) in response to cancer therapy. MIB/MS allows for the study of adaptive kinome reprogramming as a mechanism of resistance in aggressive cancers, including melanoma, against targeted kinase inhibitors such as Vemurafenib (BRAF inhibitor). By studying kinase activity en masse using mass spec technology, researchers may develop more robust therapies aimed at stably inhibiting key pathways in cancer progression.

Bruker BioSciences Corp. is also another mass spec company with a presence in the oncology field. Of note, although not promoted at AACC 2016, Bruker continues to invest in its *MALDI Tissuetyper* solution (currently RUO) for use with the *rapifleX MALDI-TOF* system. First launched at ASMS 2015, the MALDI Tissuetyper solution utilizes Bruker's proprietary smartbeam 3D laser to image (two- and/or three dimensionally) tissue sections within 30 minutes, with imaging times as fast as a few minutes for smaller biopsy samples. Through extraction of molecular information as a proteomic fingerprint, the MALDI Tissuetyper allows for use in both biomarker discovery studies and multi-marker tissue-typing/classification.

Microbiology

With mass spec being increasingly adopted in the microbiology lab, manufacturers of this technology continue to invest in new developments, such as database expansions and new applications.

bioMerieux SA was also at AACC 2016, promoting its new CE marked database and reagent kits for the identification of mycobacteria, Nocardia, and molds, adding 297 new species (allowing for identification of mycobacterium tuberculosis (TB), 45 species of non-tuberculous mycobacteria (NTM), and 48 molds) to the *VITEK MS* database. The enhanced database now allows for identification of more than 1,000 species, representing 15,172 distinct strains of bacteria, yeasts, and molds.

While Bruker did not host its own booth at AACC 2016, its *MALDIBiotyper* system was showcased through the company's distribution partners (e.g., Beckman Coulter Inc. and Becton Dickinson & Co.). Bruker remains heavily invested in its clinical mass spec business, launching in April new disposable sample target plates and partnering with the Centers for Disease Control (CDC) in June to expand its MALDI-TOF database to include a number of rare and emerging pathogens. The company also continues to develop reagent kits, such as the *MALDI Sepsityper* for direct pathogen identification from positive blood

culture bottles; of note, the MALDI Sepsityper has not yet received FDA approval (CE Marked in April 2015).

While mass spec has established itself as a suitable alternative to traditional microbiology systems for identification of species, the technology has its limitations (ie it cannot provide an antimicrobial susceptibility result). Recently, however, the potential use of MALDI-TOF for resistance testing applications has generated strong interest, stemming from the announcement of Bruker's new *MBT Selected Test of Antibiotic Resistance* (STAR) *for Beta lactamase* (BL) assay. The MBT STAR-BL product is currently available for research use only, and consists of a software module (for easy data analysis) and the MBT STAR-BL IMI kit. The MBT STAR BL allows for detection of Gram negative carbapenemase producers, using a patented, functional beta-lactamase test for selected antibiotics (eg, penicillins, third-generation cephalosporins, and cabapenems). Due to strong customer demand for

Why mass spectrometry?

At a seminar hosted at the 2016 EU meeting of the Association for Mass Spectrometry: Applications to the Clinical Lab (MSACL), a speaker uttered the words, "Friends don't let friends use immunoassay." Although the context was clearly comical in nature, this attitude is one that is often observed in the mass spectrometry community.

When comparing mass spec's benefits over other technologies, it is almost entirely immunoassay that mass spec is going up against. In drugs-of-abuse testing and therapeutic drug monitoring, immunoassay is typically used first as a screening method and then positive results are confirmed using mass spec. Immunoassay, however, has been shown to produce a high rate of false-negatives, which can have severe implications in certain settings, such as in pain management (eg in the case where the patient is suspected of hoarding or diverting the prescribed medication). The high specificity of mass spec can be seen as superior to immunoassay, especially when testing for low molecular weight analytes, such as amphetamine and other drugs.

Mass spec also enables multiplexing – testing a sample for multiple analytes simultaneously – a benefit that immunoassay lacks. When facing a patient whose regiment contains multiple drugs or when testing a patient for an array of different opiates (eg, morphine, hydrocodone, and hydromorphone), mass spec will be the obvious choice over immunoassay.

Furthermore, with qualified personnel, mass spec users can develop their own tests (ie, laboratory developed tests, or LDTs) to customize their own panels or to test for a very specific analyte. When using automated immunoassay, the lab is at the mercy of the manufacturers. Although they could develop an in-house ELISA test, in order to utilize the automated immunoassay system that provides the throughput and efficiency that immunoassay users enjoy, the lab would have to wait for this assay to be developed and approved by these IVD vendors.

This benefit, however, comes with its limitations as well. Mass spec users may be able to develop their own tests, but automated immunoassay users enjoy fully automated, random access testing with superior throughput, efficiency, and ease-of-use. Laboratory developed mass spec tests also require highly trained staff, as do the validation and troubleshooting of these methods. On the other hand, automated immunoassays require far less hands-on maintenance and can be operated relatively easily by virtually all med techs in the laboratory staff.

The fight to determine which is better, mass spec or immunoassay, will only continue to develop over time. With mass spec vendors, such as Chromsystems and RECIPE, releasing regulatory-cleared mass spec kits and others such as Shimadzu developing automated sample prep modules for mass spec, it is evident that mass spec players are seeking to secure the benefits that the automated core laboratory has enjoyed for years.

this type of testing/information, Bruker is expected to develop an IVD version.

Automation

Laboratory automation is widely seen as a discipline most applicable to core laboratory analyzers for clinical chemistry, immunoassay, and hematology, but at AACC 2016, the use of automation in sample prep for both LC-MS and clinical microbiology mass spec was exemplified.

Shimadzu Corp. displayed one of the only truly new mass spec solutions at the Clinical Lab Expo – the *CLAM-2000*, a fully automated sample preparation module for LC-MS. According to Shimadzu, although the benefits of mass spec include high sensitivity, high specificity, and multiplexing capabilities, the major bottleneck in the process is the sample preparation step, which can introduce human error in sample handling as well as contamination in the samples itself. The CLAM-2000 eliminates this bottleneck by performing all of the sample preparation steps from pre-treatment to analysis. The full pre-treatment capabilities include dispensing samples, dispensing reagents, stirring, suction filtration, incubation, and finally the automatic transfer of sample vials to an autosampler after pre-treatment. Furthermore, unlike traditional dispensing systems, the CLAM-2000 is fully automated and can process individual samples successively in parallel, which ensures uniform pre-treatment times between samples without compromising processing speed.

In terms of clinical microbiology, pre-analytical/track automation has traditionally focused on culture media specimen processing, plate incubation, and digital imaging. In recent months, however, new offerings to automate the process of MALDI-TOF plate preparation have entered the scene.

At AACC 2016, Becton Dickinson showcased its new *BD Kiestra MALDI-TOF* and *AST Preparation System*, which was first unveiled at ASM 2016. The new BD Kiestra MALDI-TOF is slated for launch by year-end 2016, and is designed as an add-on to *BD Kiestra TLA*. The system automates MALDI-TOF and antimicrobial susceptibility testing (AST) plate preparation; while AST plates will be automatically transferred onto an attached BD Phoenix 50 unit (which was launched in September 2016), MALDI-TOF plates will still need to be manually transferred to a Bruker MALDI Biotyper unit.

Similarly, COPAN has invested in its own offering for MALDI-TOF automation. The *Colibri*, first unveiled at ECCMID 2015, will be available for use with COPAN's *WASP-Lab* or as a stand-alone workstation; of note, the Colibri is not yet commercially available. The system automatically prepares AST and ID suspensions. Additionally, it can seed MALDI-TOF target plates and apply the matrix.

Although not promoted at AACC 2016, Bruker has also developed pre-analytical automation products for use alongside its mass spec systems. The *MALDI Biotyper Galaxy*, which can integrate seamlessly with the MALDI Biotyper system, allows for automatic coating of clinical samples on MALDI target plates with complete traceability. The MALDI Biotyper Galaxy works alongside the MALDI *Biotyper Pilot*, which allows for accurate sample positioning through guided MALDI target preparation.

The Future Of Clinical Mass Spec

Although significant roadblocks may stand in the way of mass spec fully infiltrating the clinical IVD space, based on trends witnessed at AACC 2016, innovations and new avenues for growth are expanding the historic perception of mass spec's utility in the core laboratory. With applications being explored in cancer and resistance testing in microbiology as well as advancements being made in pre-analytical automation solutions, mass spec has the potential to have a meaningful impact in the clinical IVD space.

Alina Kim and Sunayana Karra are analysts and Akash Kundu is associate analyst at Boston Biomedical Consultants, a Waltham, Massachusetts-based consultancy specializing in the in vitro diagnostics industry.