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REVIEW

2016 ASMS Workshop Review: Next Generation LC/MS: Critical Insights and Future Perspectives

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Background and Objectives

The pilot workshop on "Next Generation LC/MS: Critical Insights and Future Perspectives" was held on the evening of June 6, 2016 at the 64th ASMS Conference on Mass Spectrometry and Allied Topics held in San Antonio, TX. The workshop, chaired by Hongying Gao (Pfizer), consisted of stimulating talks from distinguished speakers and open discussion among the audience and invited presenters. The objectives of this workshop were to better understand the advances and limitations of current technologies; to exchange perspectives on the next generation LC/MS; and to discuss/debate the features of next generation LC/MS focusing on the following three questions: (1) What would the next generation LC/MS look like? (2) How would it change the way we do analysis? and (3) What fundamental issues need to be resolved? A real-world case in the biopharmaceutical industry was presented by Hongying Gao on the needs by industry for LC/MS innovation and technology advancements. The primary invited speakers were Alexander Makarov (Thermo Fisher Scientific) and Richard (Dick) Smith (Pacific Northwest National Laboratory). The open discussions started with Q&A and comments for Alexander Makarov and Dick Smith, followed by insights and perspectives from members of the audience and other invited presenters who shared their thoughts addressing the above questions.

Summary of Proceedings

Why a Superior LC/MS System is Needed

Hongying Gao presented a real-world case in which the knowledge of the analytes of interest (e.g., major human metabolites of a drug) evolved in drug discovery and development. Extensive metabolite scouting efforts are typically carried out in in vitro/in vivo experiments for identification and structural elucidation of the metabolites in drug discovery. The knowledge of the metabolites of importance (or interest), e.g., major human metabolites, may evolve only after in vivo human samples become available. This often takes place 6 mo to 1 y after animal samples from preclinical toxicity studies are available. To address the time gap between the animal and human samples, an unbiased scanning method using UPLC coupled with HRMS was employed to bank the data and samples without prior knowledge of the analytes of interest. Statistical analysis showed that it was feasible to quantitatively compare the data generated approximately 1 y apart using UPLC/HRMS [1]. A more advanced, robust, and sensitive UPLC/MS platform (with ion mobility) would have the capability to capture both quantitative and qualitative information of unknown analytes with a variety of physiological properties in a wide range of chemical space, and the data banking approach could be routinely applied to minimize the needs for repeating in-life experiments and long-term storage of biological samples. It was anticipated that such a superior LC/MS would change the way how analysis is performed in the biopharmaceutical/biotech industry, academia, and possibly clinical laboratories.

Challenges and Opportunities in High Resolution LC/MS

Alexander Makarov talked about the challenges and opportunities in high resolution LC/MS. The complexity of typical samples for GC/MS and LC/MS measurements could be matched to the capabilities of modern single and tandem mass spectrometers only by using additional separation or specialized sample preparation procedures. The rise of high resolution/accurate mass (HR/AM) analyzers has enabled significant reduction of this gap and reduction of requirements on chromatography, thus making sample analysis more robust and method development simpler [2–4]. However, the eventual closure of this gap would require further drastic expansion of the dynamic range of analysis without sacrificing sensitivity and speed. In addition, fundamental issues of spray-based ionization need to be addressed, such as its stability, efficiency at high analyte flow rates, and reduction of dependence on standards. The set of desired features for both routine and discovery LC/MS instruments were presented, wherein ultimate simplicity is achieved by shifting a lion's share of selectivity towards HR/AM mass spectrometry.

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How the Rise of Ion Mobility Based Manipulations might/will Change the Way LC is Used with MS

Dick Smith spoke about how the rise of ion mobility separations (IMS) and their use with MS will potentially impact the practice of LC/MS. He showed two examples from his laboratory: one where IMS was added between the HPLC and the MS for improving broad proteome measurement coverage, and a second where IMS was used in place of HPLC to provide increased measurement throughput for metabolomics and lipidomics measurements. He then briefly discussed new developments based upon structures for lossless ion manipulations (SLIM) that are providing greatly improved IMS resolution and peak capacities in conjunction with MS, and showed several examples of the separations achievable [5, 6]. He concluded by sharing his future perspectives on the impact IMS, and specifically IMS based upon SLIM, may have for the practice LC/MS. He envisioned that the IMS developments, by providing fast higher throughput separations in conjunction with efficient ion utilization, may well obviate the need for use of on-line HPLC for many future applications of MS.

Open Audience Discussions

The audience was highly engaged in Q&A during the presentations by Alexander Makarov and Dick Smith. Other invited presenters shared their perspectives on the next generation of LC/MS systems. Resolving power (for both on-line separation and mass measurement) and the limit of resolution of ion mobility separation were discussed. The efficiency of various ionization techniques was debated. Rohan Thakur (Bruker) presented a view that the future MS system would incorporate networked machine learning capabilities, thus becoming more intelligent and minimizing the need for repeat studies (measurements) that would ultimately lead to improved efficiency. Gerard Hopfgartner (Universite de Geneve) emphasized that one system may not fit for all applications, e.g., LC/MS may be designed simpler for on-site analysis at the point of care or more complicated to address new analytical challenges; compound identification, quality control, and software tool for data process across platforms were the issues to be addressed. John Fjeldsted (Agilent Technologies) pointed out that mass spectrometry needed to be fit for purpose; instrumentation for target analysis should continue to be reduced in size and complexity; for workflows focused on characterization and untargeted discovery, techniques such as IMS will play an ever-increasing role in supporting isomer and conformer analysis. Mike Morris (Waters) discussed that the peak capacity in the next generation LC/MS would increase with the increase of mass spectrometer, ion mobility, and chromatography resolutions; integrated network data would increase the confidence in results with faster sample turnaround. Hopfgartner, Fjeldsted, and Morris also shared a similar opinion that the ionization process needed to be less dependent on analyte and matrix effects so the ion responses can be normalized.

Concluding Thoughts

The pilot workshop successfully brought industrial (application) scientists, instrument experts, and academic scientists together for discussions on technology advancements in LC/MS. The challenges and needs in real life applications typically are the drivers for innovation and technology advancements. The large attendance and supportive comments from the attendees demonstrated that the discussion on the developments of LC/MS should continue at future ASMS meetings.

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