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Flow Chemistry Monitoring and Optimization Using Compact Mass Spectrometry
Advion, Inc.
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Advances in High-Performance Liquid Chromatography and Mass Spectrometry
MARCH 2016
For the record: The editorial content in this supplement was created without direct involvement of C&EN reporters or editors.
The initial clinical applications of MS have been as detection assays, offering a more sensitive and specific complement to immunoassays. Although far more expensive and complicated to use than an ELISA kit, MS can also readily distinguish closely-related molecules that might generate false-positive results in an antibody-based test, thereby achieving superior sensitivity and accuracy. For example, Lockwood cites the challenge of using immunoassays to detect the low concentrations of testosterone found in serum samples from women and children.

Clinical researchers have been steadily pushing the performance of the technology into exciting new frontiers, including broad profiling of the metabolome to identify useful prognostic or diagnostic indicators of disease states or drug response. Much of the work in this area has used a combination of liquid chromatography separation and tandem mass spectrometry (LC-MS/MS) to go after ‘targeted’ sets of known metabolites, but researchers are increasingly embarking on ‘untargeted’ screens that attempt to capture the full biomolecular diversity of patient specimens—according to one recent review, up to 5,000 distinct metabolites have been detected in humans to date.

Many metabolites undergo subtle chemical modifications that critically alter their function or bioavailability, but also make them challenging to identify via standard analysis. In one of the Top 10 Articles presented here—a collection of our most-read articles on the subject of LC and MS—the authors employ a variant of LC based on ‘in-source collision-induced dissociation’ (ISCID) to separate molecules from their modifications, which are then identified via specialized software. This made it possible to identify 900 different modified metabolites in urine samples from patients with liver cirrhosis.

LC-MS/MS has been the standard method for metabolomics profiling for some time now, but other methods are also being explored. For example, ion mobility MS (IM-MS) uses an electrical field to separate ions based on properties such as size and shape prior to MS analysis. This can in turn be coupled with ultraperformance liquid chromatography (UPLC) to achieve superior separation and enhanced metabolite identification with a higher signal-to-noise ratio.

MS-based imaging is also opening up intriguing new possibilities, which were explored in a recent feature from Analytical Chemistry. Typical experiments entail sequential collection of MS data at discrete points on the sample, generating site-specific metabolomic data that can be directly mapped to the histological features of the specimen. This could prove extremely useful for characterizing tumor heterogeneity or defining the borders of a malignancy, and can even offer insights into drug response at the cellular level.

All of these advances collectively suggest that a future is rapidly approaching in which MS-based techniques are a major component of the clinical diagnostics world. In that spirit, please enjoy this special focus on Advances in Chromatography and Mass Spectrometry.

References
TOP TEN CHROMATOGRAPHY AND MASS SPECTROMETRY PAPERS
These are the most-read papers in high-performance liquid chromatography (HPLC)/mass spectrometry (MS) from Analytical Chemistry and Journal of Proteome Research over the past 12 months.

Mass-Spectrometry-Based Molecular Characterization of Extracellular Vesicles: Lipidomics and Proteomics
Simion Kreimer†, Arseniy M. Belov†, Ionita Ghiran∥, Shashi K. Murthy†, David A. Frank⊥, and Alexander R. Ivanov‡†
†Northeastern University, Boston, Massachusetts, USA || Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA
⊥ Dana—Farber Cancer Institute, Boston, Massachusetts, USA # Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts, USA
J. Proteome Res., 2015, 14 (6), pp 2367–2384
DOI: 10.1021/pr501279t

Advances in Ultrahigh-Pressure Liquid Chromatography Technology and System Design
Jelle De Vos, Ken Broeckhoven, and Sebastiaan Eeltink*
Vrije Universiteit Brussel, Brussel, Belgium
DOI: 10.1021/acs.analchem.5b04381

Elucidation of the Ebola Virus VP24 Cellular Interaction and Disruption of Virus Biology through Targeted Inhibition of Host-Cell Protein Function
Isabel Garcia-Dorival†‡, Weining Wu†, Stuart Dowall§, Stuart Armstrong†‡, Olivier Touzelet†, Jonathan Wastling†‡, John N. Barr∥, David Matthews⊥, Miles Carroll‡§, Roger Hewson*‡§, and Julian A. Hiscox*†‡
† University of Liverpool, Liverpool, United Kingdom ‡ NIHR Health Protection Research Unit in Emerging and Zoonotic Infections, Liverpool, United Kingdom § Public Health England, Salisbury, United Kingdom || University of Leeds, Leeds, United Kingdom ¶ University of Bristol, Bristol, United Kingdom
J. Proteome Res., 2014, 13 (11), pp 5120–5135
DOI: 10.1021/pr500556d

Toward Merging Untargeted and Targeted Methods in Mass Spectrometry-Based Metabolomics and Lipidomics
Tomas Cajka† and Oliver Fiehn*†‡
† University of California Davis, Davis, California, USA ‡ King Abdulaziz University, Jeddah, Saudi Arabia
DOI: 10.1021/acs.analchem.5b04491

Mass Spectrometry and Antibody-Based Characterization of Blood Vessels from Brachylophosaurus canadensis
Timothy P. Cleland*†, Elena R. Schroeter†, Leonid Zamborg§, Wenxia Zheng†, Ji Eun Lee§∥, John C. Tran⊥, Marshall Bern#, Michael B. Duncan∥∥, Valerie S. LebleuVO◆, Dorothy R. Ahlf⊥, Paul M. Thomas⊥, Raghu KalluriVO◆∥∥, Neil L. Kelleher⊥, and Mary H. Schweitzer†∥
† North Carolina State University, Raleigh, North Carolina, USA § University of Illinois, Urbana, Illinois, USA || Korea Institute of Science and Technology, Seoul, Republic of Korea ¶ Northwestern University, Evanston, Illinois, USA # Protein Metrics, San Carlos, California, USA ∥ Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA ◆ University of Texas MD Anderson Cancer Center, Houston, Texas, USA ○ Beth Israel Deaconess Medical School, Boston, Massachusetts, USA ○ Harvard Medical School, Boston, Massachusetts, USA □ University of California Davis, Davis, California, USA
J. Proteome Res., 2015, 14 (12), pp 5252–5262
DOI: 10.1021/acs.jproteome.5b00675

These are the most-read papers in high-performance liquid chromatography (HPLC)/mass spectrometry (MS) from Analytical Chemistry and Journal of Proteome Research over the past 12 months.
Core–Shell, Ultrasmall Particles, Monoliths, and Other Support Materials in High-Performance Liquid Chromatography

Nobuo Tanaka† and David V. McCalley*
†GL Sciences Inc., Saitama, Japan * University of the West of England, Bristol, U.K.
DOI: 10.1021/acs.analchem.5b04093

Novel Approach for Analysis of Bronchoalveolar Lavage Fluid (BALF) Using HPLC-QTOF-MS-Based Lipidomics: Lipid Levels in Asthmatics and Corticosteroid-Treated Asthmatic Patients

Yun Pyo Kang†, Won Jun Leet†, Ji Yeon Hong†, Sae Bom Leet†, Jeong Hill Park†, Donghak Kim†, Sunghyouk Park†, Choon-Sik Park$, Sung-Woo Park*$, and Sung Won Kwon†
† Seoul National University, Seoul, Republic of Korea ‡ Konkuk University, Seoul, Republic of Korea § Soochunhyang University Bucheon Hospital, Bucheon, Republic of Korea
J. Proteome Res., 2014, 13 (9), pp 3919–3929
DOI: 10.1021/pr5002059

Miniature and Fieldable Mass Spectrometers: Recent Advances

Dalton T. Snyder, Christopher J. Pulliam, Zheng Ouyang, and R. Graham Cooks*
Purdue University, West Lafayette, Indiana, USA
DOI: 10.1021/acs.analchem.5b03070

High-Pressure Open-Channel On-Chip Electroosmotic Pump for Nano-flow High Performance Liquid Chromatography

Wei Wang†, Congying Gu†, Kyle B. Lynch†, Joann J. Lu†, Zhengyu Zhang†, Qiaosheng Pu‡, and Shaorong Liu†
† University of Oklahoma, Norman, Oklahoma, USA ‡ Lanzhou University, Lanzhou, P.R. China
DOI: 10.1021/ac4040345

Nontargeted Modification-Specific Metabolomics Study Based on Liquid Chromatography–High-Resolution Mass Spectrometry

Weidong Dai†, Peiyuan Yin†, Zhongda Zeng†, Hongwei Kong†, Hongwei Tong†, Zhiliang Xu†, Xin Lu†, Rainer Lehmann*§∥⊥, and Guowang Xu††
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Anal. Chem., 2016, 86 (18), pp 9146-9153
DOI: 10.1021/ac502045j
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Introduction
A vital component of developing flow chemical synthesis is the ability to monitor the reactions in real-time. Techniques such as liquid chromatography/mass spectrometry (LC/MS) and gas chromatography/mass spectrometry (GC/MS) can take too long, whilst techniques such as infrared (IR) and near-infrared (NIR) do not have the specificity required to obtain detailed information on the reaction. This note covers work carried out at Leeds University with co-workers from Durham University in the area of flow chemical synthesis using the expression Compact Mass Spectrometer (CMS) from Advion of Ithaca, NY.

Instrument Set-up
A syringe was used such that the reaction mixture was infused into the mass spectrometer via a valve. Data from the expression CMS were then fed into the reaction optimisation and data processing software suite.

Results
Data obtained for the anomeric deacetylation reaction are shown in Figure 1, which illustrates monitoring, in real-time, of the simultaneous increase in product and decrease in starting material. Intermediates and impurities are also observed, thus providing valuable information about the reaction. This information gives the chemist an advantage in reaction/process understanding that is not available from other techniques.

The detailed data obtained mean that reaction progress is understood to a much higher degree, enabling further optimization, which is vital for process development, and can provide increased mechanistic understanding that can be vital in developing the chemistries further.

Conclusions
• The expression CMS is an ideal mass spectrometer for integration with flow chemistry systems.
• The input and output options available on the expression give it a uniquely flexible interfacing capability.

• MS provides detailed and real-time information about reactions often not possible from other analytical techniques (e.g., chromatography, NMR, IR/NIR, ultraviolet spectroscopy).
• Advion is experienced in the integration of the CMS into novel synthetic chemistry solutions.

Acknowledgments
Thank you to Ian Baxendale and Christian Stanetty at Durham University as well as Richard Bourne and Nicholas Holmes at Leeds University.

Additional information: http://www.advion.com/applications/expressions/applications/reaction-monitoring-by-fia/
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