Report on 6th International meeting on MS and related techniques in advanced analytical science.

Bernie Monaghan – Contributing Editor

The "6th International MS Symposium" held in Manchester, UK 12-14th April was the latest in an occasional series of scientific meetings initiated (by Micromass) in 1998. Sponsorship of the meetings has now been taken over by Waters MS Technologies. The format is that of a legitimate scientific meeting, open to all, that typically attracts Ca 150+ delegates.

The forward to the 1998 book of abstracts sums up the original vision, which remains true today - 'a unique scientific forum focusing on high resolution MS and related techniques - that transcends the conventions of a vendor's user meeting'.

Clearly since 1998 the world of MS and Associated Techniques has changed beyond all recognition with many application areas and enabling technologies not considered as suitable for MS thirteen years ago being common place or least tagged 'emerging'.

Delegates were invited to learn about the latest advances in High Resolution MS, Ultra Performance LC, Ion Mobility Separations and Advanced Informatics Tools for Industrial, Environmental, Pharmaceutical and Life Science Applications.

- Combined Quantitative/Qualitative Analytical Strategies
- Targeted/Untargeted Screening of Complex Environmental & Food Samples
- High Definition Drug Metabolite Characterisation & Isomer Confirmation
- High Sensitivity Dried Blood Spot Analysis in DMPK Studies
- High Sensitivity Regulated BioAnalysis
- HD Visualisation of Biopharmaceuticals - Protein Structure/Folding
- HD Quantitative Profiling of Endogenous Metabolites/Lipids & Proteins
- HD Tissue Imaging MALDI

A truly International gathering of speakers, as can be seen in the programme below, gave over 30 presentations and although some were scientists from the various Waters MS research groups, many speakers from various Industrial concerns and Academic Institutions also spoke on a variety of topics. Such were the topics that were deemed worthy of discussion that parallel sessions to discuss Metabolic profiling and Molecular and Protein studies and Food/Environmental/Clinical and Proteomics were accommodated. Although the space available here prevents a review of all 30+ presentations abstracts are shown, one from each session. This is not to say that these were the star presentations (that is far too a subjective topic to get into) but just ones that caught the authors' attention for one reason or another.

SESSION 1 - TECHNOLOGIES

13:20 -13:30 Welcome
Tim Riley - Waters Corporation, Milford, MA, USA

13:30 - 14:10 From High Vacuum to Atmospheric Pressure, the Irresistible Rise of Mass Spectrometry Over the Past 100 Years.
Patrick Arpino - Société Française de Chimie, Paris, France

14:10 - 14:40 Development of an Integrated High-Performance Microfluidic LC Platform.
Geoff Gerhardt - Waters Corporation, Milford, MA, USA

14:40 - 15:10 Time of Flight Mass Spectrometry - Current Status and Future Perspectives.
Jason Wildgoose - Waters MS Technologies, Manchester, UK

15:10 – 15:40 Stacked Ring Ion Guides - Design and Application.
Kevin Giles - Waters MS Technologies, Manchester, UK

16:00 - 16:30 Identification & Quantitation of Candidate Dietary Biomarkers by Means of SIDA-UPLC-QuanToF-MS and HPLC-MS/MS.
Timo Stark - Food Chemistry & Molecular Sensory Science TUM, Germany

16:30 – 17:00 High Resolution TOF and the Impact in Lipid Biomarker Discovery... a Reality or a Dream.
Jose Castro-Perez - Merck & Co., Inc. , Rahway, NJ, USA

17:00 – 17:30 The Potential of On-Line HPLC-IMS-MS for Qualitative and Quantitative Protein Profiling in Complex Biological Samples.
Robert Tong - Waters MS Technologies, Manchester, UK

SESSION 2 - IMAGING MS

09:00 – 09:40 Ion Mobility and Molecular Histology: New Glasses for the Doctor!
Ron Heeren - FOM-AMOL Amsterdam, NL

09:40 – 10:10 High Definition MALDI Imaging
Emmanuelle Claude - Waters MS Technologies, Manchester, UK

SESSION 3A - METABOLIC PROFILING

10:45 – 11:15 Metabolite Identification, Driving the Development of Drugs
Stephen McDonald - Waters Corporation, Milford, MA, USA

11:15 – 11:45 The Development of Metabolome-Based Predictors of Non-Alcoholic Fatty Liver Disease Using UPLC/HDMSE
Jonathan Barr - OWL Genomics, Spain

11:45 – 12:15 'Title to be Announced (Metabolite Screening)'
Benno Ingelse, Department of Toxicology & Drug Disposition, MSD, Oss, NL

12:15 – 12:45 UPLC/High Resolution Mass Spectrometry Combined with Ion Mobility Separation/MSE - Techniques for the Analysis of in vivo Drug Metabolism Studies
Stefan Blech - Boehringer Ingelheim Pharma GmbH & Co, Germany.

SESSION 4A - FOOD/ENVIRONMENTAL/CHEMICAL ANALYSIS

14:00 – 14:30 Extending the Capabilities of Tandem Quadrupole MS for Ultra Trace Analysis"
Dan McMillan - Waters MS Technologies, Manchester, UK

14:30 – 15:00 Nano UPLC/QTOFMS multiscreening of regulated and emerging food contaminants.
Michel Nielen - RIKILT-Institute of Food Safety, Wageningen, NL.

15:00 – 15:30 Dinosaurs for lunch: Proteomics from Food Fraud and Archaeology Studies to Determine the Species Origin of Gelatine in Foods.
Helen Grundy - Food & Environmental Research Agency, York, UK.

16:00 - 16:30 Addressing Chemical Diversity with Novel Developments in Inlet Technology
Tim Jenkins - Waters MS Technologies, Manchester, UK

16:30 – 17:00 BAF1: A Missing Puzzle Piece in Amino Acid Allocation in Plants
Mark Stahl - ZMBP, Universität Tübingen, Germany

17:00 – 17:30 Emerging Strategies for the Early Detection of Contamination & Infection Across the Agri-food Supply Chain.
Chris Elliott - Queen's University, Belfast, UK.

SESSION 3B - MOLECULAR & PROTEIN STRUCTURE

10:45 – 11:15 Metabolite Structure Determination Using Combined Ion Mobility Separation-Mass Spectrometry & Molecular Modelling.
James Langridge - Waters MS Technologies, Manchester, UK

11:15 – 11:45 IM-MS for the Structural and Dynamical Biology.
Justin Benesch - Oxford University, UK

11:45 – 12:15 Unravelling Biomolecular Assembly Pathways by Mass Spectrometry.
Alison Ashcroft - Leeds University, UK

12:15 – 12:45 Characterizing the Higher-Order Structure of Proteins by Solution- and Gas-Phase H/D Exchange Mass Spectrometry.
Kasper D. Rand - Swiss Inst. of Bioinformatics, CH

SESSION 4B - PROTEOMICS

14:00 – 14:30 No hiding place: Strategies for Global Absolute Proteome Quantification.
Rob Beynon - Liverpool University, UK

14:30 – 15:00 Quantitative Proteomics Strategies for Interrogating the Membrane Proteome.
Kathryn Lilley - Cambridge University, UK

15:00 – 15:50 Confident Assignment of Phosphorylation Sites in Peptides by the Mascot Delta Score.
Bernhard Kuster - TUM, Munich, Germany

16:00 - 16:30 Shotgun Proteomics in a Non-Sequenced Plant Species, Fact or Fiction?
Sebastien Carpentier - Plant Research International, NL

16:30 – 17:00 Discovery and Validation of Novel Biomarkers for Gaucher Disease
Gertjan Kramer - Academic Medical Centre, Amsterdam, NL

17:00 – 17:30 Ion Mobility Separation Coupled with MS Detects Two Structural States of Alzheimer's Disease Aβ1–40 Peptide Oligomers
Michal Dadlez - IBB, Warsaw, Poland

SESSION 5 - BIOANALYSIS

09:00 – 09:30 High Sensitivity Dried Blood Spot Analysis in DMPK Studies.
Rob Plumb - Waters Corporation, Milford, MA, USA

09:30 – 10:00 ELISA vs LC-MS/MS: A real life comparison.
Timothy Sangster - Charles River, Edinburgh, UK

10:30 – 11:00 High Sensitivity Bioanalysis Using nanoUPLC with the Xevo TQ-S.
Lieve Dillen - Janssen Research & Development, BE

11:00 - 11:30 Implementation Of A Xevo TQ-S System Within A Sciex Exclusive Laboratory.
Mohammed Abrar - York Bioanalytical, York, UK

11:30 - 11:45 CLOSING REMARKS
Brian W. Smith - Waters MS Technologies, Manchester, UK

Development of an Integrated High-Performance Microfluidic LC Platform

Geoff Gerhardt, Waters Corporation, Milford, MA, USA.

A presentation was given describing the development and application of an integrated microfluidic device capable of high-performance liquid chromatography. The primary driver for this research effort was to develop a device that would address the ease-of-use/robustness issues associated with nano-scale chromatography while maintaining state-ofthe-art chromatographic performance. While the microfluidics field has been active since the late 1980's, most of systems developed have been suitable for only low-pressure electrophoretic or low-performance LC separations.

No microfluidic platform was available that could withstand pressures required for high-performance LC (for example, 10,000 psi). We recognised this deficiency and started an effort over six years ago to develop a novel, high-pressure microfluidics platform. A brief summary of this development effort was given, covering initial discovery of the multi-layer ceramic platform to our present-day embodiment of this technology.

Currently, the microfluidic consumable integrates not only the fluidic elements such as the columns, but also the electrospray interface, temperature control and data storage into a single, robust cartridge.

While the initial target for this concept was for the nano-scale LC proteomics application, further development of this high-strength ceramic platform has enabled significant expansion of its performance envelope into the small-molecule application space.

A materials research effort yielded a high-strength, inert ceramic that has enabled a microscale column format (for example, 300µm), capable of >10,000psi operation. This column format allows all the benefits of low-flow chromatography to be realised while maintaining the ease-of-use and robustness of a traditional analytical-scale LC system. Application examples of both the nano- and micro-scale integrated consumables were shown to illustrate that robust performance that can now be achieved at either the nano- or micro-scale with a microfluidic cartridge consumable.

Ion Mobility and Molecular Histology: New Glasses for the Doctor

Ron M.A. Heeren, FOM-AMOLF, Science Park 104, 1098 XG Amsterdam, The Netherlands

The study of molecular processes underlying diseases is one of the key topics in life science research. Mass spectrometry based high throughput proteomics and separation technology are common to this field and provide detailed insight in the composition of body fluids and tissue homogenates. They however lack one piece of crucial information, the detailed spatial distribution of the molecular compounds identified.

In biomedical research medical practitioners often employ histology to obtain insight in the disease-altered morphology of tissue. This only provides generic morphological information unless immuno-histochemistry is used to determine the distribution one specific known protein. Imaging mass spectrometry has evolved to bring these two disciplines, mass spectrometry and histology, together providing a new tool for biomedical research. This approach, sometimes referred to as molecular histology, can take great benefit from the introduction of gas-phase ion mobility separation. Ion mobility separation combined with imaging mass spectrometry can reveal new tissue details that remain hidden with conventional molecular imaging approaches. In this contribution wethe development and applications of this new chemical microscope were discussed.

Unravelling Biomolecular Assembly Pathways by Mass Spectrometry

Alison E Ashcroft, Astbury Centre for Structural Molecular Biology, Faculty of Biological Sciences, University of Leeds, UK

In vivo the majority of proteins function within non-covalently bound macromolecular complexes rather than alone. Unravelling the assembly pathways of these complexes is important for understanding how proteins interact with other proteins and ligands and, in cases where such complexes are associated with disease, for devising means of assembly inhibition. ESI-IMS-MS and ESI-MS/MS are highly suitable methods for probing the assembly pathways of macromolecular complexes including, for example, the self-aggregation of certain proteins into amyloid fibrils. Monitoring amyloid fibril formation in vitro from beta-2-microglobulin, ESI-MS has been used to compare, in terms of shape and stability, monomeric and oligomeric conformers detected within transient, heterogeneous protein ensembles on two different, fibril-forming pathways.

Metabolite Screening in Drug Discovery: Managing the Quan-Qual Workflow

Benno Ingelse, Department of Toxicology and Drug Disposition, MSD, Oss, The Netherlands

The new generation Time of Flight Mass Spectrometers allow accurate and sensitive quantitation of parent drug compounds. This platform will be applied to determine the metabolic stability of NCE's and simultaneously detect the most abundant metabolites (metabolic hot spots). To prevent data processing from becoming a bottle-neck we compared different approaches were investigated. The effectiveness of the mass defect filter is compared with in-silico metabolite predictions.

BAF1: A Missing Puzzle Piece in Amino Acid Allocation in Plants

Mark Stahl, Universität Tübingen, ZMBP – Zentrale Bereiche Auf der Morgenstelle 1, 72076 Tuebingen, Germany

Amino acids are the main transport form of organic nitrogen in plants. Up to now numerous import proteins have been identified, but only very little is known about cellular amino acid export. However, during processes like seed and pollen development or for transport into non-living root tracheaery elements, amino acid export is indispensable. BAF1 was identified as a bidirectional amino acid transporter in Arabidopsis thaliana. It localises to the plasma membrane of seed chalazal and root pericycle cells. Metabolomic comparison of wild type and knock out mutants revealed the importance of BAF1 in amino acid homeostasis of siliques.

Bioanalysis of Small Molecules and Biotherapeutics on Dried Blood Spot Cards using Ultra High Sensitivity MS/MS Coupled to Sub 2µm LC

Robert S Plumb[1], Paul D Rainville[1] and Christopher A Evans[2]
1. Waters Corporation, Milford, MA, USA
2. GlaxoSmithKline, 709 Swedeland Road, King of Prussia, PA 19406, USA

The use of dried blood spot cards, similar to the Guthrie card, for the sampling of preclinical animal studies has attracted a significant amount of attention over the last two years in the pharmaceutical industry. This is due to the reduction in the number of animals required for the studies, the superior quality of the PK data and the lower operating costs compared to plasma collection. However the small sample volume, 6-10µL, can pose a serious sensitivity challenge. This presentation shows how the use of an ultra high sensitivity tandem quadrupole MS/MS system, equipped with a conjoined T-Wave ion guide, coupled to a sub 2µm LC system for the analysis of small molecules and therapeutic peptides such as desmopressin in blood from the blood card. It was demonstrated how sensitivity levels as low as 100pg/mL were obtained from the injection of a small volume of sample. This presentation also described how the use of RADAR MS full scan technology was employed to optimise the separation methodology and identify which type of blood spot card would be applicable for each candidate drug compound undergoing analysis.

Summary

All in all the meeting is a worthy addition to the Mass Spectrometry circuit with interesting, emerging technologies from a leading supplier but also a view from Researchers who ultimately will be the ones who will decide if a new technology is worth 'picking up and running with' or not.