THE ENABLING ROLE OF MS AND RELATED TECHNIQUES IN THE HEALTH AND LIFE SCIENCES
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<td>09:00</td>
<td>Welcome</td>
<td>Brian W. Smith</td>
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<td>09:15</td>
<td>Opening</td>
<td>Professor Simon Gaskell</td>
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<td>09:30</td>
<td>Keynote: New IMS-MS Technologies for Proteomics based on the shapes of Anhydrous Protein Ions</td>
<td>Professor David E. Clemmer</td>
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<td>10:30</td>
<td>Technology: Combining Travelling Wave, oa-TOF and Quadrupole Technologies for Analytical Advantage</td>
<td>Dr John Hoyes</td>
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<td>11:30</td>
<td>Metabolomics: A Fishy Tale of Metabolomics</td>
<td>Dr Julian Griffin</td>
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<td>Metabolomics: Metabolomic Applications in Veterinary Medicine</td>
<td>Dr Philip Whitfield</td>
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<td>12:30</td>
<td>Metabolomics: Application of Ion Mobility Mass Spectrometry and Advanced Statistical Methods to Metabonomic/Metabolomic Studies</td>
<td>Dr John Shockcor</td>
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<td>14:30</td>
<td>Pharmaceutical: Application of Mass Spectrometry to Lipids Analysis in Drug Discovery: Biomarkers, Kinetics, and Biological Fate</td>
<td>Dr Andrew Tyler</td>
<td>Novartis, USA</td>
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<td>15:00</td>
<td>Pharmaceutical: Strategies for Drug Metabolite Characterisation using UPLC/Time-of-Flight Mass Spectrometry with Intelligent Software</td>
<td>Dr Daniel Weston</td>
<td>AstraZeneca, UK</td>
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<td>15:30</td>
<td>Bio-Pharma: Studies of Protein-Ligand Interactions with LFA-1 and Bcl-2 by Mass Spectrometry</td>
<td>Dr John Crosby</td>
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<td>16:00</td>
<td>Tea</td>
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<td>19:00 for 19:30</td>
<td>Dinner: The Yang Sing Restaurant [ 34 Princess St. ]</td>
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## Thursday 08 May 2008  [Museum of Science & Industry]

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<td>Professor Michael Dunn [UCD Conway Institute, IRL]</td>
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<td>Proteomics: Quantitative Proteomics and Systematic Bias</td>
<td>Dr Kathryn Lilley [Cambridge University]</td>
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<td>Proteomics: QCAL – A Novel Standard for Assessing Instrument Conditions for Proteomics Analysis</td>
<td>Dr Claire Eyers [Manchester University]</td>
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<td>11:30</td>
<td>Peptide Fragmentation: Evidence for Structural Variants of α- and β-Type Peptide Fragment Ions Using Combined IonMobility/Mass Spectrometry</td>
<td>Dr Isabel Riba-Garcia [Manchester University]</td>
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<td>12:00</td>
<td>Protein Structure: On the Destruction, Deconstruction, and Eventual Determination of Protein Quaternary Structure</td>
<td>Dr Brandon Ruotolo [Cambridge University]</td>
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<td>12:30</td>
<td>MS Imaging: IMS-MSI Nearly a New Palindrome for Mass Spectrometry Imaging</td>
<td>Professor Malcolm Clench [Sheffield Hallam University]</td>
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<td>13:00</td>
<td>Lunch / Applications Workshops / Posters</td>
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<td>Clinical: Practical Use of LC-MS/MS in a Routine Hospital Laboratory</td>
<td>Brian Keevil [Manchester U. Hospitals NHS Trust]</td>
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<td>15:00</td>
<td>Clinical: Analysis &amp; Quantification of Diagnostic Plasma Markers &amp; Protein Signatures for Gaucher Disease</td>
<td>Professor Johannes Aerts [University of Amsterdam, NL]</td>
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<tr>
<td>15:30</td>
<td>Clinical: Plasma Lipid Profiling of Gaucher Disease: Biochemical Markers to Evaluate Therapeutic Intervention</td>
<td>Dr Philip Whitfield [Liverpool University]</td>
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<tr>
<td>16:00</td>
<td>Clinical: Clinical Mass Spectrometry from Research to Routine</td>
<td>Dr Michael Morris [Waters MS Technologies]</td>
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<td>16:30</td>
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## Friday 09 May 2008  [Waters MS Technologies, Atlas Park]

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<tr>
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<tr>
<td>09:30-16:00</td>
<td>Workshop #1 – Label-Free Proteomics</td>
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<td>09:30-16:00</td>
<td>Workshop #2 – Metabolic Profiling</td>
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When a packet of a mixture of ions is introduced into a buffer gas under the influence of an electric field individual components will separate because of differences in their mobilities through the gas. This separation, known as ion mobility spectrometry (IMS), is efficient (in that it is very fast and offers a very high peak capacity). During the last ten years the approach has been combined with MS detection and a front end LC separation (creating a three dimensional analysis). This talk will focus on the development of these high-capacity separation. Advantages associated with parallel dissociation will be provided and the application to complex mixtures of proteins found in plasma will be discussed. Finally, we have recently constructed several instruments in which IMS drift tubes are combined in series. This allows the ability to conduct IMS-IMS and IMS-IMS-IMS studies. When many systems are strung in series (more than 20) the drift field can be applied at varying frequencies, allowing a new type of separation (an ion filter). We refer to this filtering technique as overtone mobility spectrometry. This talk will provide the first brief description of this approach.
Combining Travelling Wave, oa-TOF and Quadrupole Technologies for Analytical Advantage

John Hoyes
Waters MS Technologies Centre, Manchester, United Kingdom

Since the introduction of the “Q-TOF 1” mass spectrometer in early 1997 the orthogonal TOF analyser has iterated through several generations resulting in an instrument up to two orders of magnitude more sensitive and with much higher resolution than the first systems. The introduction of Travelling-Wave (T-Wave) technology initially designed for fast switching collision cells has seen similar leaps in its development finding new applications in Ion Mobility Separation (IMS) and in improving the duty cycle of downstream TOF analysers. The talk will focus on the development on these two complementary technologies and explains how our vision of intelligent ion management and delivery will lead to a whole range of enabling mass analyser combinations capable of addressing the evolving needs of the analytical community.

A Fishy Tale of Metabolomics

Julian Griffin
Department of Biochemistry, University of Cambridge, United Kingdom

To understand the regulation of fat metabolism and how this interacts with disease processes we have been using LC-MS to profile lipid species in a variety of tissues and blood plasma. This has included applications to understand gene function in mice and biomarker discovery in human blood plasma samples. This seminar will focus on a study of weight loss in obese women and the potential beneficial effects of polyunsaturated fats in fish oil. While GC-MS was able to determine the impact of weight loss and dietary intervention on total fatty acid content of blood plasma, LC-MS demonstrated that different lipid species were affected to different degrees and in particular that the combination of weight loss and fish oil supplementation selectively decreased the triglyceride content.
Metabolomic Applications in Veterinary Medicine
WEDNESDAY 07 MAY 2008 ■ 12:00
Phillip Whitfield
Proteomics and Functional Genomics Research Group, Faculty of Veterinary Science,
University of Liverpool, Liverpool, United Kingdom

Of all classes of biological molecules, metabolites are the most conserved across species, and report directly on the metabolic and physiological status of the subject. Metabolomics can therefore provide a coherent view of the response of biological systems to a variety of genetic and environmental influences. Furthermore, readily accessible metabolites raise the possibility of identifying surrogate biomarkers of specific disease states. This information could have significant diagnostic applications, particularly if such markers can be used to direct treatments. Metabolomics is now beginning to make a significant impact on the landscape of veterinary research. We are employing mass spectrometry-based metabolomic strategies to investigate metabolic regulation and dysfunction in animals. In an exemplar project, liquid chromatography-mass spectrometry was used to characterise the metabolic disturbances associated with canine liver disease. The analyses not only distinguished control and affected cohorts of dogs but also discriminated animals with congenital and acquired forms of hepatic disease. This approach demonstrates the potential of metabolomics to improve diagnostic capabilities and provide greater insights into the pathogenesis of disease states throughout veterinary medicine.
Application of Ion Mobility Mass Spectrometry and Advanced Statistical Methods to Metabonomic/Metabolomic Studies

WEDNESDAY 07 MAY 2008 ■ 12:30

John Shockcor¹, Jose Castro-Perez¹, Kate Yu¹, Emma MarsdenEdwards², and Henry Shion¹

1. Waters Corporation, Milford, MA, United States
2. Waters Corporation, Manchester, United Kingdom

From the post genomics and proteomics era, metabolomics has emerged as a vital area of research. Metabolic profiles of biological fluids contain a vast array of endogenous low-molecular weight metabolites. Changes in these profiles resulting from perturbations of the system can be observed using information rich analytical techniques, such as mass spectrometry. Due to the complexity of the samples new separation techniques like ultra performance liquid chromatography (UPLC) have become an accepted standard for these studies providing the researcher with large information rich data sets. Mining these data sets to extract those molecules which have changed significantly is an imposing task. Traditional profiling techniques which involve scan by scan comparison of the data have been used to compare small datasets; however, these approaches are not well suited to studies involving large numbers of samples with complex spectral information. Metabolomic approaches have been employed to mine large complex data sets with great success. These approaches typically use multivariate statistical methods, such as principal component analysis (PCA), to highlight differences between samples based on observed spectral patterns. However, these methods are often not well suited to identifying subtle changes and can be biased by large variations within a sample class. New multivariate statistical methods, like orthogonal projection to latent structures (OPLS), have been developed, which can overcome many of the problems observed when using PCA.

Another recent development, ion mobility mass spectrometry (IMS) is now also being employed to aid in extracting critical information on fragmentation to aid in elucidation of unknowns and confirm database hits from these metabolomic datasets.

We will illustrate these statistical and analytical methods with several examples obtained on a variety of sample types.
Application of Mass Spectrometry to Lipids Analysis in Drug Discovery: Biomarkers, Kinetics, and Biological Fate

WEDNESDAY 07 MAY 2008 ■ 14:30

Andrew N. Tyler

Cardiovascular & Metabolism Department, Novartis Institutes for Biomedical Research, Cambridge, MA, USA

In the fields of cardiovascular medicine and diabetes, there are numerous potential drug targets whose actions are involved in the synthesis and metabolism of lipids. Mass spectrometry is a powerful analytical tool in this regard, because it is uniquely able to profile diverse classes of lipids and related molecular species derived from in vitro and in vivo samples. In this presentation, examples of application to lipid biomarkers will be discussed, as well as studies designed to probe biosynthetic lipid pathways and the effects of enzyme pathway modulation on lipid profiles.
Strategies for Drug Metabolite Characterisation using UPLC/Time-of-Flight Mass Spectrometry with Intelligent Software

WEDNESDAY 07 MAY 2008 ▪ 15:00

Daniel J. Weston¹, Jose Castro-Perez², Emma Marsden-Edwards³

1. AstraZeneca R&D Charnwood, Clinical Pharmacology and DMPK, Loughborough, United Kingdom
2. Waters Corporation, Milford, MA, USA
3. Waters Corporation, Atlas Park, Manchester, United Kingdom

Metabolite characterisation studies provide detailed structural information regarding the metabolic fate or profile of a drug candidate. In the drug development environment, these studies face a continual need to provide high-quality data within increasingly tight timescales. In terms of sample throughput, the use of ultra-performance liquid chromatography (UPLC) provides some saving in time and resource, along with improved LC performance, but the number of samples per study is usually small. Hence, the bottleneck for these studies lies post-acquisition at the data mining, interrogation and interpretation stage, which is manually intensive.

Emerging software techniques have recently shown promise in decreasing this bottleneck, expediting the analytical process. This work details the evaluation of UPLC with electrospray time-of-flight mass spectrometry, as a first approach for metabolite characterisation, combined with chemically intelligent software and data mining tools for the analysis of nefazadone microsomal incubations. Samples were subjected to MS² routines using the SYNAPT HDMS instrument, to gain structural information on parent-related responses, followed by post-acquisition data-mining using intelligent mass-defect filtering (MDF) algorithms to assess potential metabolic cleavage. Chemically-intelligent software was used to assist in interpretation of CID fragmentation for parent-related material, using a systematic bond disconnection approach. In addition, the use of SYNAPT HDMS travelling-wave (ion mobility) technology was evaluated to help increase the selectivity of metabolite characterisation analyses and detection of parent-related responses in complex samples.

Studies of Protein-Ligand Interactions with LFA-1 and Bcl-2 by Mass Spectrometry

WEDNESDAY 07 MAY 2008 ▪ 15:30

John Crosby

School of Chemistry, University of Bristol, United Kingdom
Quantitative Differential Protein Expression Analysis of the Human Cardiac Hydrophobic Sub-Proteome in Dilated Cardiomyopathy and Ischaemic Heart Disease using Non-Ionic Detergent Phase Extraction and Label-Free LC-MS

THURSDAY 08 MAY 2008  ■  09:10

Pamela M. Donoghue¹, Chris Hughes², Johannes P.C. Vissers², James I. Langridge², and Michael J. Dunn¹

¹. Proteome Research Centre, UCD Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin, Ireland
². Waters Corporation, MS Technologies Centre, Manchester, United Kingdom

Heart diseases resulting in heart failure cause severe deterioration in the function of the myocardium, either through enlargement of the heart through processes of hypertrophy and dilatation of cardiac muscle, known as dilated cardiomyopathy (DCM), or through restricted blood flow and consequent oxygen supply to the heart caused by atherosclerosis of the coronary arteries, a pathology known as ischemic heart disease (IHD). Although the leading cause of death in the Western world, the only effective long-term treatment for end-stage heart failure is cardiac transplantation. Having previously validated a Triton X-114 phase extraction method for the analysis of cardiac membrane-associated proteins, this study attempts to identify and quantify possible biomarkers for DCM and IHD through label-free LC/MS². Pilot studies based on subcellular location and GRAVY score analysis on control cardiac tissue show a 60% enrichment of hydrophobic and membrane bound proteins in the detergent phase. The power of this technique to resolve membrane associated proteins has enabled a novel comparison of quantitative differential protein expression between DCM and IHD at a sub-proteome level. Sub-proteome analysis of such disease sub-sets affords a reduction in sample complexity potentially revealing biomarkers of cardiac failure that would otherwise remain undiscovered. In this study we enrich for hydrophobic proteins using the step-wise Triton X-114 partitioning method on control, DCM, and IHD samples and further annotate and quantify disease based protein expression changes through label-free LC/MS² analysis.
Quantitative Proteomics and Systematic Bias

THURSDAY 08 MAY 2008 ■ 10:00

Kathryn Lilley

Cambridge Centre for Proteomics, University of Cambridge, United Kingdom

QCAL – A Novel Standard for Assessing Instrument Conditions for Proteome Analysis

THURSDAY 08 MAY 2008 ■ 11:00

Claire E. Eyers¹, Deborah M. Simpson², Stephen C.C. Wong¹, Robert J. Beynon², and Simon J. Gaskell¹

¹. Michael Barber Centre for Mass Spectrometry, Manchester Interdisciplinary Biocentre, University of Manchester, Manchester M1 7DN, United Kingdom
². Protein and Functional Genomics Group, Department of Veterinary Preclinical Sciences, Veterinary Faculty University of Liverpool, L69 7ZJ, United Kingdom

If proteome data sets are to be collated, shared, and merged for higher level proteome analyses, there is a need for generally accepted strategies and reagents for optimization and standardization of instrument performance. At present, there is no single protein or peptide standard set that is capable of assessing instrument performance for peptide separation and analysis in this manner. To create such a standard, we have used the recently described QconCAT methodology to generate an artificial protein, QCAL. This protein, a concatenation of tryptic peptides that is expressed in E.coli, provides a stoichiometrically controlled mixture of peptides that are amenable to analysis by all commonly used instrumentation platforms for proteomics.
Tandem mass spectrometry (MS/MS) of peptides plays a key role in the field of proteomics, and an understanding of the fragmentation mechanisms involved is vital for data interpretation. Not all the fragment ions observed by low-energy collision-induced dissociation of protonated peptides are readily explained by the generally accepted structures for a- and b-ions. The possibility of a macrocyclic structure for b-type ions has been recently proposed. In this study, we have undertaken investigations of linear protonated YAGFL-NH2, N-acetylated-YAGFL-NH2, and cyclo-(YAGFL) peptides and their fragments using a combination of ion mobility (IM) separation and mass spectrometry. The use of IM in this work both gives insight into relative structural forms of the ion species and crucial separation of isobaric species. Our study provides compelling evidence for the formation of a stable macrocyclic structure for the b5 ion generated by fragmentation of protonated linear YAGFL-NH2. Additionally we demonstrate that the a4 ion fragment of protonated YAGFL-NH2 has at least two structures; one of which is attributable to a macrocyclic structure on the basis of its subsequent fragmentation. More generally, this work emphasizes the value of combined IM-MS/MS in probing the detailed fragmentation mechanisms of peptide ions, and illustrates the use of combined ion mobility/collisional activation/mass spectrometry analysis in achieving an effective enhancement of the resolution of the mobility separator.
On the Destruction, Deconstruction, and Eventual Determination of Protein Quaternary Structure

THURSDAY 08 MAY 2008 ■ 12:00

Brandon T. Ruotolo

Department of Chemistry, University of Cambridge, United Kingdom

Current data suggests that most proteins function as part of an assembly rather than as individuals. Such protein complexes are challenging targets for structural characterization as they often exist at low concentrations, are often unstable, and sometimes exhibit a degree of polydispersity. As such, the classical tools of structural biology (i.e., NMR and X-ray Crystallography) have been unable to completely characterize the majority of protein-protein complexes projected to exist in vivo. Our group is interested in developing tools and technologies that are capable of probing every functional and structural aspect of macromolecular protein assemblies. Currently, we are developing mass spectrometry, tandem mass spectrometry (MS/MS), ion mobility-mass spectrometry (IM-MS), and computational approaches to this end. A common theme among many of these approaches is that, in addition to measurements of intact protein assemblies, we integrate measurements of disrupted or fragmented protein assemblies in order to assemble a more complete structural picture of the macromolecular machine under investigation. This presentation will focus on our most recent progress towards developing these techniques, as well as examples of their application within structural biology.

IMS-MSI Nearly a New Palindrome for Mass Spectrometry Imaging

THURSDAY 08 MAY 2008 ■ 12:30

Malcolm R Clench

Biomedical Research Centre, Sheffield Hallam University,
Howard Street, Sheffield, S1 1WB, United Kingdom

Matrix assisted laser desorption ionisation mass spectrometry imaging has been used to image the distribution of compounds on the surface of biological tissue for ten years now. Since the first papers of the Caprioli group describing the study of protein distribution, advances in the technique have been mainly concerned with; shortening analysis times by the use of higher repetition lasers, improving the sample preparation methodology and using tandem mass spectrometry/accurate mass to improve the specificity for the examination of small molecules. Combining mass spectrometry imaging with the separation of ions by ion-mobility opens up whole new areas of analyses. In particular it appears to be very easy to identify peaks arising from for example the matrix and to separate ions from different compound classes. In this presentation features of ion mobility spectroscopy – mass spectrometry imaging (IMS-MSI) are demonstrated with examples from drug distribution studies, protein imaging and the study of the distribution of small endogenous compounds in biological tissue.
Practical Use of LC-MS/MS in a Routine Hospital Laboratory

THURSDAY 08 MAY 2008 ■ 14:30

Brian Keevil

University Hospital of South Manchester NHS Foundation Trust,
Manchester, M23 9LT, United Kingdom

LC-MS/MS is having an increasing role in the the routine service provided by Clinical Chemistry departments. It is starting to replace immunoassay methods for drugs, steroids and vitamins because it doesn’t suffer the same problems with metabolite interference. In our laboratory LC-MS/MS is a routine technique not only used during the week but also at weekends by shift workers. The talk will focus on the clinical applications of LC-MS/MS and how it can impact on patient care.

Analysis and Quantification of Diagnostic Plasma Markers and Protein Signatures for Gaucher Disease

THURSDAY 08 MAY 2008 ■ 15:00

Johannes M. Aerts

Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

A (bio) marker is an analyte that indicates the presence of a biological process linked to the clinical manifestations and outcome of a particular disease. An ideal biomarker provides indirect but ongoing determinations of disease activity. In the case of lysosomal storage disorders (LSDs), metabolites or proteins specifically secreted by storage cells are good candidates for biomarkers. Potential clinical applications of biomarkers are found in improved diagnosis, monitoring of disease progression and assessment of therapeutic correction. These applications are illustrated by reviewing the use of plasma chitotriosidase in the clinical management of patients with Gaucher disease, the most common LSD. The ongoing debate on the value of biomarkers in patient management is addressed. Novel analytical methods have revolutionized the identification and measurement of biomarkers at the protein and metabolite level.

In this presentation, novel approaches for the qualitative and quantitative proteomics analysis by nanoscale LC-MS applied to the study of protein expression response in depleted and undepleted plasma of Gaucher patients undergoing enzyme replacement therapy are presented. Particular emphasis is given to the method reproducibility of these LC-MS experiments without the use of isotopic labels. The level of chitotriosidase, an established Gaucher biomarker, was assessed by means of an absolute concentration determination technique for data-independent, alternate scanning LC-MS generated data. Disease associated proteins, including fibrinogens, complement cascade proteins, and members of the high density lipoprotein plasma content, were recognized by various clustering methods and sorting and intensity profile grouping of identified peptides. Condition-unique LC-MS protein signatures could be generated utilizing the measured plasma protein concentrations and are presented for all investigated conditions. The clustering results of the study were also used as input for gene ontology searches to determine the correlation between the molecular functions of the identified peptides and proteins.
Plasma Lipid Profiling of Gaucher Disease: Biochemical Markers to Evaluate Therapeutic Intervention

THURSDAY 08 MAY 2008 ■ 15:30

Phillip Whitfield

Proteomics and Functional Genomics Research Group, Faculty of Veterinary Science, University of Liverpool, United Kingdom

Gaucher disease is a lysosomal storage disorder characterised by a deficiency of the enzyme acid β-glucosidase. Clinical symptoms include hepatosplenomegaly, haematological involvement and bone lesions. Neurological impairment may also occur in certain patients. The advances in the treatment of Gaucher disease have highlighted the need to monitor the complex biochemical changes associated with the disease and the response of these changes to therapy. In this study the suitability of plasma lipids as biochemical markers of Gaucher disease was evaluated. Electrospray ionisation-tandem mass spectrometry was used to characterise and quantify plasma sphingolipids and phospholipids from Gaucher and control patients. Molecular species of glucosylceramide and GM₃ ganglioside were elevated in Gaucher disease, whereas species of dihexosylceramide and sphingomyelin were decreased. This strategy was further employed to assess the response of patients to enzyme replacement therapy. The findings suggest that plasma lipid profiling may be a suitable strategy to monitor the efficacy of therapies for Gaucher disease.

Clinical Mass Spectrometry from Research to Routine

THURSDAY 08 MAY 2008 ■ 16:00

Michael Morris

Waters MS Technologies Centre, Manchester, United Kingdom

Much attention is paid to the discovery of biomarkers that are indicative of a disease state, or a means of monitoring therapy. However, the transition of a biomarker from an interesting finding to a routine test is a complex one involving extensive validation. LC/MS/MS is now being established as useful analytical adjunct in many routine laboratories. This presentation will briefly highlight some of the successful transitions, and give an insight into areas where the adoption has been less dramatic.