The 20th International Reid Bioanalytical Forum

Austin Pearce Building, University of Surrey, Guildford, UK, 9-12 September 2013

The 20th International Reid Bioanalytical Forum, organised by the Forum Syndicate under the auspices of the Chromatographic Society, was attended by over 100 participants from pharma, contract research, instrument vendors and academia. Delegates attended from Europe, Canada and the US. The Forum was divided into six broad themes which included collaborative partnerships between CROs and Pharmaceutical companies, technology developments, problem solving, the bioanalytical toolbox, biomarker analysis and regulations in bioanalysis.

Overview

The Bioanalytical Forum, initiated by Dr Eric Reid in 1975, is held every two years at the University of Surrey and following an initial donation from Dr Reid is now organised by the Chromatographic Society. In recognition of the contribution of Dr Eric Reid, the series was renamed 'The International Reid Bioanalytical Forum' after Dr Reid sadly passed away in 2010 [1].

The Forum followed a familiar format for regulars, the date having moved from July to September. The meeting commenced after lunch on Monday (9 September 2013) and ended at lunchtime on the Thursday (12 September 2013). The conference included two separate exhibitions; Tuesday for instrument consumable vendors and Wednesday populated largely by CRO's. Also on permanent display in the exhibition hall were over 20 posters.

Attendance was consistent throughout the meeting from the first presentation to the last session which covered regulatory aspects, including an excellent talk from **Christine Gray (MHRA, UK)** and a presentation covering capillary micro-sampling.

The Reid Bioanalytical Forum was held in the Austin Pearce Building. Delegates (l to r) Derek Stevenson, Jordan Stobaugh and Ian Wilson clearly found the late 90's British industrialist (Esso, British Aerospace) and inspirational figure.

The social events followed a tried and tested format with a buffet meal and drinks reception in the Wates House bar on the first evening supported by Biotage, the Tuesday evening event was an off-campus dinner at Clandon House, a local National Trust property, and Wednesday was the conference dinner, sponsored by AB Sciex, in the university Hillside restaurant.

Collaborative partnership between CROs and pharmaceutical companies

The welcome, introduction and house-keeping address by Derek Stevenson was followed by the first session, chaired by **John Smeraglia**, on the topic of 'Collaborative partnership between CROs and Pharmaceutical companies'.

Neil Spooner (GSK, UK) presented on the topic of building positive relationships with CROs. He described the current trends and drivers on pharmaceutical companies to outsource increasing amounts of their bioanalytical and toxicokinetic work. GSK outsourcing of PK bioanalysis has grown from just over 30% in September 2010 to very nearly 75% in March 2012, whilst TK outsourcing has risen from about 11% to 28% in the same period. The push to outsource more bioanalysis has resulted in greater flexibility of staff resources, control of overhead costs, more transparent costs to project teams and a refocusing of internal resource. Neil concluded that the keys to success were quality, communication and trust.

The Pharmaceutical industry is, without doubt, experiencing the most turbulent time in its history. Drug development costs have escalated and fewer molecules have gained regulatory approval over recent years. Large Pharma has suffered the impact of the patent-cliff. **Christine Robinson (HLS, UK)** reviewed the challenges facing the industry along with strategies that companies are adopting in light of these challenges including diversification, consolidation, partnering, entering emerging markets, precompetitive data sharing and 'fail faster' science. Christine, bringing out her 'crystal ball' moved on to consider what the industry may look like in the future and what roles and responsibilities academia, biotech, large pharma and the CRO

industries would take in developing new medicines. Christine concluded that all is not lost as FDA approvals increased in 2012, there is a greater focus in the industry on biological treatments with reduced financial and patent cliffs and the opportunity the development for personalised medicines and companion diagnostics.

Graeme Clark (Cyprotex, UK) followed with a talk on exploratory bioanalysis and the risks associated of outsourcing this type of work. He illustrated this with a real example of a molecule which had been supplied with no structural information provided which had the potential of transforming into an acyl-glucuronide metabolite. If structural information had been provided with the molecule, the risks would have been identified earlier.

The final talk of the session was from **Richard Hucker (A4P Consulting Ltd., UK)** who reinforced ideas presented earlier on the changing face of bioanalysis. He emphasised the increasing size and complexity of clinical trials and importance of safety and efficacy biomarkers earlier in development.

After a break **Suzy Rigby (consultant, UK)** continued on the theme of new models for working more effectively in managing evolving challenges and relationships. This was followed by **Graeme Smith (HLS, UK)** who took a slightly different tack and described the use of low-tech, cost effective tools such as Six Sigma and LEAN processes for improving productivity and quality in bioanalysis.

Ian Wilson (Imperial University) spoke on the theme of 'smaller, better, faster' describing the analysis of micro-samples from chimeric and genetically modified mice for drugs and metabolites and the application of this approach to drug-drug interaction studies. Chimeric mice bred to contain up to 95% of human hepatocytes cost $5000 each and only live for two weeks, so you need to work fast.

The last talk of the day was delivered by **Iain Love (HLS, UK)** who spoke on 'Relationships in Bioanalytical Discovery Outsourcing: A Paradigm Shift'. He introduced a new concept 'FTE Burn', a measure of outsourcing efficiency - measured as the relative ratio of man-day output at the outsource to the innovator internal resource needed to monitor the project. Iain then discussed what is required of both parties to reach the ideal of high output with minimal sponsor oversight is optimal

Technology developments and novel tools for Bioanalysis

The first full day of the conference was started by **Steve Taylor (AB Sciex, UK)** who shared recent advances in the identification and quantitation of biopharmaceuticals using the Triple TOF™ 5600+ instrument. He covered intact antibody molecular weight characterisation, peptide mapping using trypsin digestion, the analysis of antibody drug conjugates and the identification of recombinant biotherapeutics sequence variants.

Professor John Stobaugh (University of Kansas, USA), a regular contributor for the Reid Bioanlytical Forum, then spoke about the determination of protein 3-nitrotyrosine, a low abundance post-translational modification which is linked to inflammation and various disease states. Current analytical methods involve derivatisation, selective enrichment followed by extreme UPLC separation on long axial columns operated at 30,000psi.

The first Reid meeting took place in 1975 so this was the 40th. The series has seen many things (multiple boat trips, patent lawyers sifting through the early proceedings etc.) but never before a father and son appearing in the same programme. Reid regular, John Stobaugh (University of Kansas) 'Chemistry and Chromatography for the Determination of Protein 3-Nitrotyosine' was joined by his son Jordan (AbbVie (formerly Abbott Laboratories; former student of Jim Jorgenson (University of North Carolina)) who spoke on "XUPLC - a 30000 psi+ nano-LC system.

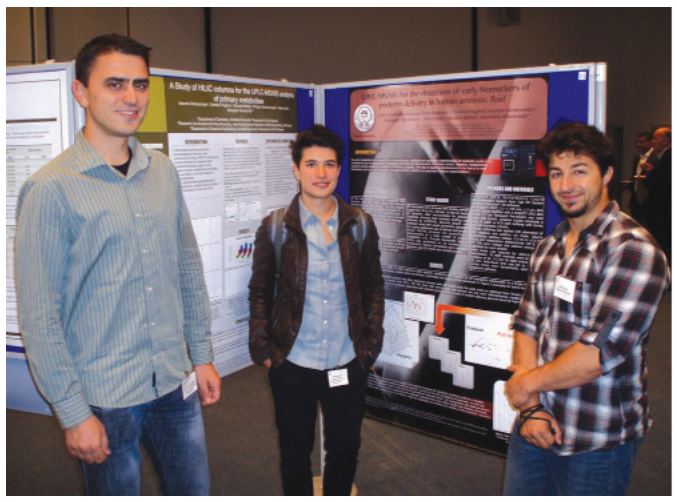
Diego Rodriguez Cabaleiro (Waters) described a series of systematic troubleshooting protocols and tips and tricks developed in order to complement their generic methodologies for the analysis of peptide molecules. More recently, research has progressed to create robust and generic methodologies for the bioanalysis of more complex recombinant proteins and monoclonal antibodies; requiring additional steps for sample preparation that need to be investigated and optimised including the use of micro fluidics chromatography and accurate mass spectrometry.

Derek Hillbeck (Thermo Scientific, UK) concluded the first session of the day with a talk focussed on HPLC of biomolecules. He discussed a number of different separation modes applicable for large molecules emphasising that knowing the physicochemical properties of your target molecule remains the key to success.

Jordan Stobaugh (AbbVie, USA) described an experimental system with a constant pressure, high temperature approach capable of >30,000 psi for one dimensional separations; extreme UHPLC. Using 25 cm Waters BEH, 1.9 µm columns, peak capacities approaching 1,000 are possible. He illustrated this with examples of complex mixture separations from fractionated yeast cell lysate digests.

Catarina Horro Pita (Quotient Bio Analytial Sciences, UK) discussed the use of derivatisation in LC-MS/MS to improve the sensitivity and selectivity of an assay, as well as analyte retention, stability and recovery; the talk was illustrated with some of the successful derivatisation protocols used recently.

Stuart Hassard (Horiba Scientific, UK) then described deltDOT LFII® technology; a multi-pixel capillary electrophoresis detector offering fast, accurate, repeatable data of higher resolution over conventional single point detectors.



Like its 'mothership' The Chromatographic Society, the Reid International Bioanalytical Forum proactively offers generous student bursaries. The metabolomics research of bursary recipients, Chrysovalantou Chatziioannou and Ioannes Sampsonides, posing here in front of their posters with Haz el Harif (University of Surrey), is part of an ongoing program of research into applications of the technique at the Aristotle University of Thessaloniki led by Georgios Theodoridis.

Problem Solving

The theme of the afternoon session was 'Problem Solving' with particular focus on bioanalytical challenges. **Zoltan Takats (Imperial College, UK)**, discussed qualitative tumour profiling during surgery using the iKnife™ using an adapted DESI ion source interfaced to a Waters triple quadrupole instrument, he described how it is possible to measure phospholipid/fatty acid distributions which can then be correlated to histological properties of tissue.

Jean-Pierre Chervet (Antec, Netherlands) presented on the use of on-line coupling of Electrochemistry (EC) with MS. This technique has shown great potential in mimicking nature's REDOX reactions in several application areas, such as drug metabolism, protein chemistry, electrochemical synthesis of metabolites, and environmental degradation. In all these applications the electrochemical cell acts as a reactor in which a controlled oxidation or reduction (REDOX reaction) takes place and the MS is used as detector.

A short audience participation section involved presentations by; **David Neville (Quotient, UK)**, who illustrated the use of internal standard response as a troubleshooting tool in bioanalytcial methods, **Elia Hall (YBS, UK)** speaking on 'A voyage of discovery: overcoming challenges in high-throughput bioanalysis', **Steve Westwood (Thermo Scientific, UK)** on 'Advances in sample preparation' and **Dan Chapman (Waters)** on 'Accepting new technology whilst managing the regulatory burden – a vendor's role'.

The Problem Solving session continued with three further talks with an emphasis on tissue analysis case studies. **Chris Kemper (Pharma Navigators, USA)** offered practical advice on 'Best Practices in Tissue Preparation for Bioanalysis' and how to collect tissue samples in the lab. **Bianca Squillaci (GSK, UK)** discussed how MALDI imaging MS providing a powerful alternative to whole body autoradiography or LC-MS analysis of tissue extracts, permitting direct detection and identification of lipids, proteins and peptides and drugs and metabolites in a tissue slice while preserving the spatial distribution. Closing the day was **Philip Timmerman (Janssen, Belgium)** who presented and commented on the EBF recommendations on tissue analysis which will be published in *Bioanalysis* soon.

Quantitative Technology

Howard Hill (consultant, UK) began the second full day with a thought provoking talk on 'Healthcare industry - where to now?' covering the trends and challenges facing the industry. The declining UK healthcare budget is £140 billion with 50% scheduled to move to community care. The US healthcare budget is unsustainable at 20% of GDP. Can pharma continue to justify current margins on products? This was followed by **Mira Doig (ABS Laboratories, UK)** who gave an overview of how bioanalysis has evolved over the last 40 years followed by **Lloyd King (UCB, UK)** on the versatility of high resolution mass spectrometry (HRMS) platforms for both quantitative and qualitative data generation in research DMPK groups.

At the 2009 BioForum, **Professor David Perrett (Barts Medical School, UK)** presented his work on a detection system that could detect protein on dental instruments. In this lecture, he updated how the system has been further developed and that an instrument is commercialy available. This session was completed by **Essam Ghazaly (The London School of Medicine & Dentistry, UK)** on the world of counterfeit drugs and was illustrated with some analytical case studies.

The 'Quantitative Technology' theme was developed to cover large molecules and Anti-Drug Antibodies (ADA) bioanalysis. **Louis Christodoulou** spoke on the subject of 'ADA assessment: the advantages of transitioning to the Electrochemical Luminescence (ECL) platform'. This presentation focussed on the advantages of using Electrochemical Luminescence (ECL) immunoassays over traditional ELISA methodologies. The wider dynamic range, parallelism and sensitivity of the homogenous ECL immunoassay allow the measurement of ADA in the presence of Drug PK (previously unachievable with the ELISA). This was followed by **Alex Hawes (Quotient Bio Analytical Sciences, UK)** who spoke on the subject of 'Challenges in keeping pace with immunogenicity advances throughout the clinical development of a biological therapeutic' and **Mark Tatlock (Development and Discovery Solutions, UK)** on 'Bioanalytical Tools for Characterisation of Monoclonal Antibody Biosimilars'.

Biomarker analysis

The theme for session 9 of the conference was Biomarker analysis – peptide and proteins by mass spectrometry. **Fabio Garofolo (Algorithm Pharma, Canada)** shared his approach to large molecule analysis using LC-MS instrumentation. The wide scan range of HRMS instruments is advantageous for intact peptide and protein quantification being able to increase the selectivity while maintaining sensitivity. **Jaap Wieling (QPS, Netherlands)** then spoke on 'Biomarkers in Alzheimer's - a variety of analytical techniques, new developments, challenges and validation approaches'.

Lurence Meunier (Celerion, Switzerland) spoke on 'Application of New LC-MS Technologies to peptide Quantitation' which was followed by Neil Benson (Xenologiq, UK) on the topic of 'Generating insight from data using model based approaches', **Barbara Bell (Covance, UK)** on 'Absolute quantitation of 4β-hydroxycholesterol in human plasma using a dual stable label LC-MS/MS approach with Atmospheric Pressure Chemical Ionisation' and **Joe Palandra (Pfizer, USA)** on 'Ultra-Sensitive Cytokine Quantitation in Tissues by Immunoaffinity nano-LC-MS/MS', concluded the second day.

Regulations in bioanalysis

The final morning focussed on regulations in bioanalysis: data integrity and assay validation. Earlier this year, the MHRA brought the first successful prosecution of a study director under the UK GLP Regulations following manipulation of bioanalytical data in a number of regulatory studies; Mr Eaton was sent to prison for 3 months [4]. Presenting for the first time publicly in the UK, **Chris Gray of the MHRA** opened the session by presenting on the issues identified in this investigation, their potential impact and how these and other data integrity issues can be identified and avoided.

Marcus Benton (QA consultant, UK) speaking on 'Readiness for a GXP inspection' - a practical guide, **Karianna Mitchell (HLS, UK)** with 'How to make a cross validation happy' – a case study and **Fabio Garofolo (Algorithm Pharma, Canada)** on 'Importance of Performing Incurred Sample Stability (ISS) for having a Rugged and Accurate Omega-3 Bioanalytical Method – an illustrative case study on an industry hot topic'. **Peter van Amsterdam (Abbott, Netherlands & GBC)** presented 'Global regulatory issues: one BA method, one validation, one report …' [3]. This was followed by two talks on the subject of micro-sampling from **Tim Sangster & Kay Sommerville (both CRL, UK)**; a detailed explanation of the use of capillary tube kits and the challenges of validating methods to support this type of sample collection. The final talk of the conference was delivered by **Rebecca Sleigh (Quotient Bio Analytical Sciences, UK)** on a 'lean' strategy for performing a validation to meet the EMA guidance, minimising analyst and instrument time, controlling costs and delivering the required experiments.

Conclusion

Once again, the Bioanalytical Forum delivered a conference high in scientific content but with an eye on the regulations. The next Forum will be held in September 2015 at the University of Surrey when the focus will be on the young bioanalyst and the delivery of high quality training.

References

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