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The 5th Annual Shanghai Symposium on Clinical & Pharmaceutical Solutions through Analysis

Renaissance Shanghai Pudong Hotel, Shanghai, China, 16–19 April 2014

The 5th Annual Shanghai Symposium on Clinical & Pharmaceutical Solutions through Analysis (CPSA Shanghai 2014) was held on 16–19 April 2014 in Shanghai, China. The meeting featured highly interactive events including diversified symposia, roundtable discussions, workshops, poster sessions and conference awards. There were over 220 participants from more than 10 countries, with 45 oral presentations and 42 posters presented. In addition, the meeting included one preconference workshop and a joint session with local bioanalytical and drug metabolism discussion groups.

Jeff Zhang of Novartis (Shanghai, China) served as the CPSA Shanghai 2014 Program Chair. The CPSA founder, Mike Lee of Milestone Development Services (PA, USA), opened the conference by welcoming the audience and giving thanks to the organizing committee and the volunteers. The theme of the CPSA Shanghai 2014 was ‘The New Era of Personalized Medicine: Innovative Approaches for Drug Discovery and Development’ [1]. Personalized medicine tailors the medical treatment to individual patient’s genetic data, which offers unique opportunities to integrate new technologies and concepts to disease prognosis, diagnosis and therapeutics.

Stephen Clarke of GlaxoSmithKline (Hertfordshire, UK) gave a plenary lecture on ‘Human First Metabolism’. Human metabolism study can provide valuable info concerning reactivity, activity and exposure of the test drugs and metabolites. Advances in modern technologies, such as NMR, MS and AMS, have greatly enhanced human metabolism research. John Yates of the Scripps Research Institute (CA, USA) presented another plenary lecture on ‘Exploring Diseases using Proteomics’. The shotgun quantitative proteomics has been applied to the identification of brain diseases, including

N15 markers of Alzheimer’s disease, depression and schizophrenia, which has produced useful data for disease projection and individual patient treatment.

The symposium included over 15 sessions and covered a broad range of topics. This conference report summarizes some highlights from the contributed sessions.

The world of antibody–drug conjugates: bioanalytical & PK/PD challenges

Ben Shen of Genentech (South San Francisco, CA, USA) presented ‘Delineating Antibody–Drug Conjugates (ADC) Absorption, Distribution, Metabolism and Excretion (ADME): Challenges and Impact on ADC Development’. The report noted several challenges in ADC ADME, including ADC stability, species difference, clinical relevant metabolite abundance, ADC accumulation and route of elimination, and so on. Another challenge is lack of clear regulatory guidance on ADC ADME. The complex molecular moiety of the ADCs also made ADC ADME study technically challenging.

Fabio Garofolo of Algorithm Pharma (Quebec, Canada) lectured on ‘Challenges and Solutions in Large Molecule Quantification using LC/MS/MS (LM by LC/MS): A Hot

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Topic in Regulated Preclinical and Clinical Bioanalysis'. ADC is a heterogeneous mixture consisting of a small molecule drug covalently bound to a monoclonal antibody via a linker. The heterogeneous nature and large molecular size ion have contributed to the complexity of the ADC assays. Several case studies using LC/MS for quantitative determination of ADCs have been presented.

Dhaval Shah of the University of Buffalo (NY, USA) gave a presentation on 'ADCs-based development model'. It was noted that PK/PD modeling of ADCs could facilitate candidate selection, preclinical to clinical transformation, informed and biodistribution of guided discovery and development. The main obstacle to the success of PK model-driven development is lack of knowledge and parameter data in correlation with ADC efficacy and safety.

Traditional Chinese medicine & natural product research

Several researchers from universities and research institutes in China shared their first-hand research work. Chuan Li of Shanghai Institute of Materia Medica (Shanghai, China) presented '*Salvia* Alcohol ADME/PK and Related Herbal Drug Interactions Influence'. *Salvia* is commonly used in China for the treatment of angina. Despite the widespread use, *Salvia miltiorrhiza* treatment has yet to be optimized. Yan Wang of Institute of Materia Medica (Beijing, China) presented '*In vivo* Metabolic Characteristics of Alkaloids in Natural Product'. The combination of herbs has been shown to improve PK profiles and reduce potential drug safety issues.

In a separate session titled 'Bioanalysis of Chinese Medicine,' Haiyan Xu of Shenyang Pharmaceutical University (Shenyang, China) presented 'Simultaneous Determination of Five Active Components of Radix Isatidis in Rat Serum by LC/MS/MS'. Xingxing Diao of Shanghai Institute of Materia Medica (Shanghai, China) introduced 'Simultaneous Determination of Butyl Phthalide and Four Metabolites in Human Plasma by LC/MS/MS'. Hongliang Jiang of Huazhong University of Science and Technology (Wuhan, China) presented 'Quantification of Two Major Bioactive Saponins of *Lysimachia capillipes* in Rat Plasma by LC/MS/MS and its Application to a PK Study'. Ling Yang of Dalian Institute of Chemical Physics (Dalian, China) discussed 'Clinical Herb-Drug Interactions: Reassessing the Variability of Biological System Specific Properties'.

PK in Chinese populations: ethnic differences & global clinical trial strategies

In this session, Jun Shi of Roche (Shanghai, China) presented 'Real Ethnic Chinese Populations to Assess the Sensitivity of the Drug Development: Research

from Roche, Union Hospital, Clinical Pharmacology'. It was noted that China would surpass Japan to become the second largest pharmaceutical market. Regulatory requirements on racial sensitivity of the data need to be considered. Race-sensitive data has been determined to be a key factor in speeding up China's inspection and acceptance of Clinical Trial Agreement (CTA).

Peiming Ma of GlaxoSmithKline (Shanghai, China) presented 'Dealing with Ethnic Differences in Clinical Development.' Racial differences are reflected in several extrinsic and intrinsic factors, such as smoking rates, diet, environment, drug interactions, and so on. Racial differences should be considered during medical treatment. Racial differences in treatment should take into account regional differences and follow rigorous statistical methods.

Applications of protein & peptide biomarkers from research to development

Chaolan Huang of the National Center for Protein Science (Shanghai, China) presented 'Protein Post-Translational Modification (PTM) Analysis and Data Processing Methods'. PTM is the key step in protein biosynthesis to determine the function of proteins. There are more than 300 different types of PTMs, many of which are known to play key roles in cell physiology and disease occurrence. MS has been used to study the PTMs, by monitoring the characteristic ions from the PTMs. Future PTM research calls for instrument technologies to provide higher sensitivity, wider dynamic range and more robust quantitative methods.

John Yates of the Scripps Research Institute presented 'Discovery and Targeted Proteomics to Study Transplant Rejection'. It was noted that approximately 10% of renal transplant subjects showed acute rejection, with a 90% chance of developing into interstitial fibrosis and tubular atrophy in 10 years. Protein expression analysis was conducted by analyzing biopsies from targeted transplant and peripheral blood lymphocytes using LC/MS.

Hu Zhou of the Shanghai Institute of Materia Medica presented 'Technology Development of Proteomic Reactor and its Application in Biomarker Discovery'. Colorectal cancer is the third most common malignant cancer, and was ranked third in mortality worldwide in 2011. The report provided a summary of the proteomic research and biomarker discovery for colorectal cancer.

Challenges & opportunities of bioanalysis in China

Philip Timmerman of Janssen Pharmaceuticals (Beerse, Belgium) presented 'Regulated Bioanalysis: A Daily Encounter with Guidelines & Guidance: A Global Picture'. The lecturer shared overarching principles of work-

ing in a regulated environment, application of different guidelines and ways to get inspection readiness.

Hisanori Hara of Novartis Pharma AG (Basel, Switzerland) presented 'Practical Aspects of Doing Regulated Bioanalysis in China – from Global R&D Perspective'. It was noted that the cost of doing bioanalysis in China was rising but still attractive and the quality was catching up to global standards. Some Contract Research Organizations (CROs) have been successfully inspected by the China Food and Drug Administration (CFDA), US FDA and EMA.

Tee Zhang of Frontage Laboratories (Shanghai, China) presented 'Challenges in Doing Bioanalysis in China – A Local CRO Perspective'. China has strict regulations on biological sample importation and exportation. The permit application process is lengthy and administrative, which has constituted a major challenge for a local CRO to provide global bioanalytical support. Other challenges include lab accreditation, employee turnover, human biological matrix (e.g., human plasma) not commercially available, language and communication challenges, regulation gap, rising cost and increasing competition.

Kelly Dong of GlaxoSmithKline R&D (Shanghai, China) presented 'Regulated Bioanalysis in China'. More and more global clinical trials are conducted in China owing to China's huge market, great patient pool and vast number of doctors and clinical Principal Investigators (PIs). One challenge is long trial approval time. Also, China requires drug import license for every shipment. The challenges in biological sample exportation have forced sponsors to set up their own labs in China or collaborate with a local CRO, which can significantly increase costs and potential discrepancies in data between different labs.

In another session titled 'Working with CROs in China: Opportunities, Challenges, and Lessons Learned,' several experts shared their perspectives and experience working with Chinese CROs. Rick Connell of Pfizer (Shanghai, China) chaired this session and introduced the topic. Hongshi Yu of WuXi AppTec (Shanghai, China) presented 'Drug Metabolism & Pharmacokinetics (DMPK) Outsourcing to China: A CRO's Perspective'. Jonathan Connick of Merck (Shanghai, China) presented 'Sourcing for Success,' where resource use strategies were discussed. One important strategy was to evaluate and help the selected partners to achieve the best ability and quality.

Moving towards next-generation development

Thomas Keller of GlaxoSmithKline (Hertfordshire, United Kingdom) presented 'Translational Systems Medicine Enabling Patient Centric Drug Develop-

ment'. Medical system was noted as a network of contacts and a new way of medical research using digital technology has emerged.

Qun Lu of Celgene (Shanghai, China) presented 'Application of the Quality-by-Design (QbD) Principles in Early Pharmaceutical Development'. QbD began with predetermined objectives, with emphasis on understanding of the product and process control. QbD principles in early drug development include drug selection, dosage and salt forms, parallel clinical program development phase and scale control. QbD can be applied to the production process to ensure the finished drug product within established specifications.

Gurmil Gendeh of Agilent Technologies (Shanghai, China) presented 'The Role and Advantages of Open Access LC/MS In Support of Recombinant Protein Drug Development'. Biologics are very complex and require rigorous analysis at each step during research and development. The analytical instruments must be able to run more samples with high efficiency. Walkup & Open Access system can provide improved accessibility, allow creative use of free resources and automatic support for more sample throughput and applications.

In another session titled 'New Technology,' Yin Zheng of Nankai University (Tianjin, China) presented 'Automation of Bioanalysis in PK Studies'. The use of on-line solid-phase extraction (SPE) and two-dimensional LC separation was discussed. The system was able to generate high-throughput for PK studies. Mike Huang of Janssen Pharmaceuticals (PA, USA) presented 'Opportunities and Challenges of Using High Resolution Mass Spectrometry (HRMS) in Regulated Bioanalysis,' HRMS was shown to hold promising applications in regulated bioanalysis including the analysis of intact proteins and distinguishing interfering components owing to its high resolution power. Tee Zhang of Frontage (Shanghai, China) presented 'Dried Blood Spots (DBS)'. The report provided a summary of the current development of DBS, including a detailed case study. There are still many regulatory challenges for DBS. DBS can find some niche applications but will not replace the plasma method.

The clinical & regulatory significance of *in vitro* & clinical transporter studies

Joseph Polli of GlaxoSmithKline (NC, USA) presented 'Drug Transporters, Drug Interactions and Drug Agency Review of Dolutegravir: A Case Study Review and Lessons Learned'. Drug transport problems for Dolutegravir, an HIV integrase inhibitor, were discussed, and considerations and strategies were proposed.

Cornelis Hop of Genentech (CA, USA) presented 'Predicting Clinical Relevance of Drug Transporters in

Drug Discovery'. It was noted that many membrane transport proteins have been identified. Transport can lead to absorption, tissue distribution, excretion and interaction between the drugs. Approximately 30 transporters could have an impact on ADME. Lack of specific transport inhibitor or overlapping substrate specificity can lead to false data. *In vitro* to *in vivo* extrapolation can also be misleading.

Mingxiang Liao of Takeda (MA, USA) presented 'Understanding Transporter Drug-Drug Interaction (DDI): Regulatory Stance and Industry Case Studies'. The *in vitro* studies can help determine if the drug is a key transit substrate, and also the uptake and efflux of the transporter proteins and their relative contributions. These provide the foundation of the key data and will help to design and understand *in vivo* studies. DDI study of the transporter inhibitor can predict the impact of transporter protein variation on drug concentration. This info can be combined with *in vitro* information to determine whether further genetic research is needed.

Technology developments in the application of MS for protein & peptide biomarker discovery

Charles Wong of National Center for Protein Science (Shanghai, China) presented 'Study of Non-Coding RNA's (miRNA and lncRNA)-Protein Interaction Based on Integrated Mass Spectrometry'. Non-coding RNAs are RNAs that do not encode proteins, including rRNA, tRNA, snRNA, snoRNA and microRNA, and so on. They are genome transcribed but are not translated into proteins. They can perform biological functions at the RNA level. RNA sequence analysis is the integration of sequencing, ionization, MS and computing technology. It has been demonstrated that MS can be used for direct analysis of RNA in biological samples.

Gary Valaskovic of New Objective (MA, USA) presented 'Sensitivity and Throughput Using Nanospray Based LC-MS: Proteomics and Beyond'. Nanospray LC-MS was shown to provide high sensitivity and throughput suitable for proteomic research. The high performance spray capillary sample analysis can be stored as a separate plug-in in ESI-MS.

Qian Zhao of Novartis (Shanghai, China) presented 'Chemical Biology Technologies for Drug Target Identification'. The report compared different drug target identification methods including affinity purification, 2D gel electrophoresis, genetic methods (yeast genomics, cell strains resistant RNA-seq), and proteomics, and so on. Use of chemical biology techniques for the identification of drug targets was illustrated through several case studies.

Translational biomarkers for accelerating drug development: bioanalytical & emerging applications

Haojing Rong of Pfizer (MA, USA) presented on 'PK/Biomarker/Efficacy Relationship of Anti-GDF8 mAb for Efficacious Dose Projection in Humans'. It has been demonstrated that a PK/PD model can be applied to preclinical pharmacology studies across different species. The target coverage can be used to predict effective human exposure. It is concluded that the PK/PD modeling can facilitate cross-species pathology study and help predict efficacious dosage in human clinical trials.

Naidong Weng of Janssen Pharmaceuticals (PA, USA) presented 'Protein and SM Biomarker Quantification'. The report introduced new trends and innovations in LC/MS bioanalytical laboratory, analysis of intact proteins using MS. The report also discussed quantification of apolipoprotein C3, a potential biomarker for prediabetes/diabetes, using HRMS. Special consideration in LC and MS sample preparation were discussed. It was concluded that use of HRMS for protein analysis has a unique advantage. 'Fit-for-purpose' quantification is a viable alternative approach for biomarker measurement.

Xiaorong Liang of Genentech (CA, USA) presented 'Small Molecule Biomarker Quantitation'. LC/MS/MS was shown to be a powerful tool for small molecule biomarker measurement. Use of a surrogate analyte such as stable isotope labeled analyte and surrogate modeling is a common approach in endogenous biomarker determination.

MS & bioanalysis: diagnostics & hospitals

Sihe Wang of Cleveland Clinic (OH, USA) presented 'Application of LC/MS in Clinical Laboratory Testing'. LC/MS/MS has unique properties for clinical lab testing, such as specificity, sensitivity, applicability, feasibility and flexibility. There are also challenges, such as complex instrument platform, limited throughput, sample preparation and laboratory information management systems. LC/MS/MS may also suffer from interferences due to same molecular weight analytes, matrix or crosstalk. LC/MS/MS, with its high sensitivity and specificity, has seen increasing applications in a clinical lab.

Hua-Fen Liu of AB SCIEX (Shanghai, China) presented 'Human Endogenous Steroids Analysis in Clinical Reference'. Steroids are endogenous compounds. The challenges in bioanalysis of steroids include lack of true blank matrix for the calibration curve, high sensitivity requirement, dynamic concentration range selection, endogenous interference due to structure similar compounds, non-specific bind-

ing and metabolic stability issues. LC/MS/MS has been successfully applied to the analysis of steroid compounds.

Shuijun Li of Xuhui Hospital (Shanghai, China) presented '25-hydroxyvitamin D: Clinical Significance, Measurement, and Method Comparison'. 25-hydroxyvitamin D is the best indicator of vitamin D. Approximately one billion people worldwide lack enough vitamin D. In Shanghai, vitamin D deficiency is common. Between 25 and 73% of people show 25-hydroxyvitamin D at 10–20 ng/ml. The report compared LC/MS/MS and electrochemiluminescence immunoassay (ECLIA) methods for 25-hydroxyvitamin D determination. LC/MS/MS was shown to provide more accurate data for clinical diagnosis.

Conference workshops

Preceding the conference, there was a satellite workshop in Shanghai. The Shanghai workshop was held on 14 April and focused on 'Mass-based protein analysis'. The workshop was jointly organized by CPSA Shanghai and Institute of Biomedical Sciences of Fudan University in Shanghai. John Yates of the Scripps Research Institute, Pengyuan Yang of Fudan University (Shanghai, China), Gary Valaskovic of New Objective, Chaolan Huang of the National Center for Protein Science (Shanghai, China), and Jianliu Lu of East China Normal University, shared their research work and perspectives on protein research and quantitative analysis.

There were many vendor workshops throughout the conference. At a Thermo Fisher workshop, Urban A. Kiernan presented 'Mass Immunization of High Sensitivity Protein Drugs Quantitative and Qualitative Analysis'. Jerry Jia presented 'New Generation Orbitrap LCMS Biotherapeutics Identification'. The report demonstrated use of new generation Orbitrap MS for intact protein analysis and intact antibody identification. At an Agilent workshop, Gurmil Gendeh presented 'Biosimilars and Antibody Drug Conjugates Analysis Strategy'. At an AB Sciex technical seminar, Suma Ramagiri presented 'LC/MS/MS Analysis of Complex Antibody–Drug Conjugate (ADC)'. Hua-fen Liu presented 'Endocrine Hormone Analysis in Clinical Research'.

Joint Session with local bioanalytical & metabolism discussion groups & RDPAC preclinical focus group

As is tradition, CPSA Shanghai 2014 held a joint session with local bioanalytical and drug metabolism discussion groups & R&D-based Pharmaceutical Association Committee (RDPAC) preclinical focus group on the last day of the conference. For this year, the

focus was 'Challenges and Opportunities of DMPK Studies in CFDA New Drug Submissions'. There were four invited presentations. Dafang Zhong of Shanghai Institute of Materia Medica (Shanghai, China) presented 'Interpretation of the Chinese Guideline of Non-Clinical Drug Metabolism and Pharmacokinetics Studies'. George Liu of Sanofi (Shanghai, China) presented 'Accelerating Drug Development with Quality Pharmacokinetics Data in China: Sanofi's Experience'. Yi Gu of Hutchinson China (Shanghai, China) presented 'Human Relevance: The Implications From The Updated CFDA Nonclinical PK/DM Guideline'. Changyong Yang of Hengrui Pharmaceutical (Shanghai, China) presented 'Hengrui's Focus on DMPK Studies in Novel Drug Development Process'. All the presentations were well received by the audience.

Conference awards

The CPSA Shanghai meeting attracted many young scientists and researchers. To recognize their work and poster presentations, the meeting has set up Young Scientist Excellence Award and Innovator Award since year 2012. For this year, there were 11 Young Scientist Award winners: Lishan Lin, Jinghua Yu, Jiangbo Du, Xiaoting Tian, and Yong Yang of Shanghai Institute of Materia Medica (Shanghai, China), Shalu Jhagra of the National Institute of Pharmaceutical Education & Research (Kolkata, India), Na Yu of Shanghai Jiao Tong University (Shanghai, China), Hu Gang and Yanlin Zhu of ChemPartner (Shanghai, China), Xinxin Wen of WuXiAppTec (Shanghai, China), Zhixiang Yan of University of Macau (Macau, China). CPSA Shanghai 2014 Innovation Awards were awarded to Joseph F Bower of Covance (Shanghai, China), Linda Lin of Fanmugu Information Technology Co., Ltd (Shanghai, China), Jim Murphy and Hui Wang of Waters (Shanghai, China).

There were many memorable events during CPSA Shanghai 2014, which were not covered in this conference report. Plans are already underway for next year's conference, CPSA Shanghai 2015. Phillip Timmerman of Janssen (Beerse, Belgium) will serve as Program Chair and the meeting, which will be held on 15–17 April 2015 at the Renaissance Shanghai Pudong Hotel. For more details and information visit the conference website at <http://www.cpsa-shanghai.com>.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment,

consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Reference

- 1 CPSA Shanghai website,
<http://www.cpsa-shanghai.com/2014/program.shtml>