Special Report
Drug Metabolism and Pharmacokinetics in Drug Discovery and Development

The Ninth National Conference of Drug and xenobiotic metabolism was held in October 23-26, 2009 in Wuhan, Hubei, China. More than 400 persons attended the academic conference. The Conference hosted by the Division of Drug Metabolism, Chinese Pharmacological Society (CSSX, CPS), co-hosted by the International Society of Study for Xenobiotics (ISSX) and Chinese Journal of Clinical Pharmacology and Therapeutics magazine.

On the morning, October 24, 2009, the opening ceremony was held. Professor Wang Guang-Ji, vice chairman CSSX, presided over the opening ceremony, Academician Chang-Xiao Liu opening address, a brief review of three years, the major work and purpose of the field in China. Professor Russell Prough, chairman of ISSX, and Dr. Theresa Smolarek, co-Chairman of the Academic Council this conference, respectively speeches on China's field of drug metabolism and pharmacokinetics of achievements in recent years expressed his appreciation.

This conference has fully demonstrated that in the past three years, Chinese research area of drug and xenobiotic metabolism of the latest developments and achievements made, in-depth study of drug metabolism and pharmacokinetics to better support the "create new medicines," National Science and Technology major projects in key technology and platform studies. Meeting received more than 210 articles, a total of 98 conducted for academic exchange at this conference. Conference was divided
into three phases, the first stage is inviting topic reports; Chang-Xiao Liu, Guang-Ji Wang, Russell Prough, Anthony Lu, Da-Fang Zhong, Yuichi Sugiyama, Jiang Zheng, Ming-Ge Zhu, Xiao-Dong Liu, Zong-Hui Yuan, Chen-Yan Gao, Iraq Hsiulin, Jin Wu, Zhang Jian, Jiayue Zhang, and Ling Zhang, respectively, made invited reports; third is symposium on “drug metabolism and drug Dynamics in drug research and development of the application” jointly sponsored by CSSX and Pfizer company.

At this conference, 22 young scientists took part in the exciting young radical sub-venue of outstanding paper reports selected first, second and third prizes of 2, 4, and 8 persons, of which Zhang Jian, School of Pharmaceutical Sciences, Dalian Medical University, and Liu Ke-Rong, the Shanghai Institute of Materia Medica, Chinese Academy of Sciences, won the first prize.

On October 24 breakfast meeting, Academician Chang-Xiao Liu, chairman of CSSX and Professor Russell Prough, ISSX President, and Professor Yuichi Sugiyama JSSX President, held friendly talks on the Chinese scholars to participate in the 2012 Asia-Pacific ISSX Conference, hosted by China in 2016 ISSX Conference, attracting more ISSX many Chinese scholars to become members and co-run Asian Journal of Pharmacodynamics and Pharmacokinetics reached a consensus on issues.

The Conference was a complete success. The conference thanks Central China Agricultural University for organization, and expressed thanks Pfizer pharmaceutical company and other companies for the great sponsorship. Meet the conference in Nanjing in 2012 goodbye.

In this special report, information on topic symposium on drug metabolism and pharmacokinetics in new drug discovery and development were introduced.

Recent advance on drug metabolism and pharmacokinetics studies in China

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Division of Drug Metabolism, Chinese Pharmacological Society (DDMC, CPS), which is also called “China Society for study of Xenobiotics (CSSX, CPS)” was established in 1986. From 1968 to 2009, we hold nine national meetings up-today. National and international academic activities are major academic exchanges of this society.

During the passed 24 years after establishment of CSSX, China Drug Metabolism and Pharmacokinetic Studies have a rapid development. Some books and journals on pharmacokinetics and drug metabolism were published in China. Since 1980, Chinese researchers published about 5000 papers on pharmacokinetics and metabolism of drugs and xenobiotics in journals. The research teams, research levels, and research conditions are greatly improved, with the international gap has significantly narrowed. In order to practice studies on pre-clinical and clinical pharmacokinetics, State Drug Administration of China (SDA) edited four guidelines, pre-clinical and clinical pharmacokinetics, and bioavailability/bioequivalence. These guidelines are established under reference with ICH (International Conference on Harmonization) technical files, FDA and WHO guidelines.

In 2005, Hangzhou International Conference on Drug Metabolism, 2006, Dalian on behalf of the Eighth National Conference on Medicine as well as the 2008 Shanghai 2nd Asia-Pacific International Conference on metabolism and pharmacokinetics of drugs and xenobiotics in 2008, Shanghai, have shown that the characteristics of China's development of the discipline. the international society for study of xenobiotics (ISSX) attaches great importance to this meeting. ISSX Newsletters reported that three meetings.

This review paper introduced the recent 5-year progress on drug metabolism and pharmacokinetics studies in China. The main progress in recent years, reflected in the following areas:
In the recent 5 years, Chinese researchers made contribution to drug metabolism and pharmacokinetics fields. Drug metabolic pathways, enzymes and enzyme complexes are responsible for the metabolism of drug and xenobiotics. New analytical methods and new instrumentation have been developed for the separation and identification of drugs and their metabolites. New analytical methods and new instrumentation have been developed for the separation and identification of drugs and their metabolites. The theories and technologies have applied to drug metabolism and pharmacokinetics of traditional Chinese medicine, including quantitatively describing the kinetic changes of absorption, distribution, metabolism and elimination/excretion of complex system of the traditional Chinese medicine (TCM) products. The important advances are as following aspects:

Drug discovery drugs at early stage on behalf of the Study: At early stage of drug discovery, drug designed for use in silico and in vivo for predicting pharmacokinetic characteristics of new compounds. Caco-2 model and the drug-metabolizing enzyme induction or inhibition as a candidate drug discovery research provides preliminary basis to select new molecule entries.

Liu Xiao-Dong et al carried out studies on “Impaired function and expression of P-glycoprotein in blood–brain barrier of streptozotocin-induced diabetic rats” and “Repetitive/temporal hypoxia increased P-glycoprotein expression in cultured rat brain microvascular endothelial cells in vitro”. These results obtained importance advances.

Pharmacokinetic studies of research and development of New drugs: Increasingly improved ADME / T pre-clinical studies and improved methods and technology are able to ensure the development of the state pharmacokinetic laboratories and able to fit the foundation with international standards, researchers in our country on behalf of the Technical Guidelines for the support of experts has improved steadily, biotechnology, drug research is also a combination of multi-methods study Chinese pharmacokinetic experts in the country on behalf of the pharmacokinetics of drafting and revision of technical guidelines to make it consistent with international norms.

Studies on pharmacokinetics of biotech drugs, prodrugs and chiral drugs are excellent progress in School of Pharmaceutical Sciences of Dalian Medical University, Beijing Institute of Pharmacology and Toxicology, and Tianjin Institute of Pharmaceutical research.

Drug metabolism and Pharmacokinetics studies on complex system of TCM products New concept on pharmacokinetic-marker: At the second APR-ISSX Meeting hold on May 11-14, 2008, in Shanghai, China, Liu CX presented a concept of pharmacokinetic-marker in an oral presentation titled “The challenge of Drug Metabolism and Pharmacokinetics Research in Traditional Chinese Medicines (TCM)”. It was indicated that the pharmacokinetic-markers should be active compounds presented in TCM complex preparation or their metabolites, the markers should be determined in biological sample after administration of the preparation, and related with pharmacological activities in therapeutics of TCM.

Determining which constituents of an herbal product have favorable drug-like properties will extend our knowledge of the basis for pharmacological efficacy and safety. An herbal constituent can be defined as drug-like when it possesses the desired potency, a wide safety margin, and appropriate pharmacokinetic properties and exists in adequate abundance in the herbal product. A deficit in these properties limits the usefulness of the herbal constituent for the herbal product. For a drug, the pharmacologic effect is attained when the drug or its active metabolite reaches and sustains an adequate concentration at an appropriate site of action; this hypothesis should also be applied to the herbal product. Both the dose levels and fates of active constituents in the body govern their target-site concentrations after administration of an herbal product. The relevant pharmacokinetic properties include ability of an herbal chemical to be absorbed from the site of administration and to pass through multiple biological barriers to reach the action target, sufficient metabolic stability to achieve therapeutically meaningful systemic and target-site concentrations, and appropriate metabolic lability to
be eliminated effectively by the excretory processes. PK markers may be used to show systemic exposure to the herbal product in animals and/or humans. For a multi-herb product, identification of PK markers derived from each component herb is important for evaluating the combination rationality and for investigating possible synergistic interactions between the component herbs. Such studies are also relevant to designing rational dosage regimens, evaluating potential herb-drug or herb-herb interactions, and developing new formulations. Li Chuan et al study provided that the current study focused on estimating the pharmacokinetic properties of the main active constituents from Danshen (Radix Salviae miltiorrhizae) and Sanqi (Panax Notogensing).

Study on bioactive flavonoid glucuronides

Scutellarin, scutellarein 7-O-β-D-glucuronide, is one of the major bioactive flavonoid glucuronides isolated from a Chinese herb, Erigeron breviscapus (Vant). Zhong Da-Fang et al first identified scutellarin metabolites in humans with liquid chromatography/ion trap mass spectrometry (LC/MSn). On this basis, we developed a rapid, selective, and sufficiently sensitive LC/MS/MS method to simultaneously determine scutellarin and its major metabolite in human plasma and to characterize the absorption and the plasma pharmacokinetics after a p.o. administration of 60 mg of scutellarin. The use of LC/ESI/MS in multistage full-scan mode allowed us to identify the metabolites of scutellarin in human urine and plasma samples. Two positional isomers were observed as its monoglucuronide metabolites in human urine, in which the isomer conjugated with the 6-OH group was the major metabolite in vivo and could be used as a biomarker of scutellarin intake. Pharmacokinetic behavior of isoscitellarin indicated that scutellarin is most likely hydrolyzed by intestinal β-glucuronidase of bacterial origin, followed by a reconjugation step in the intestinal cell and/or in the liver with glucuronic acid after absorption of the aglycone, which showed the positional selectivity and species difference. In humans, the 6-OH group of the aglycone of scutellarin was the preferential site for glucuronosyl conjugation compared with 4-, 5-, and 7-OH groups.

Identification of nontarget components from herbal preparations: The World Health Organization estimated that 65-80% of the world population used herbal medicines as the primary form of healthcare. However, it has been well acknowledged that for herbal medicines, the identification of components contained is of great significance to their quality control and to the disclosure of the secret underlying their effectiveness. Accordingly, qualitative and quantitative determinations of components contained in herbal medicines have now become a very hot issue. Therefore, the rapid and reliable identification of chemical components contained in herbal preparations remains still a great challenge, despite recent advances in various analytical technologies.

Wang Guangji et al study provided a novel and generally applicable approach to identifying nontarget components from herbal preparations, based on the use of liquid chromatography ion trap time-of-flight mass spectrometry (LC/MS-IT-TOF). With the benefit from such a network, it is feasible to sequentially characterize the structures of all diagnostic ions once a single component has been de novo identified. The structures of the diagnostic ions could then be used as “a priori” information for selecting the exact candidates containing the substructures of the corresponding diagnostic ions from the primary database hits. This strategy enables a nearly 7-fold narrowing of the database hits and thus substantially enhances the analytical efficiency and sharpness. The novel method for determination and identification has been successfully applied to the global identification of nontarget components in Mai-Luo-Ning injection (MLN), a well-known herbal prescription. Peak Classifications and Network Establishment are technology keys. It is a completely different case in this study for nontarget identification since they know nothing beforehand about the diagnostic ions for nontarget compounds. The developed methodology would be useful for the identifications of complicated nontarget components from various complex mixtures such as herbal preparations.

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Regulation of P450 and aldehyde dehydrogenase gene expression by oxidant stress

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Vascular tissues and liver express enzymes that metabolize lipid aldehydes, 4-hydroxy-2-nonenal (4-HNE) and propene-2-al (acrolein) formed during oxidative stress. They are highly reactive α,β-unsaturated aldehydes implicated in the pathogenesis of several diseases including myocardial infarction and inflammation. These aldehydes have been suggested to activate transcription factors such as Nuclear factor erythroid-2 related factor 2 (Nrf2) and c-Fos/c-Jun (AP1) whose canonical responsive elements are similar. We have identified two classes of enzymes involved in oxidative metabolism of lipid aldehydes in vascular tissues and have sought to characterize their participation in these processes. Our work with purified recombinant liver Aldh1a1 demonstrates efficient metabolism of HNE (Km 95 µM) and acrolein (Km 727 µM), indicating that Aldh1a1 may protect hepatocytes and cardiomyocytes against cytotoxic effects of these aldehydes. We have also demonstrated that CYP2C29 is expressed in these same tissues and also facely metabolizes lipid aldehydes. Expression microarray analysis established the effect of oxidants and electrophilic compounds on the expression of hepatic Aldh1a1 and CYP2C29. Mice were administered AIN76A (control) diet, diet containing 0.45% butylated hydroxyanisole (BHA, a synthetic phenolic antioxidant and a well characterized inducer of Nrf2 and AP-1 transcription factors) or 5 mg/kg acrolein per os. The microarray data indicate significant induction of these xenobiotic metabolizing enzymes by acrolein and BHA. In addition, hepatic Aldh and CYP activity was differentially regulated by acrolein and BHA. To decipher the signaling pathways involved in their induction, we analyzed the mRNA levels in WT and Nrf2−/− mice exposed to BHA. The exposure of mice to BHA resulted in ~2-3-fold increase in mRNA levels of hepatic Aldh1a1 and Cyp2c29 in WT and Nrf2−/− mice compared to control. However, basal expression of both was significantly reduced in Nrf2−/− mice compared to WT mice. We hypothesize that BHA- and acrolein-induced expression of these genes is mediated by AP-1 transcription factor. To test this hypothesis, transient transfection experiments were conducted in HepG2 cells with luciferase reporter vectors containing the 5'-flanking regions of Aldh1a1 and CYP2C29. While co-transfection with Nrf2 expression plasmid had no effect, over-expression of c-Jun or c-Jun/c-Fos resulted in ~4-fold induction in transcriptional activity for either gene. We further showed that c-Jun mediates Aldh1a1 promoter activity as a homodimer, while c-Jun/c-Fos heterodimer regulated Cyp2c29 promoter activity. Deletion analysis showed AP-1 sites were responsible for induction by AP1 signaling. Inhibition of JNK and ERK action also decreased transcriptional activation of the reporters. Electrophoretic mobility shift assays demonstrated that nuclear proteins, including c-Jun, bind to the responsive elements. Binding of nuclear c-Jun protein was ablated by AP1 mutation, while mutation of the GC residues of the 2C29 TRE increased DNA-c-Jun protein complex formation. Our results suggest that induction of aldehyde metabolizing enzymes by BHA and other electrophiles is principally regulated by c-Jun or c-Fos/c-Jun heterodimers, respectively, but not Nrf2, suggesting tissue specific regulation in vascular and liver tissue.

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Membrane transporters and drug response

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Drug transporters are expressed in many tissues, such as the intestine, liver, kidney, and the brain, and play key roles in drug absorption, distribution and excretion. In this presentation, I will summarize the significant role played by drug transporters in drug disposition, focusing particularly on their potential use during the drug discovery and development process. The use of transporter function offers the possibility of delivering a drug to the target organ, avoiding distribution to other organs (thereby reducing the chance of toxic side-effects), controlling the elimination process, and/or improving oral bioavailability. It is useful to select a lead compound that may or may not interact with transporters, depending on whether such an interaction is desirable. The expression system of transporters is an efficient tool for screening the activity of individual transport processes. The changes in pharmacokinetics due to genetic polymorphisms and drug-drug interactions involving transporters can often have a direct and adverse effect on the therapeutic safety and efficacy of many important drugs.

Vectorial transport across epithelial cells is involved in the absorption/uptake and elimination of drugs in the small intestine, liver and kidney. The vectorial transport of a large number of organic anions is achieved by uptake and efflux systems. We have established double-transfected MDCK II cells where hepatic uptake transporters and efflux transporters are expressed on the basal and apical membrane, respectively, as an in vitro model for hepatobiliary transport. This system is useful for drug discovery and development studies and for investigating drug-drug interactions involving hepatobiliary transport.

In this presentation, I will show you how to establish a physiologically based pharmacokinetic (PBPK) model that includes the transporter-mediated membrane transport processes and to investigate the effect of changes in transporter function on the pharmacokinetics and, ultimately, the pharmacological and/or toxicological effects. We constructed a PBPK model for statins and simulated the plasma and tissue concentrations in rats at various doses. The parameters of membrane transport were taken from our previous studies. The simulated data were comparable to the observed data that exhibited non-linear pharmacokinetics. We also tried to extrapolate from in vitro to in vivo in human taking thus obtained analyses in rats into consideration. This PBPK model can then be applied to predict changes of drug concentration in plasma and target organs caused by changes in transporter function and expression level.

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The challenges of dealing with promiscuous cytochrome P450 and PXR

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Unlike classical enzymes, drug-metabolizing enzymes such as cytochrome P450, UDP-glucuronyltransferase, epoxide hydrolase and flavin-containing monooxygenase all exhibit broad substrate specificities, low turnover rates, atypical kinetics and other unusual properties. Receptors such as pregnane X receptor (PXR), constitutive androstane receptor (CAR) and aromatic hydrocarbon receptor (AhR) responsible for the induction of various drug-metabolizing enzymes also have broad

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substrate specificities. Cytochrome P450 and PXR are two important proteins intimately involved in drug metabolism. Promiscuous proteins, by definition, are known for diversity, but not for specificity in their interactions with drugs. Large substrate-binding cavities (SBCs), binding of more than one substrate/ligand and binding of substrates in alternative orientations and locations within the SBCs, mobility of a substrate at the active site, and substantial substrate-induced conformational changes of the SBCs are common features of the promiscuous cytochrome P450 and PXR. These important parameters should be carefully considered in dealing with drug metabolism and drug toxicity evaluation. It also presents a great challenge in drug development, particularly in our attempts to optimize the DMPK properties of drug candidates and to predict the DMPK parameters by \textit{in silico} approaches based solely on the chemical structure of drugs.

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**Metabolic activation and toxicity of natural product bisbenzylisoquinoline alkaloids**

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Bisbenzylisoquinolines (BBIQs) are a large and diverse family of alkaloids found in many plants, and herbs containing BBIQ alkaloids have been used as traditional medicines in many cultures in China, India, Japan, Chile, and in many other nations. More than 400 BBIQ alkaloids have been identified to date, mainly from families of \textit{Menispermaceae}, \textit{Ranunculaceae}, \textit{Annonnaceae}, and \textit{Moniaceae}. Tetrandrine and dauricine have been studied most extensively, and both exhibit anti-inflammatory, cardiovascular, membrane modulatory, P-glycoprotein modulatory, platelet aggregation inhibitory, and central effects. In addition, tetrandrine was found to possess anti-allergic, antimicrobial, anti-silicotic, and immunomodulatory, and apoptosis-inductive effects. The promising pharmacological activities of BBIQs, combined with their natural abundance, have shown a great potential for clinic use as pharmaceutical agents. However, human therapeutic and dietary exposures have not been studied with the same level of scrutiny required of new candidate drugs, and more careful characterization of toxic potentials of these compounds is needed, to minimize the risks of unwanted events during studies of therapeutic potential of these agents.

Recently, we found both dauricine and tetrandrine produced selective lung injury in mice. Intraperitoneal administration of tetrandrine and dauricine at 150 mg/kg caused significant elevation of lactate dehydrogenase activity in bronchoalveolar lavage fluids, along with observed swelling of alveolar epithelia and hemorrhage. Interestingly, the pulmonary toxicity was reversed by pretreatment with ketoconazole, a CYP3A inhibitor, indicating that the toxicity requires cytochrome-P450-mediated metabolic activation. This encouraged us to seek reactive metabolites derived from the two alkaloids. Our \textit{in vitro} and \textit{in vivo} studies showed that both dauricine and tetrandrine were transformed to the corresponding quinone methide metabolites. Also, the formation of the quinone methide metabolites depended on the presence of NADPH. As expected, ketoconazole showed inhibitory effect on the generation of the quinone methide metabolites, and CYP3A4 was found to be the major cytochrome P-450 responsible for the production of the quinone methide metabolites. Quinone methides are known to be electrophilic species, and we propose that the quinone methide intermediates may involve at least in part the pulmonary toxicity induced by tetrandrine and dauricine. The study to be presented appears a good example of practice for drug metabolism-directed mechanistic investigation of toxic action.
Requirments of drug metabolism data for drug development and registrations in USA

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Regulatory guidances direct trends of drug metabolism research in the pharmaceutical industry. In the late 1990s the USA and Europe issued regulatory guidances on drug-drug interactions (DDI). Consequently, drug metabolism research has shifted its focus to early in vitro assessment of potential DDI of drug candidates, including screening of CYP enzyme inhibition and induction, and reaction phenotyping of metabolizing enzymes. In 2008, USFDA finalized Guidance for Industry: Safety Testing of Drug Metabolites, emphasizing the critical role of animal and human ADME studies in the selection and validation of preclinical species for safety evaluation of drug candidates. To avoid delays in the drug development process due to the discovery of unique human metabolites in the late stages of clinical trials, many pharmaceutical companies are currently developing new strategies for early assessments of metabolite exposure in humans related to preclinical species. Those include plasma metabolite profiling and quantification in first-in-human study and early radiolabeled human ADME study. Regulatory guidances also provide detailed recommendations on study design, analytical method validation and compliance and data interpretation in bioanalytical and DDI studies. During the drug development and registration processes, the FDA regulations require a sponsor to submit Investigational New Drug Applications (INA), Investigator’s Brochure (IB), Carcinogenicity Study Protocol and New Drug Applications (NDA), in which certain types of drug metabolism data are included. In this presentation, regulatory guidances relevant to drug metabolism issued by USFDA and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) are briefly reviewed. Common drug metabolism and disposition studies in support of clinical development and regulatory submissions are described. In particular, the overall strategies, study designs, experimental approaches and special considerations in the assessment of metabolite safety and drug-drug interaction potential are discussed.

The Influence of DMPK in Modern Drug Discovery - An Industrial Perspective

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In the past decade, in spite of increasing investment in R&D and significant advancement in scientific technologies, the pharmaceutical industry has experienced a steady decline in creating numbers of successful drug products into the market. The analysis of causes of failure reveals that finding an appropriate drug metabolism and pharmacokinetics (DMPK) profile, particularly during early discovery, remains as a major hurdle to reduce risk and improve productivity, which recognized the pivotal role of DMPK in such process. In nowadays, drug discovery has been staged into several phases including Exploratory Target Validation/Selection, Compound Selection, Lead Optimization (LD) and Candidate Selection (CS) with different priorities and focuses at each stage respectively. To better partner with discovery process, DMPK line has established an array of assays and tools, which have been widely
applied at each discovery stage to optimize candidate’s ADME (absorption, disposition, metabolism and excretion) properties, to investigate potential drug-drug interaction (DDI), to improve predictions of human PK and dose. This presentation will provide an overview of various DMPK assays and tools such as in vitro HTS, in silico approaches, in vivo PK screening, translational PK/PD modeling and simulation and biomarker identification and etc, as well as their applications in each discovery stage.

Application of Modeling & Simulation in Oncology Drug Development

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Phase 2 and 3 trials. The failure rate of Phase 2 trials was approximately 70%, while the most expensive Phase 3 trial failure rate was about 60%. The major cause for failure was due to lack of effectiveness. If we can differentiate “good compounds” from “bad compounds” before launching expensive clinical studies, it would support “GO” or “NO GO” decision making, and improve the rate of success in anti-cancer drug development. To address this need, one of major initiatives taken by both FDA and pharmaceutical companies is to leverage prior quantitative knowledge to build disease-drug-trial models to help make better GO/NO GO decision making. For example, FDA has established a nonsmall cell lung cancer (NSCLC) tumor size-patient survival model, and Pharsight also reported tumor size-patient survival models for metastatic breast cancer and metastatic colorectal cancer. In this presentation, two case studies are used to demonstrate the application of disease-drug-trial models in anti-cancer drug development. In case study #1, the FDA’s NSCLC tumor size-patient survival model was used to simulate a randomized Phase 2 trial to assess the effect of a new anti-cancer drug X vs. the stand of care (SOC) on patient survival. The simulated survival outcome provided a quantitative basis for an end of Phase 1 decision making. In case study #2, the disease progression-survival-drop out models of docetaxel were used to simulate a Phase 3 trial to evaluate the impact of a higher docetaxel dose on the overall survival and safety of NSCLC patients with high alpha1 acid-glycoprotein levels, based on which a Phase 3 GO or NO GO decision was made. In summary, cancer-drug-trial models can be used to simulate Phase 2/3 trials to support decision making at key milestones. Such models can be continuously updated when new data become available, and serve as knowledge management tools. However, the use of modeling and simulation in anti-cancer drug development is still at its early stage and limited. A broader implementation of modeling and simulation represents one of the opportunities to enhance the success rate in anti-cancer drug development.

Applications of PK/PD Modeling and Simulation in Drug Discovery and Translational Research

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The area of Preclinical Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling & Simulation encompasses a multitude of quantitative approaches to integrate preclinical pharmacology, bio-marker response and safety data toward the selection of the most promising drug targets and the development of the most optimal drug candidates. Application of PK/PD modeling and simulation in drug discovery
program has been rapidly evolving over the last few years. Early integration of PK/PD modeling in drug discovery enables a more rational progression of projects from discovery through development thus resulting in lower late stage attrition. Specifically, quantitative exposure-response analysis enables target validation and CIR, series optimization, biomarker qualification, lead optimization and human PK/PD simulation and dose prediction. Moreover, the discipline of preclinical PK/PD modeling has advanced from utilizing empirical PK/PD description to mechanistic or semi-mechanistic modeling. The aims of this presentation are to 1) develop a common vocabulary and understanding of the principals of preclinical PKPD modeling and simulation; 2) define and describe opportunities for PKPD to enable drug discovery; 3) highlight the impact of conducting mechanism-based modeling in early discovery with selected examples from Neuroscience therapeutic area.

The Cutting-Edge Drug Metabolism Science in Pharmaceutical Industry –Integrate In Silico Prediction into Early Drug Discovery

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As part of the early drug discovery process, it becomes critical for the lead chemical series possessing desirable ADME (absorption, distribution, metabolism and excretion) and PK (pharmacokinetics) properties as well as good physicochemical properties for the ultimate clinical success. Integration of drug-like ADME/PK properties and their pharmacological potencies into early chemical series selection has become an increased awareness and practice in pharmaceutical industries. Even before the chemical design and optimization process begins, potential issues in ADME area need to be identified so that they can be addressed in parallel with the more traditional aspect of potency. In the other aspect, medicinal chemistry has been successful in synthesizing large libraries of compounds for novel therapeutic targets to generate a huge amount of chemical database. Consequently, in silico (computational) prediction of ADME and physical chemical properties is required in drug design due to its ability of handling multiple chemical series, saving time and cost compared to routine laboratory work. In this presentation, several examples will be discussed to demonstrate how ADME/PK strategies can be applied to early drug discovery to enable rapid progression of high quality hits into leads by using in silico tools. These strategies include classical ADME tools, physicochemical properties, in silico approaches and data visualization tools. Several internal in silico approaches and commercial software will be introduced.

Translational Aspects of Hepatobiliary Transporter Research: From Basic concepts to applications

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Biliary excretion is mediated by liver transporters located on the sinusoidal and canalicular membrane of hepatocytes. The transporters including uptake transporters (solute carrier) and efflux transporters drive the dynamic hepatic vectorial transport. As obtaining clinical bile sample is difficult in practice, the prediction of biliary secretion in humans is highly dependent on preclinical data or in
vitro models. During the past decades, in vitro models and/or preclinical species have been very useful for predicting drug disposition in human, particularly in early stages of drug discovery. However, the confidence in human PK prediction is generally limited for the drugs mainly eliminated by hepatic enzymatic metabolism and/or urinary excretion, but remains very challenging for those compounds that are mainly secreted into bile.

The unknown difference in mass recovery of hepatobiliary transporters between in vitro model and liver, or species difference in hepatobiliary transporter protein might significantly affect the precision of prediction as the transport kinetics of a given compound is characterized by \( K_m \) and \( V_{\text{max}} \), in which \( V_{\text{max}} \) is determined by the protein amount of transporters. Lack of quantitative information of targeted protein expression limited the use of the model for accurate explanation to human. Extremely, the models might not effectively eliminate the unwanted properties that result in the failures of clinical trial. Therefore, accurate quantification of ADME/Tox related protein contents is essential for reliable assessment of ADME/Tox properties. Recently, the proteomics based LC-MS/MS absolute quantitative method, also termed as AQUA, has been utilized in protein quantification. The widespread use of this technology greatly improves the understanding in area of translation medicine, transporter/enzyme induction, species difference, etc. The presentation will discuss our recent efforts on exploring cutting edge research on quantitative measurement of hepatobiliary transporters as a stoichiometric manner to provide a fundamental support for extrapolation from in vitro to in vivo, or from preclinical to human and further promote the progression of pharmaceutical practice in drug discovery.

Beyond Small Molecules - DMPK of Biotherapeutics

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Although small molecules remain to be the mainstream of therapeutic agents, biotechnologically-derived therapeutics including recombinant proteins, peptides, antibodies, antibody fragments, engineered antibodies or newer developments such as antisense oligonucleotides and RNAi have been rapidly growing in recent years. The global sales of biologic medicine reached $120 billion in 2008 compared to $75 billion in 2007. Major pharmaceutical companies are investing into biotherapeutics and spending considerable amount time and resources building up their biotherapeutics programs and associated capacities. Pfizer is rapidly developing our biotech capability and capacity to become a top tier biotherapeutic company by the end of the year.

Biotherapeutics have many unique ADME features that also offer unique opportunities and/or challenges, compared to small molecules therapeutics. Most of them are formulated as parenteral formulations because of their poor oral bioavailability. Selection of the most appropriate route of administration for biotherapeutics requires comprehensive knowledge of their absorption characteristics beyond physicochemical properties, such as chemical and metabolic stability at the absorption site, immunoreactivity, permeability passing through different biomembranes, and active uptake and exsorption processes, etc. Since most biotherapeutics are large in size, their apparent volume of distribution is usually small and limited to the volume of extracellular space. This may limit their ability to reach optimum target site exposure to exert the intended pharmacological response. However, due to their high specificity to therapeutic targets, site-specific and target orientated receptor-mediated uptake can assist in their biodistribution and get access to their targets by design. The metabolism of biologic products is often not mediated by drug metabolizing enzymes that are typically responsible for the metabolism of small molecules. For examples, proteins and peptides are nearly exclusively metabolized via the same catabolic
pathways as endogenous proteins, resulted in amino acid recycle and contribute to the de novo biosynthesis of other body proteins. Elimination of biotherapeutics may follow a combination of different pathways including renal excretion, hepatic metabolism, proteolysis and receptor-mediated endocytosis. Pharmacokinetics as well as exposure/response evaluations for biotherapeutics are often complicated by their similarity to endogenous molecules, which requires sensitive and specific analytical methods for quantification of biotherapeutics in biological matrices. Immunoassays and bioassays have been the primary methods used for quantitation of biotherapeutics and the advancements of bioanalytical technologies have also assisted in the development of biotherapeutics. The unique DMPK of biotherapeutics along with their quantitation methods will be discussed in this presentation.

Current Status and Future Development for Pharmacokinetic Evaluation of Biologics

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Biologics are large macromolecules often produced by genetic or protein engineering. Biologics are becoming the drug candidates of choice due to weak generic competition and their abilities to target specific disease states. However, biologics with complex three-dimensional structures produce pharmacokinetic profile that tends to be more complex than in small molecules and therefore resulting in significant challenges for the clear mechanism of action. Unlike small molecules, biologics have more issues with the absorption and distribution than they do with metabolism and excretion. This presentation will review the current status and future development for pharmacokinetic evaluation of biologics.