株式会社菱化システム スポンサードセッション

ホリスティック・アプローチによる医薬品開発の生産性向上

日時： 10 月 28 日（火） 14:00 ～ 15:30
場所： タワーホール船堀　２階　桃源
座長： 東海大学　特任教授　平山 令明

残念ながら、医薬品開発の成功率は極めて低いのが現状です。ゲノム解明により、その成功率の大幅な向上が期待されましたが、状況は決して好転しているとは言えません。一方、開発の生産性を上げるために必要となる情報は益々多岐に渡り、その量も爆発的に増加しています。

従って、これらの複雑化する情報を正確かつ効率的に活用し、投資効率が高く時宜を得た最適な意思決定を行う必要性・緊急性が高まっています。医薬品開発の上流から下流に関わる全ての関係者が、これらの情報や知識の解析が包括的かつ柔軟にできる高度な医薬品開発支援システムを共有することができれば、適切な意思決定が行えます。PROUS INSTITUTE SYMMETRY は、このようなホリスティック・アプローチにより、医薬品開発の生産性向上を図る理想的な医薬品開発支援システムです。

本セッションでは、PROUS INSTITUTE SYMMETRY の中で包括的に扱うことができ、かつ医薬品開発の生産性と密接に関わる重要なトピックスである「ドラッグ・リポジショニング」と「不純物による毒性の予測」を取り上げます。研究者にはもとより、医薬品開発の企画からマーケティングに至るまで、あらゆる開発の局面に携わる多くの方々にも大いに参考になる内容です。多くの方々のご出席をお待ちしています。

プログラム

14:00 – 14:10　**包括的な医薬品開発システムの必要性**

東海大学
特任教授　平山 令明

14:10 – 14:45　**Next Generation Drug Repositioning Strategies**

Prous Institute for Biomedical Research
Vice President of R&D　Josep Prous, Jr., Ph.D.

14:45 – 15:20　**US FDA/CDER Practices for ICH M7 (Q)SAR Computational Toxicology Analysis**

Founder, OmnyCorp
元 FDA/ CDER 上級職員
R. Daniel Benz, Ph.D.

15:20 – 15:30　**総合討論**

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Next Generation Drug Repositioning Strategies

Josep Prous, Jr.
jprous@prousresearch.com

Prous Institute for Biomedical Research, Rambla Catalunya 135, 08008, Barcelona, Spain

Keywords: Safety and efficacy profiling, drug repositioning, *in silico* drug discovery, chemoinformatics

Over the past decade, and despite major advances in new technologies, the pharmaceutical sector has witnessed how the number of new drugs introduced in the market every year has stayed level or decreased while the cost of drug discovery and development has significantly increased.

In this context, drug repositioning – aimed at identifying new clinical opportunities for existing drugs - has emerged as a useful strategy to overcome the productivity challenge in drug R&D thanks to its associated diminished risk and cost.

In order to maximize and accelerate drug repositioning strategies, Prous Institute for Biomedical Research has developed SYMMETRY, an innovative *in silico* solution which enables the generation of new research hypotheses and predicts with a high degree of accuracy the pharmacological and toxicological profile of small molecules, supporting decisions in the design and optimization of drug candidates.

SYMMETRY is applied based on a combination of Prous Institute proprietary data (from expert analysis of patents, journals and congresses), public databases and experimental information and provides a wide variety of potential approaches to drug repositioning including:

- Molecular mechanism of action and indication discovery of new and known drugs
- Phenotypic and therapeutic activity reprofiling
- Indication discovery based on gene expression signatures
- Indication discovery from similarity of adverse effects
- Structural repositioning of known drugs

This unique Prous Institute integrated approach to drug repositioning is based on a series of proprietary algorithms and models including a Global Mechanism of Action (MoA) Model which predicts the potential mechanisms of action of small molecules. It is trained with over 1 million compounds covering 600 mechanisms of action, including both targets of therapeutic interest as well as those related to toxicities or adverse effects.

The development and validation of SYMMETRY's along with case studies of the platform's applications in drug repositioning will be presented during the seminar.

US FDA/CDER Practices for ICH M7 (Q)SAR Computational Toxicology Analysis

R. Daniel Benz
Dan.Benz@comcast.net

OmnyCorp, Rockville, Maryland 20853 USA

Keywords: (Q)SAR Computational Toxicology, ICH M7, US FDA/CDER

The US Food and Drug Administration's Center for Drug Evaluation and Research (FDA/CDER) (Quantitative) Structure-Activity Relationship [(Q)SAR] Computational Toxicology Group (QCTG) was first established in the mid-1990's. QCTG has been an applied regulatory research group that: 1) compiles very large databases of the results of toxicological and clinical testing; 2) develops consistent rules for converting in vitro, animal and human experimental results into numerical values for computer analysis; 3) evaluates (Q)SAR software such as Symmetry; 4) helps develop toxicological and clinical effect prediction program systems through collaborations with software companies such as the Prous Institute for Biomedical Research; and 5) provides FDA/CDER safety reviewers with computational toxicology evaluations for drugs, metabolites, contaminants, excipients, degradants, etc. QCTG predicts quickly and accurately with *in silico* software in vitro and animal toxicological effects, as well as adverse human clinical effects of interest to FDA/CDER. Making use of (Q)SAR tools can speed the development of safer drugs by rapid identification and elimination of safety concerns for APIs, metabolites, and impurities.

In June, 2014, The International Conference on Harmonisation (ICH), Guideline M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk was released at "step 4" as recommended for final adoption. This is the first international guideline allowing the option of using *in silico* analyses instead of performing certain laboratory tests for demonstrating the safety of drug impurities. ICH M7 offers the option of performing (Q)SAR analyses for bacterial mutagenicity for the qualification of pharmaceutical impurities if actual laboratory testing has not already been done. The FDA/CDER QCTG follows procedures that are consistent with ICH M7 for its computational toxicology evaluations.

This talk will present many details of the current practices that have been used by the QCTG. For the ICH M7-related consultations performed for FDA/CDER safety evaluators, QCTG provides predictions of the likelihood that drug impurities may cause mutations in the strains of Salmonella typhimurium and Escherichia coli specified by ICH S2(R1). (Q)SAR predictions are made for two separate endpoints, one focused on laboratory testing results of Salmonella strains sensitive to DNA G:C base-pair mutations, and another based on testing results of Salmonella and E. coli strains sensitive to A:T mutations.

ICH M7 calls for the use of two different computational methodologies and also the use of expert analysis in creating bacterial mutagenicity (Q)SAR predictions. For internal FDA/CDER evaluations, the QCTG has used the results from three different software systems and both methodologies, expert rule-based and statistical-based, to increase the sensitivity and negative predictivity of predictions and to increase the number of test chemicals for which valid overall calls can be made. Data demonstrating the value of using more than one software methodology and system, and tables showing how the results from multiple methodologies and systems are interpreted to arrive at an overall prediction by FDA/CDER will be presented. In addition, the QCTG practices used to combine the results from the individual G:C and A:T models to make a summary prediction of potential bacterial mutagenicity will be explained.