[14:50 – 15:30]

Drug Development in the age of pharmacogenomics:

Issues facing Japan for genomics based drug development.

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It is important for drug development to have balance between drug efficacy, pharmacodynamics (PD), and safety, whereas the most importance has been placed on the evaluation of efficacy in the early stages. However, the importance of early stage screening of PD and safety has recently been recognized from accumulated experience of drug development being halted in late stages by inappropriate PD and safety profiles. In PD screening, prediction of CYPs inhibition or drug absorption is improved with establishment of methodology. Thus as the next step, it is very important for business survival tactics how the pharmaceutical firms improve reliability and efficiency of toxicity screening in the early stages. The so-called omics technology is expected to become an efficient and reliable toxicity screening. Genomics technology has dramatically evolved with the completion of the genome sequencing for several species. Microarray is currently a major technology of functional genomics field, which can detect changes in numerous mRNA levels of toxicologically relevant genes such as drug metabolizing enzymes, cell cycle- and cell injury-related genes simultaneously. Such large-scale detection of cellular mRNA levels by microarray aids researchers to elucidate integrated biological systems, compared to traditional low-throughput technologies such as Northern blot or Q-RT-PCR. We have been utilizing Affymetrix

GeneChip for toxicogenomics analysis. We present some practical cases of toxicogenomics analysis such as comprehensive expression analysis of drug metabolizing enzyme genes [1] and evaluation of drug-induced hepatic glutathione deficiency [2].

Expected effectiveness of drug are vary between patients (25-80%) and depend on conditions being treated. [3] Similarly, an incidence of more than a million adverse drug reactions per year has been reported. [4] Nearly 60% of drugs commonly used were subject to genetically-variable metabolism [5]. Pharmacogenomics (PGx) cannot improve the efficacy of a given drug, but it might help in selecting well-responding patients and in minimizing the risk of adverse drug reactions. A tabulated relationship for the determination of the increasing in response rate for the responding genotypic subgroup of patients is provided as an aid to determining whether it is worth doing a PGx study for clinical trial. Despite the considerable advances of genomics research, relatively little remains known regarding the clinical application of PGx. It is necessary to accumulate the practical clinical applications of PGx.

For Pharmacokinetics related PGx study, it is imperative to construct a reference database of polymorphisms in drug metabolizing enzymes to standardize the data and analytical procedure. In Japan, a database of polymorphism in drug metabolizing enzyme was constructed by the Pharma SNP consortium (43 member

companies of the Japan Pharmaceutical Manufacturers Association (JPMA))[6]. The database consists of data of map positions of single nucleotide polymorphisms (SNPs) in a pharmacokinetics-related gene and frequency of SNPs in the general Japanese population. Immortalized B cells raised from this study were deposited at Japan health science research resource bank. These data and cell lines might be useful for future study especially for the Japanese population. In the safety PGx, we have experience in a genetic association study of unexpected adverse drug reactions to trogliazone, which is a 2,4-thiazolidinedione antidiabetic agent with insulin-sensitizing activities. This agent had been used efficiently in a large number of patients but was withdrawn from the market in 2000 because of idiosyncratic hepatotoxicity. To address the susceptible genetic factors responsible for the hepatotoxicity we performed a genetic association study [7]. We studied 51 candidate genes related to drug metabolism, apoptosis, production and elimination of reactive oxygen species and signal transduction pathways of peroxisome proliferator-activated receptor gamma 2 and insulin. We have concluded that double null mutation of GSTT1 and GSTM1 might influence the troglitazone-associated hepatotoxicity risk. From this study we have learned a lot of points to remember to conduct PGx studies in clinical trials. For example, safety PGx study can require as few as 20 cases, if provided a large number of controls are

available. In other word, it is important to keep patients DNA samples throughout the clinical trial including Phase IV. In addition, ethical issues in PGx came out as a general concern. We have to explain risk and benefits of PGx study and the purpose of genetic study in PGx, especially the difference from diagnostic and prognostic genetic test for disease susceptibility and genetic disorder.

A recent FDA Guidance for Industry has encouraged the submission of pharmacogenomics data with new drug applications. In Japan, the ministry of health, labor and welfare issued the notification "Submitting clinical trials information in which pharmacogenomics approaches were used by the regulatory agency for making a guidance document for pharmacogenomic approaches on pharmaceutical developments" in March this year and start collecting the information. At the moment Japanese pharmaceutical industries are afraid to proceed with clinical applications of PGx compared to foreign pharmaceutical companies. This reluctance may be due to a fear from uncertainty of public acceptance concerning genetic data handling and the lack of regulatory It is expected, however, that PGx studies in clinical trial will dramatically increase over the coming years.

We think PGx is an insurance policy for new drugs coming to market. PGx testing during clinical trials ensures that the drug will have a longer, profitable lifespan

with less risk of adverse reactions during Phase IV.

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