Killing of a new drug candidate at late phase of the clinical trials, especially at large scale clinical trials, mean the loss of huge investment, and it is a serious damage for pharmaceutical industries. One of possible reason for discontinuation of the drug development is severe adverse events at clinical trials, so it is important to detect a toxicity of new drug entity (NDE) or its candidates in the earlier stage of drug development. Thus, we are conducting as much pre-clinical experiments to elucidate undesirable property of NDE candidates; i.e., animal experiments with rodents, dogs and monkeys (acute or chronic toxicity, genotoxicity, reproductive toxicity, immunotoxicity, carcinogenicity, and safety pharmacology, etc). We are also conducting many series of in vitro studies.

Many pilot studies are conducted at early discovery stage, and GLP studies are conducted at IND-enabling stage or later. Problem is that still chronic toxicity or idiosyncratic toxicity of NDE is very difficult to be predicted from short-term toxicity studies. Many in vitro studies are employed at early discovery stage due to throughput of the study, and another hurdle is the issue of ‘in vitro-in vivo extrapolation’. People are making great efforts to develop novel in vitro methods to perform better prediction, and some pilot study system are utilizing human materials.

In some case, toxicogenomics data is powerful tool to predict toxicity of the NDE. Advantage of toxicogenomics is high sensitivity, and we could detect a toxicity of NDE at lower dose or after shorter-term repeated dose of NDE. Such Toxicogenomics data will help us to put a rough rank order of each NDE candidates at earlier stage than ever. In the case of hepatotoxicity and nephrotoxicity, some feasible probe, such as Kim-1, is proposed already. Background dataset of another area are rapidly expanding.

By the way, serious adverse event is sometimes human specific and not found in TOX studies in animal. Species differences in DMPK of NDE sometimes make the safety assessment more complicated. Safety evaluation of metabolite is highlighted recently, suggesting importance of better understanding of species differences in drug metabolism. DMPK researcher will play one of major role in discussion of human specific or human dominant metabolite, and in evaluation of reactive metabolite. So far, we have to handle each issue on case-by-case basis. To sophisticate the approach to safety evaluation of human metabolite, we need to compile intelligence from case studies to avoid conducting too much additional TOX studies.

Evaluation of enzyme induction would be an example of joint work of DMPK and TOX researchers. Pilot screening with human hepatocytes will be conducted at DMPK team, and TOX team will cover the monitoring of some enzyme activities in TOX studies in rodents and non-rodents.

DMPK research will provide a lot of insight for better understanding of physiological (pharmacological or toxicological) response to NDE. PK/PD and TK/TD studies should grow to maturity by enhancing the collaboration of DMPK researcher with pharmacology and TOX researchers.

Biography

Dr. Baba has finished post-graduate course of Kyushu University in 1987, then he joined Shionogi & Co., Ltd. He majored in drug metabolism, and he spent "sabbatical year" at Vanderbilt University (TN, USA; Prof. F.P. Guengerich) in 1992. He acted as Head of DMPK (2005-2006) and Head of Drug Safety Evaluation (2007-2008) sequentially in Developmental Research Laboratories, Shionogi & Co., Ltd. He is currently (2009 - ) General Manager of Marketing Department.