

## Novel Alternative Methods in Toxicity Testing

### Introduction

Tetsuo Satoh

Laboratory of Biochemical Pharmacology and Biototoxicology

Faculty of Pharmaceutical Sciences, Chiba University

Chiba 263, Japan

The science of toxicology is the understanding of the mechanisms by which exogenous agents produce deleterious effects in biological systems. The actions of chemicals such as drugs are ultimately exerted at the cellular and gene levels. Over the past decade, several *in vitro* alternative methods such as cultured cells for assessing the toxicity of various xenobiotics have been proposed to reduce the use of animals. In this workshop three advanced methods will be presented. These methods are novel important models for toxicologic studies. Dr. Tabuchi's group has established two immortalized gastric surface mucosa cell lines from the primary culture of gastric fundic mucosal cells of adult transgenic mice harboring a temperature-sensitive simian virus 40 large T-antigen gene. As the immortalized cell lines of various tissues possess unique characteristics to maintain their normal functions for several months, these cell lines are extremely useful for not only toxicity testing but also pharmacological screening in new drug development. Professor Funatsu have studied the formation of spherical multicellular aggregates of adult rat hepatocytes (spheroid) having tissue like structure. The spheroid shown here is a prototype module of an artificial liver support system. Thus, the urea synthesis activity of the artificial liver was maintained at least 10 days in 100% rat blood plasma. Dr. Takezawa and his coworkers have developed a novel culture system of multicellular spheroids considered "organoids" by utilizing a thermo-responsive polymer as a substratum of anchorage dependent cells. His final goal is to reconstitute the organoids of various normal organs, e.g., liver, skin etc. and also abnormal diseased organs such as tumor. Thus, organoids are very useful tool to predict the metabolism of drugs and chemicals in physiological and pathological conditions. Finally, Dr. Ono is going to talk about the substrate specificity of ten human P450 isoforms expressed in Hep G2 cells using a recombinant vaccinia virus. The results presented in this workshop indicate that cDNA-expressed P450s will allow predictive tests to determine how drugs or other chemicals will be metabolized by individual P450 isoform(s) before they are used for clinical studies.

An important component of toxicology is the identification of hazardous substances prior to their introduction into the environment. Thus, cell systems, because of their convenience and the fact that testing can be precisely controlled according to defined protocols, play an important role in the

assessment of potential chemicals. Moreover, at a time when chemical testing has reached gigantic proportions, cell systems offer one means of reducing the use of experimental animals.

It is clear from the broad support for this workshop and the large participation in it that cell toxicology and gene technology have arrived as a discipline and as a useful methodology. As the organizer, I hope that this workshop will further contribute to advancement in these area in Korea.