[S1-5] [10/17/2002 (Thurs) 12:10~12:30/Hall A]

Establishment of new cytotoxicity screening system using Caco-2 cells

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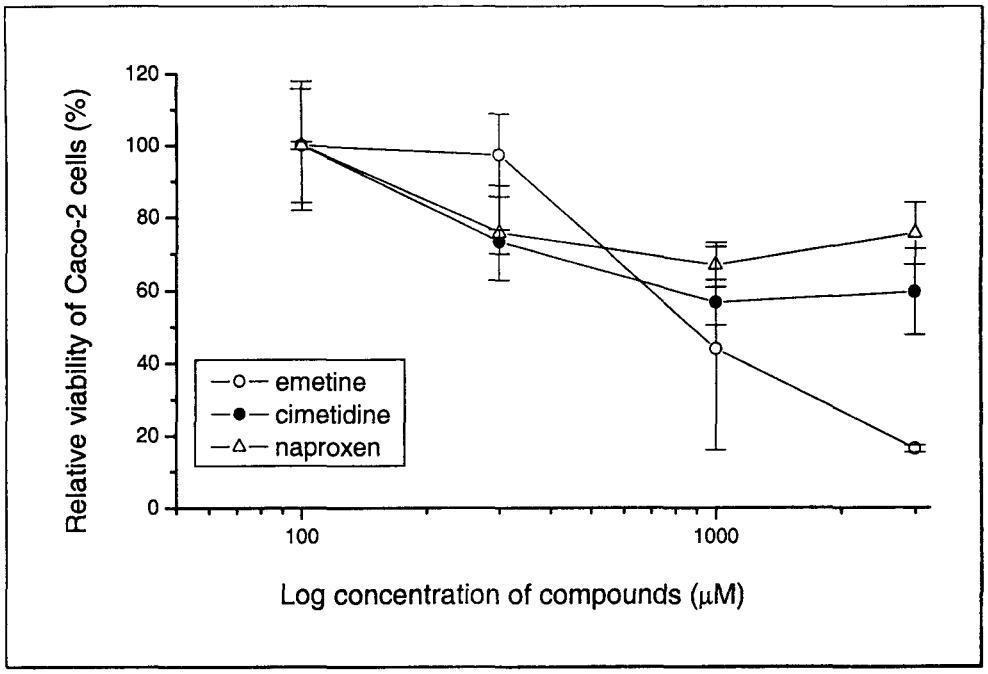
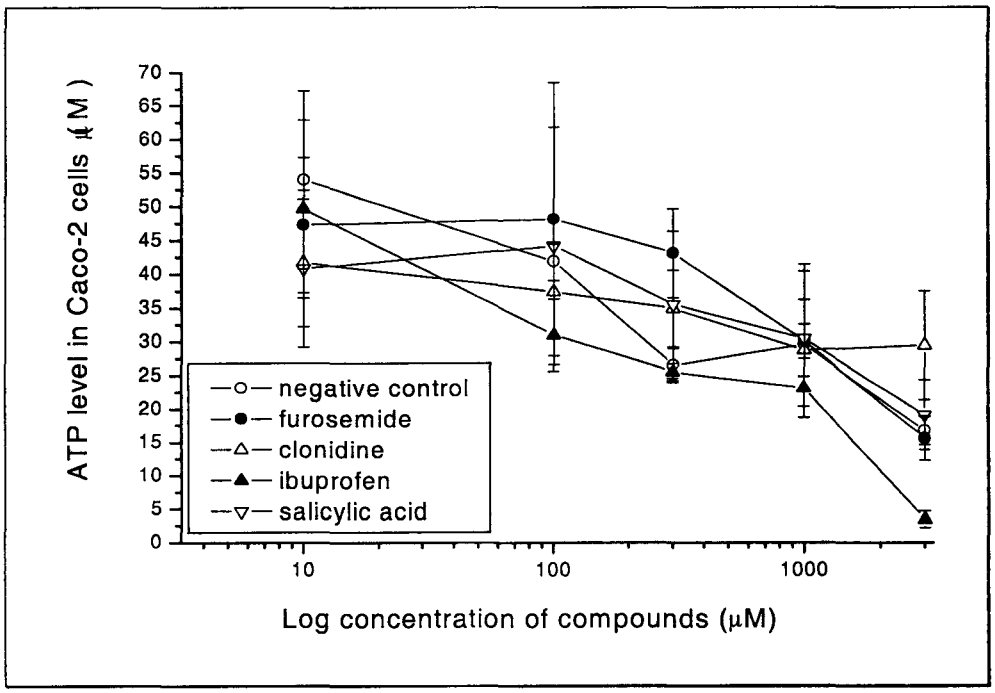
With the recent development of combinatorial chemistry, recombinant biotechnology and rational drug design, millions of compounds are being produced in the laboratories of pharmaceutical companies. These new drug candidates are evaluated their efficacy and toxicity through *in vivo* animal model studies which is very important in drug development. From these studies, very successful drug candidates are selected[1].

Traditionally, *in vivo* animal model has been widely used for the evaluation of toxicity and effect of new drug candidates. Various animal species such as mouse, rat, rabbit, dog and monkey have been served as the animal model for the toxicity study. The cost and the length of study period, however, are the drawbacks of the *in vivo* animal model. Recently, *in vitro* human hepatocyte is adapted to the screening model for toxicity and hepatic metabolism of new drug candidates in many laboratories[2]. However, the cost of human hepatocytes is very expensive.

The purpose of this study is to investigate the use of Caco-2 cells instead of human hepatocytes for the screening of cytotoxicity of new drug candidates. The culture of Caco-2 cells is well established[3] and is very economic compared with that of human hepatocytes.

Approximately, 30~40 drug molecules were tested for their toxicity in Caco-2 cells using ATP[4], MTT[5] and neutral red uptake[6] assay. In addition, about 30 drug molecules were studied for their toxicity in human hepatocytes[7] using ATP assay. The toxicity of each molecule was evaluated as a function of AUV (area under the viability curve). Finally, the correlation of AUVs between the Caco-2 cell model and the human hepatocytes was investigated to evaluate the utility of Caco-2 cells for the cytotoxicity screening system.


Relative viability of Caco-2 cells (%)
120
100
80
60
40
20
0
100
1000
Log concentration of compounds (μM)
emetine
cimetidine
naproxen


ATP level in Caco-2 cells (μM)
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
10
100
1000
Log concentration of compounds (μM)
negative control
furosemide
clonidine
ibuprofen
salicylic acid