



Predicting long-term toxic effects using computer models based on systems characterization of organotypic cultures

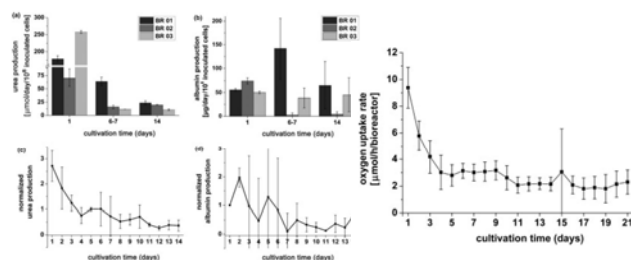
## The hollow fiber 3D bioreactor: a tool for studies of hepatotoxicity

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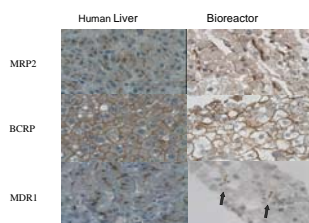
### ABSTRACT

The hollow fiber bioreactor system (developed by Gerlach et al.) provides a novel *in vitro* system for studying drug – induced hepatotoxicity. The use of the bioreactor permits for the study of drug metabolism and toxicity because the cells are able to maintain their phenotype for a long duration of time ( $\approx 3$  weeks). Results from experiments illustrate that the cell cultures are able to form and maintain *in vivo* like hepatic structural (i.e. hepatocytes, epithelial cells, Kupffer cells and bile ducts) and functional (i.e. CYP450 enzymes activities, oxygen consumption, glucose, albumin, lactate and urea production) characteristics. Here we present the initial experience with applications in toxicology. The results suggest that the hepatic 3D bioreactor system can be used for not only long-term metabolic and toxicological studies, but may be a useful model to study the chronic toxicological effects due to repeated exposure to drugs.

### General characteristics



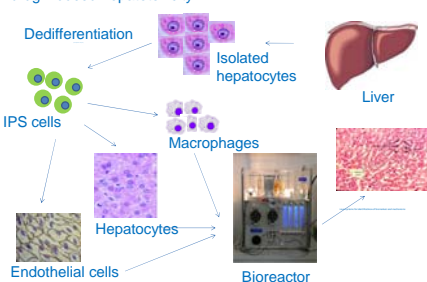
Liver-specific parameters of primary human hepatocytes from three different donors cultivated in 3D bioreactors (Mueller et al *J Tissue Eng Regen Med* (2011).



Morphology and expression of transporter in human liver and in the bioreactor system

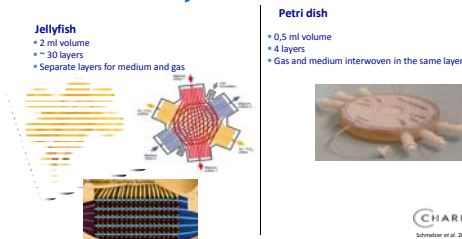
Zeilinger et al., *Tissue Eng Part C Methods*. 2011 17:549-56.

### Regeneration of liver for studies of drug induced hepatotoxicity

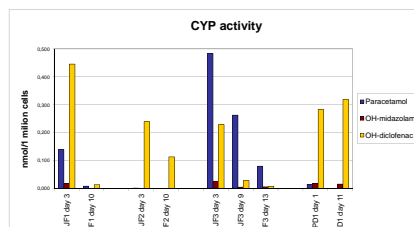


Strategy for formation of *in vitro* human hepatic systems for toxicity studies from hepatocytes of patients sensitive or not sensitive for drug toxicity

### 3D bioreactor system



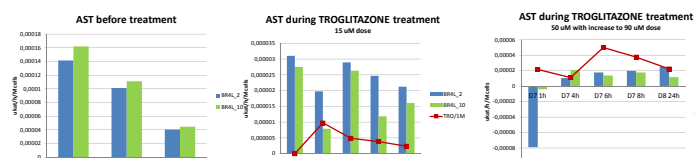
Type of bioreactor systems of 2 ml and 0.5 ml volumes



Maintenance of P450 activities in in four experiments utilizing the two different bioreactors, JF, Jelly Fish, and PD, Petri dish (2 layer 0.5 ml)

### Application of the hollow fiber bioreactor to toxicity studies.

We have applied the bioreactor system for studies of paracetamol toxicity and troglitazone toxicity. Time and dose titrations have been carried out and transferases, urea, glucose production and oxygen consumption monitored. It was found that continuous measurements of the drugs in the circulation is of importance because of the absorption problem. En example with troglitazone is given below



Transferase levels in 0,5 ml 4 layer liver bioreactor treated with troglitazone (blue) or control (green) in comparison to the actual troglitazone concentrations during long term conditions

### Conclusions

#### Advantages

The 3D hollow fiber bioreactor technique has been used with success both at Karolinska Institutet as well as in Saarland University. In many cases highly relevant liver structures and functions are maintained in the bioreactors for several weeks.

#### Limitations

There is a high interindividual variation in the properties of the bioreactors and a problem with absorption of basic drugs. The system is not useful for high throughput assays, but important for understanding mechanisms and biomarkers.

#### Future

We will continue to utilize the bioreactor and improve its experimental conditions to study drug – induced hepatotoxicity. Additional cytotoxicity assessments will be employed in the studies. Furthermore, an extended aim of the studies will be to investigate early biomarkers of toxicity. The 3D bioreactor system is also currently being used to differentiate iPS cells into hepatocytes. Thus taken all together, the results suggest that the 3D bioreactor system is a promising tool to study hepatic drug metabolism and toxicity.

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