Liver Models for the Development of New Antiviral Drugs

Fig.1. Incubator for the cultivation of liver models.

The emergence of novel viruses such as the MERS coronavirus and new variants of well-known viruses such as avian influenza viruses still constitutes a major medical problem and demonstrates the necessity to develop new antiviral drugs. Normally, the process of drug development involves testing of new compounds in animal models. However, this approach has two major disadvantages: It is associated with suffering of the animals and the animal physiology may differ substantially from that of humans.
We therefore established a humanized liver model for the development of new antiviral drugs. The first step to this end was to isolate livers from rats, followed by complete removal of all rodent cells by chemical treatment. At the end of this procedure, a scaffold remained that is known as the extracellular matrix. After connecting the blood vessels to an artificial “blood”/media flow, this matrix was repopulated with human cells and cultivated in a special incubator shown in Figure 1.

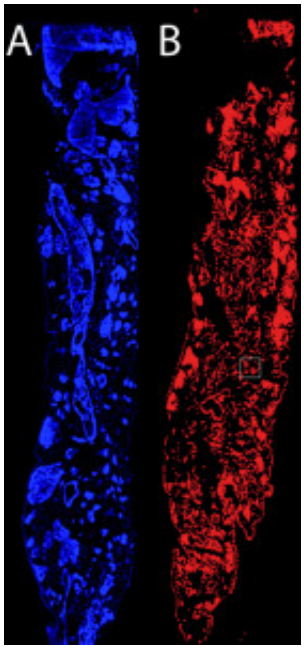

Fig. 2. Fluorescence microscopy images of the infected humanized liver. A) Repopulation of the scaffold with human liver cells. The blue fluorescent dye labels the cell nuclei. B) The red fluorescence shows the production of the reporter in cells that were infected by the viruses.

Successful reconstitution of the liver with human cells can be visualized by staining the cell nuclei with a blue fluorescent dye (Figure 2A). The resulting humanized liver model provides typical physiological characteristics of a human liver and is therefore superior to standard animal models in many aspects.

In our study, we used the humanized liver model to carry out infection studies. For the proof-of-concept experiments, we used a harmless virus, known as the adeno-associated virus or AAV. The natural virus was modified to produce a reporter that allowed tracing the infection. After infection of the liver model with the virus, we could demonstrate that it spread virtually throughout the complete liver and produced the reporter (Figure 2B). The AAV also contained a component that turned off deleterious genes, i.e. genes that induce cancer growth or genes of another virus. Our analysis confirmed that we were able to efficiently transfer this silencer into the liver model.

The liver model for infection studies provides various advantages compared to conventional approaches. It permits studying cells in a three dimensional network which differs substantially from two dimensional cell cultures widely used in biomedical research. In addition, replacement of the animal cells by human cells provides a model to obtain more relevant data concerning virus spread, antiviral activity of new compounds and their potential side effects in human patients than standard animal models do. Finally, the approach contributes to the protection of animals, as the livers were exclusively harvested from superficial rats that were sacrificed for other purposes. Thus, no additional animals were needed for the experiments and suffering of living laboratory animals

was prevented. The next step will be to produce the liver scaffold by artificial three-dimensional bioprinting, thus completely avoiding the use of components of animal source. Regardless of these future aims, our current model is ready to be used for the development of new drugs against pathogens such as the hepatitis B and C viruses which claim more than a million lives every year and hepatitis E viruses which are an upcoming threat to human health.

Publication

Use of a three-dimensional humanized liver model for the study of viral gene vectors.
Wagner A, Röhrs V, Materne EM, Hiller T, Kedzierski R, Fechner H, Lauster R, Kurreck J
J Biotechnol. 2015 Sep 6;212:134-143