

## FIRST NORMAL HUMAN HEPATOCYTE CULTURE SYSTEM SUPPORTING THE GROWTH OF NATURAL ISOLATE OF HEPATITIS C VIRUS

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For the first time, it has been possible to sustainably infect normal human liver cell cultures with natural hepatitis C virus (HCV) isolates, using a cell culture method described in a paper by M. Buck published on 16 July in PLOS ONE [1].

The existing methods that are used to study HCV in laboratory cell culture have serious drawbacks.

The most widely used system is based on Huh-7 human hepatocellular carcinoma cells. It allows the efficient production of infectious HCV particles from synthetic cloned RNA. However, only a limited range of HCV RNA clones that can be used in this way are available, and the system does not support the growth of natural HCV isolates. Moreover, the Huh-7 cells are carcinoma cells with several abnormalities compared to normal liver cells.

Other approaches for HCV infection of cells in culture include modified immortalised human hepatocyte cells that similarly to the Huh-7 cells do not necessarily show the same behaviour as normal differentiated human liver cells, and a primary human hepatocyte cell line which only allows for very inefficient infection with HCV.

Buck has taken primary human hepatocytes from normal liver explants and succeeded to find culture conditions that support infection with naturally occurring HCV (genotypes 1-4). She cultured hepatocytes from 29 healthy liver explants and infected them with one of 36 HCV patient isolates. A robust infection was obtained with 33 of the isolates.

The cells remained infected for at least three weeks and mimicked the natural infection of hepatocytes in the patient with respect to the kinetics of RNA replication, protein production and virion release, virion density, inhibition by HCV antibodies, sensitivity to HCV replication inhibitors, and the physiological response of the cells to the infection. The virions produced in these cell lines can be used to infect human hepatocytes in culture. Whether they will be able to produce an infection in chimpanzees and humanised mice remains to be shown.

The system is as efficient in growing HCV as the Huh-7 system, but has the advantage that natural virus isolates can be propagated in normal liver cells, in which the natural infection can be simulated more accurately than in immortalised or modified cells that may show abnormal behaviour. Cells from donors with different medical, ethnic and genetical background can now be used to study the effect of medical conditions, such as insulin resistance, on the development of HCV infection, the influence of HCV infection on the

development of hepatocellular carcinoma, or the reasons why the only currently available treatment – interferon-alpha in combination with ribavirin is only effective in about 50% of individuals.

This method has the potential to complement the existing systems to facilitate the development of a vaccine and the testing of anti-HCV drugs.

### References

1. Buck M. Direct infection and replication of naturally occurring hepatitis C virus genotypes 1, 2, 3 and 4 in normal human hepatocyte cultures. PLoS ONE. 2008 Jul 16;3(7):e2660. Available from: <http://www.plosone.org/article/info:doi/10.1371/journal.pone.0002660>

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