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Mouse model would have predicted toxicity of drug that killed five in 1993 clinical trial

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Over 20 years after the fatal fialuridine trial, a study published this week in *PLOS Medicine* demonstrates that mice with humanized livers recapitulate the drug's toxicity. The work suggests that this mouse model should be added to the repertoire of tools used in preclinical screening of drugs for liver toxicity before they are given to human participants in clinical trials.

A retrospective analysis by the US National Academy of Sciences of all preclinical fialuridine toxicity tests, which included studies in mice, rats, dogs, and monkeys, concluded that the available animal data provided no indication that the drug would cause liver failure in humans. Working on a mouse model in which approximately 90% of the animal's liver cells are replaced by human liver cells, Jeffrey Glenn and Gary Peltz, from Stanford University, USA, and colleagues now show that it is possible to detect the toxicity of fialuridine, and possibly other drugs that poison human liver cells.

When the researchers treated mice with humanized livers with fialuridine, they found that the drug caused liver failure. The clinical symptoms (jaundice and lethargy), laboratory abnormalities (elevated transaminase and lactate levels), and anatomical changes to the liver in the drug-treated mice mirrored those observed in human participants in the fialuridine trial.

To test whether the mouse model could specifically identify the toxicity of fialuridine but would not raise "false alarm" on other drugs, the

researchers treated the humanized liver mice with a second drug called sofosbuvir. Sofosbuvir belongs to the same class of drugs as fialuridine, but it has been tested in humans and was found not to have liver toxicity at doses within a few orders of magnitude of the effective dose. Sofosbuvir-treated mice did not show symptoms of liver failure.

Because the humanized mice used in these studies have an impaired immune system, they cannot be used to warn of toxicity that is mediated by the immune system. Nevertheless, since the liver is the "detox" organ, toxicity caused by drugs that act directly on the liver is a common problem in drug development. And because of important differences between human and animal livers, the researchers say "toxicology studies using mice with humanized livers could have a large impact on drug development and could improve the safety of drugs that will subsequently be tested in humans". They express hope that, as suggested by their findings, "the use of 21st century methodologies could improve the safety of 21st century drug development".

More information: Xu D, Nishimura T, Nishimura S, Zhang H, Zheng M, et al. (2014) Fialuridine Induces Acute Liver Failure in Chimeric TK-NOG Mice: A Model for Detecting Hepatic Drug Toxicity Prior to Human Testing. *PLoS Med* 11(4): e1001628. DOI: 10.1371/journal.pmed.1001628

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