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Researchers turn mouse into factory for human liver cells

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Oregon Health & Science University researchers have figured out how to turn a mouse into a factory for human liver cells that can be used to test how pharmaceuticals are metabolized.

The technique, published in the journal Nature Biotechnology, could soon become the gold standard not only for examining drug metabolism in the liver, which helps scientists determine a drug's toxicity. But it also can be used as a platform for testing new therapies against infectious diseases that attack the liver, such as hepatitis C and malaria.

"This has the potential, if it becomes easy to use and widely available, to change the way drugs are tested," said study leader Markus Grompe, M.D., professor of molecular and medical genetics, and pediatrics, OHSU School of Medicine.

"In terms of fostering research, this will be great for malaria, this will be great for hepatitis, this will be great for liver stem cells, this will be great for gene therapy. It will allow a lot of what's going on only in rodents to be taken into a much more clinical setting. So I'm very happy about it."

Arundeep S. Pradhan, director of OHSU's Technology & Research Collaborations office, which is responsible for transferring the university's research discoveries to the commercial sector, said market demand for Grompe's discovery is high. OHSU has filed a patent application on the technology and, in cooperation with Grompe, has spun it off into a Portland-based start-up company named Yecuris through the

university's Springboard Program.

"Yecuris is a viable start-up company based on significant developments at OHSU," Pradhan said. "The products developed by Yecuris have the potential to ease one of the bottlenecks in drug development: the testing of drugs for liver toxicity."

The worldwide market for human liver cells the pharmaceutical industry uses for testing candidate drug compounds is estimated at $2 billion a year, according to a business plan for Yecuris. That's because the liver is the principal site for the metabolism of drug compounds.

"Chemicals are converted to other chemicals in the liver, and you can't predict how the compound you developed in the lab will be converted," Grompe said. "Often, it's not the drug that's toxic, but the resulting metabolites. The conversion of drugs cannot be predicted with any current technology, such as computer models. You actually have to see what human liver cells do with any given drug."

And human liver cells must be used instead of cells from laboratory animals because liver enzymes that break down these compounds are species specific. "Animal liver cells process drugs quite differently than human liver cells do," he said.

Another obstacle for drug companies is the human liver cell market is filled with poor-quality or nonviable cells isolated primarily from human cadaver livers left over after high-quality livers needed for transplants are harvested. Plus, the cells are only available when specimens become available, which can be any hour of the day or night, and they must be used immediately.

"There are a number of companies that take these leftover livers, process them and ship the cells to people who need them for testing," Grompe

said. "You have no control over when you get them, and you have no control over the quality when you get them. Many batches of cells are bad, low quality." And human liver cells from living sources are difficult to expand in laboratory tissue cultures.

In the last decade, scientists have studied whether mice could be genetically engineered and bred to grow human liver cells. Early results since 2004 showed it could be done, but the mice were difficult to breed, the time window for transplanting human liver cells into the mice was narrow, and the mouse liver, despite efforts to make the animal immunodeficient, often rejected the human cells.

Grompe's laboratory now has a system in which those disadvantages have been engineered out. It has created a severely immunodeficient mouse strain that develops liver disease only when the animals don't receive a protective drug called NTBC, allowing liver disease to be turned on and off.

"Our mice on this medicine are perfectly healthy, normal mice, and only when we take them off the NTBC do they get liver disease," Grompe said. "It's an easy system that any research lab should be able to set up, which is very different from what's around now."

In fact, the human liver cells from the repopulated mouse livers are indistinguishable from normal human liver cells, according to the study. "The healthy human liver cells take over and replace the sick mouse liver cells," Grompe said. "You end up with a healthy mouse that makes human blood clotting factors, all the proteins the liver makes, human bile, everything."

The mice also retain their unique traits for multiple generations, and each mouse can be implanted with human liver cells at least four times. Grompe estimates that each round of implantation can generate more

than 20 million viable human liver cells.

"We think we will have a real edge in terms of quality and availability of cells," Grompe said. "We have a product. All we need to do is scale up and start selling it to anyone who wants to buy it."

In the coming months, Grompe's lab will develop a library of human liver cells from common variations of human drug metabolism. "Different humans metabolize drugs differently. So we want to create a library of cells from different humans to capture some of that variability," Grompe said.

Source: Oregon Health & Science University