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Team first to grow liver stem cells in culture, demonstrate therapeutic benefit

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For decades scientists around the world have attempted to regenerate primary liver cells known as hepatocytes because of their numerous biomedical applications, including hepatitis research, drug metabolism and toxicity studies, as well as transplantation for cirrhosis and other chronic liver conditions. But no lab in the world has been successful in identifying and growing liver stem cells in culture—using any available technique – until now.

In the journal *Nature*, physician-scientists in the Papé Family Pediatric Research Institute at Oregon Health & Science University Doernbecher Children's Hospital, Portland, Ore., along with investigators at the Hubrecht Institute for Developmental Biology and Stem Cell Research, Utrecht, Netherlands, describe a new method through which they were able to infinitely expand liver stem cells from a mouse in a dish.

"This study raises the hope that the human equivalent of these mouse liver stem cells can be grown in a similar way and efficiently converted into functional liver cells," said Markus Grompe, M.D., study co-author, director of the Papé Family Pediatric Research Institute at OHSU Doernbecher Children's Hospital; and professor of pediatrics, and molecular and medical genetics in the OHSU School of Medicine.

In a previous *Nature* study, investigators at the Hubrecht Institute, led by Hans Clever, M.D, Ph.D., were the first to identify stem cells in the small intestine and colon by observing the expression of the adult stem cell marker Lgr5 and growth in response to a growth factor called Wnt.

They also hypothesized that the unique expression pattern of Lgr5 could mark stem cells in other adult tissues, including the liver, an organ for which stem cell identification remained elusive.

In the current *Nature* study, Grompe and colleagues in the Papé Family Pediatric Research Institute at OHSU Doernbecher used a modified version of the Clever method and discovered that Wnt-induced Lgr5 expression not only marks stem cell production in the liver, but it also defines a class of stem cells that become active when the liver is damaged.

The scientists were able to grow these liver stem cells exponentially in a dish – an accomplishment never before achieved – and then transplant them in a specially designed mouse model of liver disease, where they continued to grow and show a modest therapeutic effect.

"We were able to massively expand the liver cells and subsequently convert them to hepatocytes at a modest percentage. Going forward, we will enlist other growth factors and conditions to improve that percentage. Liver stem cell therapy for chronic liver disease in humans is coming," said Grompe.

More information: "In vitro expansion of single Lgr5+ liver stem cells induced by Wnt-driven regeneration," *Nature*, 2013.

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