**Scientists Fabricate Rudimentary Human Livers**

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Researchers in Japan have [used human stem cells to create tiny human livers](http://dx.doi.org/10.1038/nature12271) like those that arise early in fetal life. When the scientists transplanted the rudimentary livers into mice, the little organs grew, made human liver proteins, and metabolized drugs as human livers do.

They and others caution that these are early days and this is still very much basic research. The liver buds, as they are called, did not turn into complete livers, and the method would have to be scaled up enormously to make enough replacement liver buds to treat a patient. Even then, the investigators say, they expect to replace only 30 percent of a patient’s liver. What they are making is more like a patch than a full liver.

But the promise, in a field that has seen a great deal of dashed hopes, is immense, medical experts said.

“This is a major breakthrough of monumental significance,” said Dr. Hillel Tobias, director of transplantation at the New York University School of Medicine. Dr. Tobias is chairman of the American Liver Foundation’s national medical advisory committee.

“Very impressive,” said Eric Lagasse of the University of Pittsburgh, who studies cell transplantation and liver disease. “It’s novel and very exciting.”

The study was published on Wednesday in the journal Nature.

Although human studies are years away, said Dr. Leonard Zon, director of the stem cell research program at Boston Children’s Hospital, this, to his knowledge, is the first time anyone has used human stem cells, created from human skin cells, to make a functioning solid organ, like a liver, as opposed to bone marrow, a jellylike organ.

Ever since they discovered how to get human stem cells — first from embryos and now, more often, from skin cells — researchers have dreamed of using the cells for replacement tissues and organs. The stem cells can turn into any type of human cell, and so it seemed logical to simply turn them into liver cells, for example, and add them to livers to fill in dead or damaged areas.

But those studies did not succeed. Liver cells did not take up residence in the liver; they did not develop blood supplies or signaling systems. They were not a cure for disease.

Other researchers tried making livers or other organs by growing cells on scaffolds. But that did not work well either. Cells would fall off the scaffolds and die, and the result was never a functioning solid organ.

Researchers have made specialized human cells in petri dishes, but not three-dimensional structures, like a liver.

The investigators, led by Dr. Takanori Takebe of the Yokohama City University Graduate School of Medicine, began with human skin cells, turning them into stem cells. By adding various stimulators and drivers of cell growth, they then turned the stem cells into human liver cells and began trying to make replacement livers.

They say they stumbled upon their solution. When they grew the human liver cells in petri dishes along with blood vessel cells from human umbilical cords and human connective tissue, that mix of cells, to their surprise, spontaneously assembled itself into three-dimensional liver buds, resembling the liver at about five or six weeks of gestation in humans.

Then the researchers transplanted the liver buds into mice, putting them in two places: on the brain and into the abdomen. The brain site allowed them to watch the buds grow. The investigators covered the hole in each animal’s skull with transparent plastic, giving them a direct view of the developing liver buds. The buds grew and developed blood supplies, attaching themselves to the blood vessels of the mice.

The abdominal site allowed them to put more buds in — 12 buds in each of two places in the abdomen, compared with one bud in the brain — which let the investigators ask if the liver buds were functioning like human livers.

They were. They made human liver proteins and also metabolized drugs that human livers — but not mouse livers — metabolize.

The approach makes sense, said Kenneth Zaret, a professor of cellular and developmental biology at the University of Pennsylvania. His research helped establish that blood and connective tissue cells promote dramatic liver growth early in development and help livers establish their own blood supply. On their own, without those other types of cells, liver cells do not develop or form organs.

“They were letting nature do its thing rather than trying to conceive of what the right signals might be,” Dr. Zaret said. But, he said, the mice were studied for only a couple of months. He would like to see what happens over a longer time.

“We don’t know if the cells will grow out of control or will poop out,” Dr. Zaret said.

Even if the liver buds never fulfill their clinical promise, they still could be enormously important for pharmaceutical research, Dr. Zon said. Drugs must be tested to see if they damage the liver, a major site of drug toxicity. Companies do this with liver cells taken from cadavers and grown in petri dishes. But the liver buds could be a big improvement and offer a large supply of rudimentary livers for testing.

“That would be huge,” Dr. Zon said. “It would open up lots of drugs in the pipeline and bring them to the clinic much more quickly.”

Dr. Takebe and his colleagues, though, are more focused on scaling up their process so they can think of trying to take it to the clinic, perhaps to treat babies and children whose livers have failed. Dr. Takebe estimates they would need hundreds of thousands, perhaps millions, of liver buds to replace 30 percent of the liver.

Dr. Tobias, the transplant surgeon, hopes they succeed.

“This is obviously the wave of the future,” he said.

