An in vitro and in vivo comparison among three different human hepatic stem cell populations.

Grant Award Details

An in vitro and in vivo comparison among three different human hepatic stem cell populations.

Grant Type: Comprehensive Grant

Grant Number: RC1-00359

Investigator:

Name:	Mark Zern
Institution:	University of California, Davis
Type:	PI

Disease Focus: Liver Disease, Metabolic Disorders

Human Stem Cell Use: Adult Stem Cell, Embryonic Stem Cell

Award Value: $2,251,223

Status: Closed

Progress Reports

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4

View Report

Grant Application Details

Application Title: An in vitro and in vivo comparison among three different human hepatic stem cell populations

Public Abstract:

Because there is still considerable morbidity and mortality associated with the process of transplantation, and because more than a thousand people die each year while on the liver transplantation list, it is evident that improved and safer liver transplantation would be valuable, as would approaches that provide for an increased number of transplantations in a timely manner. A technology that might address these issues is the development of a human liver cell line that can be employed in liver cell transplantation or in a bioartificial assist device. Developing such a cell line from human embryonic stem cells (hESC) or from other human stem cell sources would provide a valuable tool for pharmacology studies, as well as for use in cell-based therapeutics.

In the proposed studies, we will differentiate human embryonic stem cells or fetal liver cells or bone-marrow derived cells so that they act like liver cells in culture. Once it has been established that the cells are acting like liver cells by producing normal human liver proteins, and that they do not act like cancer cells, the cells will be injected into the livers of immunoincompetent mice that do not rejects human cells. Then we will evaluate whether the cells grow and thrive in the mouse livers, whether they still produce high levels of human liver-specific proteins, whether they produce tumors in the mouse livers, and whether they can replace damaged mouse liver cells with human cells. One of the ways this will be done is to label the cells with a marker gene and to image the marker gene in the livers of the mice with special x-ray machines that can distinguish a few hundred human cells in the mouse liver. Finally, we will infuse the human liver stem cells into the liver of monkeys to determine if they will grow in the monkey livers, because the monkeys are more similar to man. Such studies should be done in nonhuman primates before clinical studies are undertaken to employ these cells to replace abnormal liver cells in man. Our intent is these studies is to compare and contrast three types of stem cells to determine which will be the most effective cells to use in human studies.

If the studies are successfully undertaken, we will establish a clinically useful and safe liver cell line that could be used to repopulate an injured liver in a safer and less expensive manner than with liver transplantation; moreover, all people who had liver failure or an inherited liver disease could be treated, because there would be an unlimited supply of liver cells.

Statement of Benefit to California:

In California, as in all parts of the US, there are not enough livers available for transplantation for all the people who need them. The result is that many more people die of liver failure than is necessary. One way to improve this situation is the transplantation of liver cells rather than whole organ transplantation. We are attempting to develop liver cell lines from stem cells that will act like normal liver cells. If the cells that we develop function well and do not act like cancer cells in culture, we will then transplant them into special mouse models of liver disease and see if the human cells can rescue the mouse from its liver disease. As a final test, we will see if the cells function in primate livers. In our studies, we will compare human embryonic stem cells with adult stem cells to determine which will be the most effective cells to transplant into people. If the studies are successfully undertaken, it means that we will have a stem cell line that can then be employed in human studies to determine their safety and effectiveness.
