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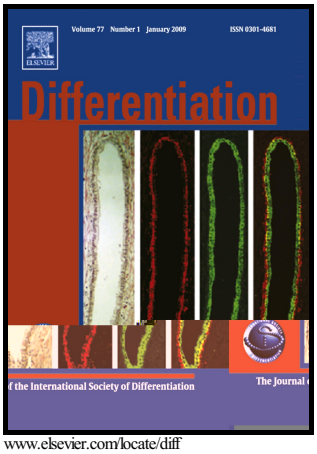

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Evaluating the regenerative potential and functionality of human liver cells in mice

Antson Kiat Yee Tan[1], Kyle M. Loh[2] & Lay Teng Ang[1,*]

[1]Stem Cell & Developmental Biology Group, Genome Institute of Singapore, A*STAR, Singapore 138672
[2]Stanford Institute for Stem Cell Biology and Regenerative Medicine and the Stanford—UC Berkeley Siebel Stem Cell Institute, Stanford University School of Medicine, Stanford, CA 94305 USA
*Correspondence: anglt1@gis.a-star.edu.sg

Abstract
Liver diseases afflict millions of patients worldwide. Currently, the only long-term treatment for liver failure is the transplantation of a new liver. However, intravenously transplanting a suspension of human hepatocytes might be a less-invasive approach to partially reconstitute lost liver functions in human patients as evinced by promising outcomes in clinical trials. The purpose of this essay is to emphasize outstanding questions that continue to surround hepatocyte transplantation. While adult primary human hepatocytes are the gold standard for transplantation, hepatocytes are heterogeneous. Whether all hepatocytes engraft equally and what specifically defines an "engraftable" hepatocyte capable of long-term liver reconstitution remains unclear. To this end, mouse models of liver injury enable the evaluation of human hepatocytes and their behavior upon transplantation into a complex injured liver environment. While mouse models may not be fully representative of the injured human liver and human hepatocytes tend to engraft mice less efficiently than mouse hepatocytes, valuable lessons have nonetheless been learned from transplanting human hepatocytes into mouse models. With an eye to the future, it will be crucial to eventually detail the optimal biological source (whether *in vivo*- or *in vitro*-derived) and presumptive heterogeneity of human hepatocytes and to understand the mechanisms through which they engraft and regenerate liver tissue *in vivo*.

Introduction

The liver is essential to life: it discharges a wide range of crucial roles, including bodily metabolism and neutralization of toxins, amongst other functions[1-4]. Despite its ability to regenerate upon two-thirds physical resection[5], the liver cannot sustain injuries beyond a certain threshold. After extensive damage, liver functions (including detoxification) fail, leading to the accumulation of toxins and eventually, coma and death[6, 7]. Liver disease is one of the 12 leading causes of adult death in the United States (U.S.)[8] and it is estimated that annually >1 million patients die worldwide due to liver failure[9].

Therefore there is a pressing need for new therapeutic interventions to restore liver functions after injury. Currently, the only effective long-term treatment for liver failure is to transplant a new liver derived from another human being[10-12]. However, liver t[redacted]rs[12-