shown to result from mutations in genes encoding Notch receptors or their ligands. (See, e.g., Nam *et al.*, *Curr. Opin. Chem. Biol.* 6:501-509, 2002.)

Certain anti-Notch2 antagonist antibodies having therapeutic efficacy have been described. (See U.S. Patent Application Publication No. US 2009/0081238 A1, expressly incorporated by reference in its entirety herein.) For example, such antibodies bind to the negative regulatory region (NRR) of Notch2, block Notch2 signaling, and inhibit the growth of melanoma cell lines, diffuse large B-cell lymphoma (DLBCL) cell lines, and marginal zone B cells. Certain anti-Notch2 antibodies described therein bind to the LNR-A domain (the first of the three LIN12/Notch Repeats) and the HD-C domain of Notch2 NRR.

Adult liver has the capacity to regenerate after injury. It has been speculated that biliary-hepatocyte progenitor cells (oval cells) in or near intrahepatic bile ducts can differentiate into adult hepatocytes (Brues and Marble, J. Exp. Med., 65(1):15 (1937); Zajicek *et al.*, Liver, 5(6):293 (1985)), which subsequently mature as they move toward the central vein and eventually undergo apoptosis and elimination (Benedetti *et al.*, J. Hepatol., 7(3):319 (1988)). Recent lineage-tracing studies have supported a role of progenitor cells in liver homeostasis and repair, but the signals that govern precursor differentiation into hepatocytes are poorly understood. While Notch signaling is known to be critical for the proper formation of the intrahepatic biliary system during development (Lozier *et al.*, PLoS One 3(3):e1851 (2008); McCright *et al.*, Development 129(4):1075 (2002)), it was not known what role, if any, Notch signaling plays in adult hepatocyte formation and in adult hepatobiliary disease.

Chronic liver disease is marked by gradual destruction of liver tissue, especially of hepatocytes and the functional lobular unit, leading to fibrosis (replacement of liver tissue with scar tissue) and cirrhosis (fibrosis with ineffective nodular regeneration and associated loss of liver function). Moreover, chronic liver disease often includes pathological biliary hyperplasia and may increase the risk of liver cancer.

There is a need in the art for further therapeutic methods of treating liver conditions. The invention described herein meets the above-described needs and provides other benefits.

SUMMARY

The present ~~invention~~ disclosure relates to the treatment of liver conditions using Notch2 antagonists. The present ~~invention~~ disclosure is based, in part, on the observation that anti-Notch2 NRR antibodies (a) improve liver histologic appearance and hepatocyte function in an acute liver

damage model *in vivo* and (b) reduce biliary damage and improve hepatocyte function in a chronic liver damage model *in vivo*.

In one aspect, there is provided use of a Notch2-specific antagonist in the manufacture of a medicament for treating a liver condition characterized by liver damage in a patient having such condition.

In one aspect, there is provided a method of inducing hepatic differentiation, the method comprising the step of contacting an oval cell *in vitro* with an effective amount of a Notch2-specific antagonist, thereby inducing hepatic differentiation of the oval cell.

In one aspect, there is provided use of a Notch2-specific antagonist in the manufacture of a medicament for inducing hepatic differentiation, wherein the medicament is to be contacted with an oval cell *in vivo* to thereby induce hepatic differentiation of the oval cell.

In one aspect, there is provided use of a Notch2-specific antagonist in the manufacture of a medicament for reducing aberrant bile duct proliferation in a patient in need thereof.

In one ~~aspect~~ embodiment, a method of treating a liver condition characterized by liver damage is provided, the method comprising administering to a patient having such condition an effective amount of a Notch2-specific antagonist. In certain embodiments, the liver condition is chronic liver disease. In certain embodiments, the liver condition is liver fibrosis.

In any of the above embodiments, the Notch2-specific antagonist may be an anti-Notch2 antagonist antibody. In certain embodiments, the anti-Notch2 antagonist antibody is an anti-Notch2 NRR antibody. In one such embodiment, the anti-Notch2 NRR antibody binds to the LNR-A and HD-C domains of Notch2 NRR. In another such embodiment, the anti-Notch2 NRR antibody is Antibody D, Antibody D-1, Antibody D-2, or Antibody D-3. In another such embodiment, the anti-Notch2 NRR antibody comprises the heavy and light chain variable region CDRs of Antibody D, Antibody D-1, Antibody D-2, or Antibody D-3. In certain embodiments, the anti-Notch2 antagonist antibody is an anti-Notch2 antibody that binds to one or more EGF-like repeats of Notch2.

The above and further aspects and embodiments of the ~~invention~~ disclosure are provided herein.

BRIEF DESCRIPTION OF THE FIGURES

Figures 1A-G show transcriptional profiling of hepatic progenitor cells and Identification of active Notch signaling in hepatic progenitors *in vivo*.

Figures 2A-O show that Notch signaling inhibition promotes hepatocyte differentiation of hepatic progenitors *in vitro*.

Figures 3A-J show that inhibition of Notch2 signaling *in vivo* promotes hepatocyte differentiation and improved liver function in chronic and acute liver damage models.

Figures 4A-E illustrate a liver progenitor cell isolation strategy.

Figures 5A-H show an analysis of oval cell-specific gene expression signature.

Figures 6A-E show a validation of oval cell gene signature and expression pattern of putative hepatic stem cell markers.

Figures 7A-B show a strategy for *in vitro* differentiation.

Figures 8A-F show the efficacy of anti-Notch2 antibody treatment *in vivo* and its effect on liver growth and proliferation following partial hepatectomy.

WHAT IS CLAIMED IS:

1. ~~A method of~~ Use of a Notch2-specific antagonist in the manufacture of a medicament for treating a liver condition characterized by liver damage~~, the method comprising administering to~~ in a patient having such condition ~~an effective amount of a Notch2-specific antagonist~~.

2. The ~~method~~ use of claim 1, wherein the liver condition is chronic liver disease.

3. The ~~method~~ use of claim 2, wherein the chronic liver disease is liver fibrosis.

4. The ~~method~~ use of claim 2 wherein the chronic liver disease is liver cirrhosis.

5. The ~~method~~ use of claim 1, wherein the liver condition is an acute liver condition.

6. The ~~method~~ use of claim 5, wherein the acute liver condition is acetaminophen toxicity.

7. The ~~method~~ use of claim 1, wherein the Notch2-specific antagonist is an anti-Notch2 antagonist antibody.

8. The ~~method~~ use of claim 7, wherein the anti-Notch2 antagonist antibody is an anti-Notch2 NRR antibody.

9. The ~~method~~ use of claim 8, wherein the anti-Notch2 NRR antibody binds to the LNR-A and HD-C domains of Notch2 NRR.

10. The ~~method~~ use of claim 8, wherein the anti-Notch2 NRR antibody is Antibody D, Antibody D-1, Antibody D-2, or Antibody D-3.

11. The ~~method~~ use of claim 8, wherein the anti-Notch2 NRR antibody comprises the heavy and light chain variable region CDRs of Antibody D, Antibody D-1, Antibody D-2, or Antibody D-3.

12. The ~~method~~ use of claim 7, wherein the anti-Notch2 antagonist antibody is an anti-Notch2 antibody that binds to one or more EGF-like repeats of Notch2.

13. The ~~method~~ use of claim 1, wherein the Notch2-specific antagonist is to be administered by intramuscular, intraperitoneal, intracerobrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation route.

14. A method of inducing hepatic differentiation, the method comprising the step of contacting an oval cell *in vitro* with an effective amount of a Notch2-specific antagonist, thereby inducing hepatic differentiation of the oval cell.

~~15. The method of claim 14, wherein the oval cell is contacted with the Notch2-specific antagonist *in vitro*.~~

~~16. The method of claim 14, wherein the oval cell is contacted with the Notch2-specific antagonist *in vivo*.~~

~~17. A method of reducing aberrant bile duct proliferation in a patient in need thereof, the method comprising the step of administering to the patient an effective amount of a Notch2-specific antagonist, thereby reducing aberrant bile duct proliferation.~~

15. Use of a Notch2-specific antagonist in the manufacture of a medicament for inducing hepatic differentiation, wherein the medicament is to be contacted with an oval cell *in vivo* to thereby induce hepatic differentiation of the oval cell.

16. Use of a Notch2-specific antagonist in the manufacture of a medicament for reducing aberrant bile duct proliferation in a patient in need thereof.