nuclear factor 6 (HNF6), and cytochrome P450 3A4 (CYP3A4), HNF4a, E-cadherin, DAPI, and Epcam. Such expression may occur, for example, at day 40 to day 50. The expression level may be similar to that observed in human liver cells, for example, that of an adult liver cell.

[0052] In one aspect, the liver organoid may be characterized in that the liver organoid has bile transport activity.

[0053] In one aspect, the liver organoid may be derived from a stem cell and may comprise a luminal structure further containing internalized microvilli and mesenchymal cells. The luminal structure may be surrounded by polarized hepatocytes and a basement membrane. The liver organoid may comprise functional stellate cells and functional Kupffer cells.

[0054] The liver organoid may, in certain aspects, be characterized by having one or more of the following: bile production capacity, bile transport activity, Complement factor H expression of at least 50 ng/mL/1xe^6 cells/24hr, Complement factor B of at least 40 ng/mL/1xe^6 cells/24hr, C3 expression of at least 1000 ng/mL/1xe^6 cells/24hr; C4 expression of at least 1000 ng/mL/1xe^6 cells/24hr, fibrinogen production of at least 1,000 ng/mL/1xe^6 cells/24hr and albumin production of at least 1,000 ng/mL/1xe^6 cells/24hr. In one aspect, the liver organoid may be characterized by having total hepatic protein expression of at least 10,000 ng/mL / 1xe^6 cells/24 hours. The liver organoid may be characterized in that it may express one or more genes selected from PROX1, RBP4, CYP2C9, CYP3A4, ABCC11, CFH, C3, C5, ALB, FBG, MRP2, ALCAM, CD68, CD34, CD31. In one aspect, the liver organoid may comprise cells comprising a drug metabolism cytochrome variant, such as, for example, a CY2C9*2 variant. The liver organoid may comprise a vasculature, such as that described in US 20160177270.

[0055] In one aspect, the liver organoid may be characterized in that the liver organoid does not comprise inflammatory cells, for example T-cells or other inflammatory secreted proteins.

[0056] In one aspect, a method of screening for a serious adverse event (SAE) is disclosed. The SAE may be liver failure and/or drug induced liver injury (DILI). The method may include the step of contacting a drug of interest, of which toxicity is of interest, with a liver organoid as described herein. In one aspect, the method may comprise the step of measuring intake and/or efflux of fluorescein diacetate (FD), wherein impaired efflux indicates that said drug is likely to induce a serious adverse event. The toxicity of a drug of interest may be determined by measurement of a parameter selected from mitochondria membrane potential, measurement of ROS, swelling of liver mitochondria, and combinations thereof, wherein injury to said mitochondria indicates that said drug is likely to induce a serious adverse event. In one aspect, the method comprises the step of assaying organoid viability, wherein impaired or decreased organoid viability indicates that said a drug of interest is likely to induce a serious adverse event.

[0057] In one aspect, a method of treating an individual having liver damage is disclosed, wherein the method may comprise the step implanting a liver organoid as described herein into an individual in need thereof. The liver damage may include, for example, metabolic liver disease, end stage liver disease, or a combination thereof.

[0058] In one aspect, methods for identifying a preferred therapeutic agent for an individual are disclosed. In this aspect, the method may include the step of contacting a liver organoid derived from an iPSC of interest with a candidate compound, such as wherein the iPSC of interest comprises one or more mutations found in said individual, or such as wherein said iPSC of interest is derived from the same ethnic

CLAIMS

What is claimed is:

1. A liver organoid derived from pluripotent stem cells (PSCs), said liver organoid comprising mesenchymal cells and a luminal structure comprising internalized microvilli, wherein said luminal structure is surrounded by polarized hepatocytes.

2. The liver organoid of claim 1 wherein said pluripotent stem cells (PSCs) are human induced pluripotent stem cells (iPSCs) or embryonic stem cells (ESCs).

3. The liver organoid of claim 1 or claim 2 wherein said liver organoid comprises functional stellate cells and functional Kupffer cells.

4. The liver organoid of any one of claims 1-3, wherein said liver organoid is characterized by having one or more of the following: bile production capacity, bile transport activity, Complement factor H expression of at least 50 ng/mL/1xe^6 cells/24hr, Complement factor B of at least 40 ng/mL/1xe^6 cells/24hr, C3 expression of at least 1000 ng/mL/1xe^6 cells/24hr, C4 expression of at least 1000 ng/mL/1xe^6 cells/24hr, fibrinogen production of at least 1,000 ng/mL/1xe^6 cells/24hr and albumin production of at least 1,000 ng/mL/1xe^6 cells/24hr.

5. The liver organoid of any one of claims 1-4, wherein said liver organoid is characterized by having total hepatic protein expression of at least 10,000 ng/mL / 1xe^6 cells/24 hours.

6. The liver organoid of any one of claims 1-5, wherein said liver organoid expresses one or more genes selected from PROX1, RBP4, CYP2C9, CYP3A4, ABCC11, CFH, C3, C5, ALB, FBG, MRP2, ALCAM, CD68, CD34, CD31.

7. The liver organoid of any one of claims 1-6, wherein said liver organoid comprises a drug metabolism cytochrome variant, preferably a CY2C9*2 variant.

8. The liver organoid of any one of claims 1-7, wherein said liver organoid does not comprise inflammatory cells, for example T-cells or other inflammatory secreted proteins.

9. An *in vitro* method of screening for a serious adverse event (SAE), preferably liver failure and/or drug induced liver injury (DILI), comprising the step of contacting a drug of interest with the liver organoid of any one of claims 1-8.

10. The method of claim 9, wherein said method comprises the step of measuring intake and/or efflux of fluorescein diacetate (FD), wherein impaired efflux indicates that said drug is likely to induce a serious adverse event.

11. The method of claim 9 or 10, wherein said drug of interest has a toxicity determined by measurement of a parameter associated with mitochondrial injury and selected from mitochondria membrane potential, measurement of ROS, swelling of liver mitochondria, and combinations thereof, wherein injury to said mitochondria indicates that said drug is likely to induce a serious adverse event.

12. The method of any one of claims 9-11, wherein said method comprises the step of assaying organoid viability, wherein an impaired organoid viability determination indicates that said drug is likely to induce a serious adverse event.

13. Use of the liver organoid of any one of claims 1-8 in the manufacture of a medicament for treating an individual having liver damage.

14. The use of claim 13, wherein said liver damage is selected from metabolic liver disease, end stage liver disease, or both.

15. An *in vitro* method of testing a candidate compound for a first individual, comprising contacting the liver organoid of any one of claims 1-8 with a candidate compound.

16. The method of claim 15, wherein said liver organoid comprises one or more mutations found in said first individual.

17. The method of claim 15 or 16, wherein said liver organoid is derived from cells obtained from a second individual from the same ethnic background as said first individual.

18. The method of any one of claims 15-17, wherein said organoid is derived from cells obtained from said first individual.