

WHAT IS CLAIMED:

1. A method of differentiating cells of the definitive endoderm (DE) lineage into posterior foregut lineage comprising contacting said stem cells with: one or more retinoic acid activators; and/or one or more inhibitors of TGF β signaling, optionally further comprising contacting said stem cells with one or more activators of BMP signaling, optionally further comprising contacting said stem cells with one or more activators of FGF signaling, optionally wherein the cells of the posterior foregut lineage comprise elevated gene expression of posterior foregut lineage markers and decreased expression of dorsal foregut markers relative to undifferentiated cells, optionally wherein the duration of the method is about 1 to 84 hours.
2. A method of differentiating cells of the posterior foregut lineage into liver bud progenitors comprising contacting said cells of the posterior foregut lineage with: one or more activators of TGF β signaling, one or more modulators of Wnt signaling; and/or one or more activators of cyclic AMP/PKA signaling, optionally further comprising contacting said cells of the posterior foregut lineage with one or more activators of BMP signaling, optionally wherein the liver bud progenitors comprise elevated gene expression of liver bud progenitor markers and decreased expression of pancreatic progenitor markers relative to undifferentiated cells, optionally wherein the liver bud progenitors comprise elevated gene expression of markers comprising AFP, TBX3, HNF4A, PROX1, HNF1B, HNF6, CEBPA α or a combination thereof, relative to undifferentiated cells, optionally wherein the one or more modulators of Wnt signaling comprise an inhibitor of Wnt signaling and/or an activator of Wnt signaling, optionally wherein the inhibitor of Wnt signaling is contacted with the cells of the posterior foregut lineage for duration of about 1 to 72 hours, and subsequently the activator of Wnt signaling is contacted with the cells of the posterior foregut lineage for duration of about 24 to 48 hours, optionally wherein the duration of the method is for about 1 to 120 hours, optionally wherein said cells of the posterior foregut lineage are obtained from the method of claim 1.
3. A method of differentiating liver bud progenitors into hepatic progenitors comprising: contacting said liver bud progenitors with one or more inhibitors of Notch signaling, optionally

further comprising contacting the cells with: one or more inhibitors of Notch signaling; one or more activators of ascorbic acid signaling, one or more activators of cyclic AMP/PKA signaling; and/or one or more activators of insulin signaling, optionally

5 wherein the duration of contact is for about 48 hours, optionally

wherein the duration of contact is for at least 1 to 108 hours, optionally further comprising contacting said liver bud progenitors with one or more differentiation factors selected from the group comprising of: activators of ascorbic acid signaling; activators of glucocorticoid signaling; activators of cyclic AMP/PKA signaling; 10 activators of insulin signaling; activators of oncostatin M signaling; an amino acid mixture, and/or activators of L-glutathione signaling, optionally further comprising

contacting the cells with one or more differentiation factors selected from the group comprising of: activators of BMP signaling; inhibitors of PKG signaling; activators of glucocorticoid signaling; phospholipid precursors; activators of oncostatin M 15 signaling; an amino acid mixture, and activators of L-glutathione signaling, optionally wherein the hepatic progenitors comprise elevated gene expression of hepatic markers and decreased expression of biliary markers relative to undifferentiated cells, optionally

wherein the hepatic progenitors comprise elevated gene expression of markers 20 comprises ALBUMIN, c-MET, HNF4A, CEBPA or a combination thereof, relative to undifferentiated cells, optionally wherein the hepatic progenitors comprise decreased gene expression of biliary marker SOX9 relative to undifferentiated cells optionally,

wherein said liver bud progenitors are obtained from the method of claim 2.

- 25 4. A method of differentiating hepatic progenitors into perivenous hepatocyte-like cells comprising contacting said hepatic progenitors with: one or more inhibitors of Notch signaling, one or more activators of glucocorticoid signaling, one or more activators of insulin signaling; one or more activators of ascorbic acid signaling, and/or one or more activators of TGF β signaling, optionally further comprising contacting the 30 hepatic progenitors with one or more activators of retinoic acid signaling, optionally further comprising contacting said hepatic progenitors with one or more activators of progesterone signaling, optionally further comprising contacting said hepatic progenitors with one or more activators of vitamin D signaling, optionally further comprising contacting said hepatic progenitors with one or more activators of PKG

signaling, optionally wherein the perivenous hepatocyte-like cells comprise elevated gene expression of perivenous hepatocytes markers and decreased expression of hepatocyte-like cell markers relative to undifferentiated cells, optionally wherein the perivenous hepatocyte markers comprise GS, CYP3A4, AAT, AXIN2 or a combination thereof, optionally wherein the duration of the method is about 1 to 168 hours, optionally

wherein said hepatic progenitors are obtained from the method of claim 3.

5. A method of differentiating hepatic progenitors into hepatocyte-like cells comprising contacting said hepatic progenitors with: one or more activators of cyclic AMP/PKA signaling, one or more activators of glucocorticoid signaling; one or more activators of insulin signaling; one or more activators of ascorbic acid signaling, and/or one or more inhibitors of Notch signaling, optionally further comprising contacting said hepatic progenitors with one or more modulators of Wnt signaling, optionally further comprising contacting said hepatic progenitors with one or more inhibitors of PKG signaling, optionally wherein the hepatocyte-like cells comprise elevated gene expression of hepatocyte-like cell markers and decreased expression of perivenous markers relative to undifferentiated cells, optionally wherein the hepatocyte-like cell markers comprise FAH, PAH, HGD, HPD, PAH, TAT, Albumin, AAT, ARG1, CPS1 or a combination thereof, optionally wherein the duration of the method is for about 1 to 168 hours, optionally wherein said hepatic progenitors are obtained from the method of claim 3.
6. A method of maintaining liver bud progenitors in a self-renewal state comprising contacting said liver bud progenitors with: one or more activators of FGF signaling; and/or one or more activators of Wnt signaling, optionally further comprising contacting said liver bud progenitors with one or more activators of BMP signaling optionally,
further comprising contacting said liver bud progenitors with one or more epidermal growth factors, optionally further comprising contacting said liver bud progenitors with one or more modulators of Notch signaling, optionally wherein said liver bud progenitors are obtained from the method of claim 2.
7. The method of claim 6, wherein the liver bud progenitors are further differentiated into hepatic progenitors according to the method of claim 3.
8. A method of maintaining hepatocytes or hepatocyte-like cells in a perivenous state comprising contacting said cells with one or more inhibitors of Notch signaling and/or one or more activators of Wnt signaling, optionally further comprising

contacting said hepatocytes or hepatocyte-like cells with: one or more inhibitors of TGFb; and/or one or more activators of estrogen signaling; one or more inhibitors of cyclic AMP/PKA signaling, optionally wherein said cells are obtained from the method of claim 4, optionally wherein said hepatocytes or hepatocyte-like cells are obtained from a human liver.

9. A method of maintaining hepatocytes in a periportal state comprising contacting said cells with one or more activators of cyclic AMP/PKA signaling, optionally wherein said hepatocytes are obtained from a human liver.

10. A kit for differentiating

a) cells of the definitive endoderm (DE) lineage into posterior foregut lineage comprising one or more of the following factors: one or more retinoic acid activators; and/or one or more inhibitors of TGFβ signaling; or

b) cells of the posterior foregut lineage into liver bud progenitors comprising one or more of the following factors: one or more activators of TGFβ signaling; one or more modulators of Wnt signaling; and/or one or more activators of cyclic AMP/PKA signaling; or

c) liver bud progenitors into hepatic progenitors comprising one or more of the following factors one or more inhibitors of Notch signaling; or

d) liver bud progenitors into hepatic progenitors comprising one or more of the following factors: one or more inhibitors of Notch signaling; activators of ascorbic acid signaling; one or more activators of cyclic AMP/PKA signaling; and/or one or more activators of insulin signaling; or

e) hepatic progenitors into perivenous hepatocyte-like cells comprising one or more of the following factors: one or more inhibitors of Notch signaling; one or more activators of glucocorticoid signaling; one or more activators of insulin signaling; one or more activators of ascorbic acid signaling; and/or one or more activators of TGFβ signaling; or

f) hepatic progenitors into hepatocytes or hepatocyte-like cells comprising one or more of the following factors: one or more activators of cyclic AMP/PKA signaling; one or more activators of glucocorticoid signaling; one or more activators of insulin signaling; one or more activators of ascorbic acid signaling; and/or one or more inhibitors of Notch signaling.

11. A kit for maintaining

a) liver bud progenitors in a self-renewal state comprising one or more of the following factors: one or more activators of FGF signaling; and/or one or more activators of Wnt signaling, optionally

further comprising one or more of the following factors: one or more activators of BMP signaling; one or more epidermal growth factors; one or more inhibitors of TGF β signaling; and/or one or more inhibitors of Notch signaling; or

b) hepatocytes or hepatocyte-like cells in a perivenous state comprising one or more of the following factors: one or more inhibitors of Notch signaling and/or one or more activators of Wnt signaling, optionally further comprising one or more of the following factors: one or more inhibitors of TGF β ; and/or one or more activators of estrogen signaling; one or more inhibitors of cyclic AMP/PKA signaling or

c) hepatocytes or hepatocyte-like cells in a periportal state comprising one or more activators of cyclic AMP/PKA signaling.

12. A surface marker for isolating or selecting for LB cells selected from CD99 or

a surface marker for isolating or selecting for human pluripotent stem cells (PSCs) cells comprising CD10; or

a surface marker for isolating or selecting for endoderm cells comprising CD184.

13. A method of screening for a cellular response, the method comprising: a) contacting a population of cells generated according to any one of Claims 1-12 with a pharmacological agent; and b) evaluating the population of cells for a cellular response induced by the pharmacological agent, optionally wherein the screening is *in vitro* screening and the contacting is performed *in vitro*, optionally wherein the screening is *in vivo* screening and the contacting is performed by administering the pharmacological agent to a host animal that comprises the population of cells.

14. A method of screening for a phenotype, the method comprising: a) administering to a host animal a population of cells generated according to any one of Claims 1-12 wherein the cells of the population of cells comprise a genetic modification in at least one genetic locus; and b) evaluating the host animal for a detectable phenotype induced by the administered population of cells, optionally wherein the genetic modification in at least one genetic locus results in the disruption or deletion of at least one gene, optionally wherein the population of cells comprise liver cells and the detectable phenotype comprises a survival enhancement.

15. Use of a therapeutically effective amount of cells generated according to any one of Claims 1-12 in the manufacture of a medicament for treating a subject for a

condition, wherein the medicament is to be administered to the subject, optionally wherein the medicament is to be co-administered with at least one pro-survival or pro-engraftment factor, optionally wherein the cells comprise a genetic modification in at least one genetic locus.