CLAIMS

What is claimed is:

1. A method of inducing formation of a liver organoid from definitive endoderm (DE), comprising the steps of:

a) contacting definitive endoderm (DE) with an FGF pathway activator and a GSK3 inhibitor, for a period of time sufficient to form posterior foregut spheroids; and

b) incubating said posterior foregut spheroids of step a) in the presence of retinoic acid (RA) for a period of time sufficient to form said liver organoid,

wherein the liver organoid is characterized by albumin secretion and comprises a luminal structure comprising internalized microvilli comprising mesenchymal cells, wherein said luminal structure is surrounded by polarized hepatocytes and basement membrane..

2. The method of claim 1, wherein the DE of step a) are not contacted with a BMP pathway inhibitor.

3. The method of claim 1 or 2, wherein the posterior foregut spheroids of step b) are not contacted with a BMP pathway inhibitor.

4. The method of any one of claims 1-3, wherein the period of time of step a) is from about 1 day to about 3 days.

5. The method of any one of claims 1-4, wherein the period of time of step b) is from about 1 day to about 5 days.

6. The method of any one of claims 1-5, further comprising c) incubating said liver organoid of step b) with hepatocyte culture medium for a period of time sufficient to mature said liver organoid.

7. The method of claim 6, wherein the period of time of step c) is from about 20 days to about 30 days.

8. The method of claim 6 or 7, wherein the hepatocyte culture medium comprises at least one of hepatocyte growth factor, dexamethasone, or Oncostatin M.

9. The method of any one of claims 1-8, wherein the DE is derived from stem cells.

10. The method of claim 9, wherein said stem cells are human iPSCs.

11. The method of any one of claims 1-10, wherein said foregut spheroids are embedded in a basement membrane matrix.

12. The method of claim 11, wherein the basement membrane matrix is Matrigel.

13. The method of any one of the preceding claims, wherein the liver organoid expresses alpha-fetoprotein (AFP), albumin (ALB), retinol binding protein (RBP4), cytokeratin 19 (CK19), hepatocyte nuclear factor 6 (HNF6), and cytochrome P450 3A4 (CYP3A4).

14. The method of any one of the preceding claims, wherein liver organoid has bile transport activity.