CLAIMS

1. An adult liver progenitor cell characterized in that said cell is measured positive for:
   (a) at least one hepatic marker selected from albumin, HNF-3B, HNF-4, CYP1A2, CYP2C9, CYP2E1 and CYP3A4;
   (b) at least one mesenchymal marker selected from Vimentin, CD90, CD73, CD44, and CD29;
   (c) at least one liver-specific activity selected from urea secretion, bilirubin conjugation, alpha-1-antitrypsin secretion, and CYP3A4 activity;
   (d) Sushi domain containing protein 2 (SUSD2); and
   (e) Cytokeratin-19 (CK-19).

2. The cell of Claim 1 characterized in that the cell is measured negative for one or more of CD140b, CD45, CD117, CD31, CD133, and CD326.

3. The cell of Claim 1 or 2 wherein said cell is further measured positive for Cytokeratin-18 (CK-18) and/or alpha smooth muscle actin (ASMA).

4. The cell of any one of the preceding Claims wherein said cell is further measured positive for at least one liver-specific activity selected from sulfotransferase activity, tryptophan-2,3-dioxygenase activity, liver carboxylase activity, ammonia metabolism, and glycogen storage.

5. The cell of any one of the preceding Claims wherein said cell is further measured positive for at least one coagulation-related secreted protein selected from fibrinogen alpha, fibrinogen beta, fibrinogen gamma, Factor V, Factor VII, Factor VIII, Factor IX, and Factor XIII.

6. The cell of any one of the preceding claims wherein said cell is measured:

(a) positive for albumin, Vimentin, CD90, CD73, urea secretion, bilirubin conjugation, alpha-1-antitrypsin secretion, CYP3A4 activity, Sushi domain containing protein 2, Cytokeratin-19, and liver carboxylase activity; and

(b) negative for CD140b.

7. The cell of any one of the preceding Claims wherein said cell is adherent and presents cuboidal meso-epithelial morphology.

8. The cell of any one of the preceding Claims wherein said cell is capable of forming three-dimensional cell clusters in suspension and/or differentiating into cells presenting liver-specific activities.

9. The isolated cell population comprising at least 60% or between 60% and 99% or between 70% or 90% of cells of any one of the preceding Claims.

10. The cell population of Claim 9 wherein the population comprises adherent cells or form three-dimensional cell clusters in suspension.

11. The cell population of Claim 10 wherein the population presents inducible Phase I CYP-dependent activity and uptake of at least one of Taurocholate, Estrone-3-sulfate, and 1-methyl-4-phenylpyridinium.

12. The cell population of any one of Claims 9 to 11 wherein said cell population is differentiated into cells presenting liver-specific activities.

13. The cell or population of any one of the preceding Claims wherein said cell or population is modified by means of one or more chemical agents, cell culture medium, growth factors, and/or nucleic acid vectors.

14. A method for obtaining adult liver progenitor cells comprising:

(a) disassociating adult liver or a part thereof to form a population of primary liver cells;

(b) generating a preparation of the population of primary liver cells of (a);

(c) culturing cells comprised in the preparation of (b) onto a support that allows adherence and growth of cells thereto and the emergence of a population of cells having cuboidal meso-epithelial morphology;

(d) passaging the cells of (c) at least once; and

(e) isolating a population of cells obtained after the passaging of step (d) that maintain a cuboidal meso-epithelial morphology, that are positive for at least one hepatic marker and at least one mesenchymal marker, and that have at least one liver-specific activity.

15. The method of Claim 14 wherein the primary liver cells of step (a) are of human origin.

16. The method of Claim 14 or 15 wherein the preparations of the primary liver cells of step (b) are cryopreserved.

17. The method of any one of the Claims 14 to 16 wherein the cells of step (c) and/or the cell population of step (e) are measured positive for at least one marker selected from cytokeratin 19, albumin, alpha-1-antitrypsin secretion, Sushi domain containing protein 2, and CYP3A4.

18. The method of any one of the Claims 14 to 17 wherein the cells of step (c) and/or the cell population of step (e) are measured positive for:

(i) at least one mesenchymal marker selected from Vimentin, CD90, CD73, CD44, and CD29;

(ii) at least one hepatic marker selected from HNF-3B, HNF-4, albumin, CYP1A2, CYP2C9, CYP2E1 and CYP3A4;

(iii) at least one liver-specific metabolic activity chosen from urea secretion, bilirubin conjugation, alpha-1-antitrypsin secretion, and CYP3A4 activity;

(iv) Sushi domain containing protein 2; and

(v) Cytokeratin-19 (CK-19).

19. The method of Claim 18 wherein the cells of step (c) and/or the cell population of step (e) are measured positive for Cytokeratin-18 (CK-18) and/or alpha smooth muscle actin (ASMA) and are measured negative for CD140b.

20. The method of any one of Claims 14 to 19 wherein the cell population of step (e) is maintained in cell culture conditions that allow formation of three-dimensional cell clusters in suspension.

21. The method of Claim 20 wherein the cell population is produced and maintained in a low adherence container or in a bioreactor.

22. The method of any one of Claims 14 to 21 wherein said method further comprise a step (f) in which the cell population of step (e) is maintained in a cell culture condition to differentiate them into cells presenting liver-specific activities.

23. A cell population obtainable by a method of any one of the Claims from 14 to 22 and comprising at least 60% or between 60% and 99% or between 70% and 90% of cells that present the features of Claim 18 or 19.

24. The cell population of Claim 23 wherein said cells are adherent cells or form three-dimensional cell clusters in suspension.

25. A cell population of claim 24 wherein said cells present inducible Phase I CYP-dependent activity and uptake of Taurocholate, Estrone-3-sulfate, or 1-methyl-4-phenylpyridinium.

26. The cell population of any one of the Claims from 23 to 25 wherein said cells present liver-specific activities.

27. A cell population of Claim 23 or 24 wherein said cell population is modified by means of one or more chemical agents, cell culture medium, one or more growth factors, and/or one or more nucleic acid vectors.

28. A biological material isolated from the cell or population of any one of the Claims from 1 to 13 or Claims 23 to 27, wherein the biological material is a conditioned cell culture media, a protein extract, a membrane vesicle, or any fraction thereof comprising one or more isolated proteins, nucleic acids, metabolites, and/or antigens.

29 A composition comprising the cell or population according to any one of the Claims 1 to 13 or Claims 23 to 27, or comprising the biological material of claim 28.

30. The cell or population of any one of Claims 1 to 13 or Claims 23 to 27, a biological material of Claim 28, or the composition of Claim 29 for use in treating a liver disease.

31. The use of Claim 30 wherein the liver disease is an inborn error of liver metabolism, an inherited Blood Coagulation Disorder, progressive familial intrahepatic cholestasis type 1 / 2 / 3, alpha 1-Antitrypsin Deficiency, defect of liver cell transporters, Porphyria, fatty liver or other fibrotic liver disease, primary biliary cirrhosis, sclerosing cholangitis, liver degenerative disease, or acute or chronic liver failure.

32. A method for evaluating the efficacy, the metabolism, the stability, and/or the toxicity of one or more exogenous components, said method comprising:

(a) providing the cell or population of any one of Claims 1 to 13 or Claims 23 to 27, the composition of Claim 29, or the biological material of Claim 28;

(b) exposing said cell, said cell population, said composition, or said biological material to one or more exogenous components selected from chemical compounds, proteins, nucleic acids, lipids, sugars, metals, salts, viruses, bacteria, and cells; and

(c) detecting the effects of said one or more exogenous components on said cell population, said composition, or said biological compound and/or detecting the presence, localization, or modification of said one or more exogenous components following the exposure to said cell population, said composition, or said biological material.

33. The method of Claim 32 wherein step (c) of said method comprises detecting the effects on cell morphology, on cell viability, on up- or down-regulation of liver-specific or unspecific proteins, and/or on the degradation, aggregation, activation, or inhibition of proteins within said cell, said cell population, said composition, or said biological material.

34. The method of Claim 32 or 33 wherein step (c) of said method comprises detecting the internalization of said one or more exogenous components into, or the physical association with, said cell, said cell population, said composition, or said biological material.

35. The method of any one of Claims 32 to 34 wherein said cell, said cell population, said composition, or said biological material is provided to an animal in step (a), one or more exogenous components is administered to an animal in step (b), and wherein step (c) comprises detecting the effects of said one or more exogenous components on said cell, said cell population, said composition, said biological material, or on said animal, and/or detecting the presence, localization, or modification of said one or more exogenous components following the exposure to said cell, said cell population, said composition, or said biological material in the animal.

36. The method of any one of Claims 32 to 35 wherein said cell, said cell population, said composition, or said biological material is exposed in step (b), simultaneously or sequentially in any order, to

(i) one or more exogenous components that have an effect on cell morphology, cell viability, up- or down-regulation of liver-specific or unspecific proteins, and/or that degrade, aggregate, activate, or inhibit proteins within said cell, said cell population, said composition, or said biological material; and

(ii) one or more exogenous components intended to block or avoid the effects of the one or more exogenous components of (i) within said cell, said cell population, said composition, or said biological material.

37. The method of Claim 38 wherein the one or more exogenous components of (i) comprises a infectious, tumorigenic, cytotoxic, or genotoxic agent, and the further exogenous components of (ii) comprises a protein, a nucleic acid, a cell, a virus, or a chemical compound.

38. Use of a cell population of any one of Claims 1 to 13 or Claims 23 to 27, a composition of Claim 29, or a biological material of Claim 28 for evaluating the efficacy, the metabolism, the stability, and/or the toxicity of one or more exogenous components selected from chemical compounds, proteins, nucleic acids, lipids, sugars, metals, salts, viruses, bacteria, and cells.

39. A kit comprising a cell, cell population of any one of Claims 1 to 13 or Claims 23 to 27, a composition of Claim 29, or a biological material of Claim 28.

40. The kit of claim 39 wherein said kit further comprises one or more vials containing said cell population, said composition, or said biological material and one or more of the following elements: devices, disposable materials, solutions, chemical products, biological products, and/or instructions for using elements of said kit.

CLAIMS

1. An adult liver progenitor cell characterized in that said cell is measured positive for:
   (a) at least one hepatic marker selected from albumin, HNF-3B, HNF-4, CYP1 A2, CYP2C9, CYP2E1 and CYP3A4;
   (b) at least one mesenchymal marker selected from Vimentin, CD90, CD73, CD44, and CD29;
   (c) at least one liver-specific activity selected from urea secretion, bilirubin conjugation, alpha-1 -antitrypsin secretion, and CYP3A4 activity;
   (d) Sushi domain containing protein 2 (SUSD2); and
   (e) Cytokeratin-19 (CK-19).

   characterized in that the cell is measured negative for one or more of CD140b, CD45, CD117, CD31, CD133, and CD326, wherein said cell is further measured positive for Cytokeratin-18 (CK-18) and/or alpha smooth muscle actin (ASMA), and wherein said cell is further measured positive for at least one liver-specific activity selected from sulfotransferase activity, tryptophan-2,3-dioxygenase activity, liver carboxylase activity, ammonia metabolism, and glycogen storage.

2. The cell of Claim 1 wherein said cell is measured:
   (a) positive for albumin, Vimentin, CD90, CD73, urea secretion, bilirubin conjugation, alpha-1 -antitrypsin secretion, CYP3A4 activity, Sushi domain containing protein 2, Cytokeratin-19, and liver carboxylase activity; and
   (b) negative for CD140b.

3. The cell of Claim 1 or 2 wherein said cell is capable of forming three-dimensional cell clusters in suspension and/or differentiating into cells presenting liver- specific activities.

4. The isolated cell population comprising at least 60% or between 60% and 99% or between 70% or 90% of cells of any one of the preceding Claims.

5. The cell population of Claim 4 wherein the population comprises adherent cells or form three-dimensional cell clusters in suspension and presents inducible Phase I CYP- dependent activity and uptake of at least one of Taurocholate, Estrone-3-sulfate, and 1-methyl-4-phenylpyridinium.

6. The cell or cell population of any one of the preceding Claims wherein said cell or population is modified by means of one or more chemical agents, cell culture medium, growth factors, and/or nucleic acid vectors.

7. A method for obtaining adult liver progenitor cells of human origin comprising:
   (a) disassociating adult liver or a part thereof to form a population of primary liver cells;
   (b) generating a preparation of the population of primary liver cells of (a);
   (c) culturing cells comprised in the preparation of (b) onto a support that allows adherence and growth of cells thereto and the emergence of a population of cells having cuboidal meso-epithelial morphology;
   (d) passaging the cells of (c) at least once; and
   (e) isolating a population of cells obtained after the passaging of step (d) that maintain a cuboidal meso-epithelial morphology, that are positive for at least one hepatic marker and at least one mesenchymal marker, and that have at least one liver-specific activity;

   wherein the cells of step (c) and/or the cell population of step (e) are measured positive for cytokeratin 19, albumin, alpha-1-antitrypsin secretion, Sushi domain containing protein 2, and CYP3A4.

8. The method of Claim 7 wherein the cells of step (c) and/or the cell population of step (e) are further measured positive for Cytokeratin-18 (CK-18) and/or alpha smooth muscle actin (ASMA) and are measured negative for CD140b.

9. The method of Claim 7 to 8 wherein the cell population of step (e) is maintained in cell culture conditions that allow formation of three-dimensional cell clusters in suspension.

10. A composition comprising the cell or cell population according to any one of the Claims 1 to 6.

11. The cell or cell population of any one of Claims 1 to 6, or the composition of Claim 10, for use in treating a liver disease.

12. The cell or cell population of any one of Claims 1 to 6, or the composition of Claim 10 for use in treating a liver disease, wherein the liver disease is an inborn error of liver metabolism, an inherited Blood Coagulation Disorder, progressive familial intrahepatic cholestasis type 1 / 2 / 3, alpha 1 -Antitrypsin Deficiency, defect of liver cell transporters, Porphyria, fatty liver or other fibrotic liver disease, primary biliary cirrhosis, sclerosing cholangitis, liver degenerative disease, or acute or chronic liver failure.

13. A method for evaluating the efficacy, the metabolism, the stability, and/or the toxicity of one or more exogenous components, said method comprising:
    (a) providing the cell or cell population of any one of Claims 1 to 6, or the composition of Claim 10;
    (b) exposing said cell, said cell population, said composition, or said biological material to one or more exogenous components selected from chemical compounds, proteins, nucleic acids, lipids, sugars, metals, salts, viruses, bacteria, and cells; and
    (c) detecting the effects of said one or more exogenous components on said cell population, said composition, or said biological compound and/or detecting the presence, localization, or modification of said one or more exogenous components following the exposure to said cell population, said composition, or said biological material.

14. Use of a cell or a cell population of any one of Claims 1 to 6, or a composition of Claim 10, for evaluating the efficacy, the metabolism, the stability, and/or the toxicity of one or more exogenous components selected from chemical compounds, proteins, nucleic acids, lipids, sugars, metals, salts, viruses, bacteria, and cells.

15. A kit comprising a cell or a cell population of any one of Claims 1 to 6 or a composition of Claim 10, wherein said kit further comprises one or more vials containing said cell population, or said composition, and one or more of the following elements: devices, disposable materials, solutions, chemical products, biological products, and/or instructions for use in the prevention or treatment of a liver disease.

16. A kit comprising a cell or a cell population of any one of Claims 1 to 6 or a composition of Claim 10, wherein said kit further comprises one or more vials containing said cell population, or said composition, and one or more of the following elements: devices, disposable materials, solutions, chemical products, biological products, and/or instructions for use in the in-vitro evaluation of the efficacy, the metabolism, the stability, and/or the toxicity of one or more exogenous components selected from chemical compounds, proteins, nucleic acids, lipids, sugars, metals, salts, viruses, bacteria, and cells.

17. The use of a kit comprising a cell or a cell population of any one of Claims 1 to 6 or a composition of Claim 10, wherein said kit further comprises one or more vials containing said cell population, or said composition, and one or more of the following elements: devices, disposable materials, solutions, chemical products, biological products, and/or instructions, in the manufacture of a medicament for the treatment of liver disease.

18. The use of Claim 17, wherein the liver disease is an inborn error of liver metabolism, an inherited Blood Coagulation Disorder, progressive familial intrahepatic cholestasis type 1 / 2 / 3, alpha 1 -Antitrypsin Deficiency, defect of liver cell transporters, Porphyria, fatty liver or other fibrotic liver disease, primary biliary cirrhosis, sclerosing cholangitis, liver degenerative disease, or acute or chronic liver failure.