

Claims

1. Use of a mixture in the manufacture of a medicament for engrafting cells onto and/or into an organ in a diseased or dysfunctional condition in a subject, the mixture comprising:
 - a plurality of cells and one or more biomaterials, wherein the plurality of cells are not totipotent cells and are not liver cells,
 - in which the plurality of cells comprise one or more combinations of one or more epithelial cells and one or more mesenchymal cell partners thereof,
 - and wherein the mixture in the form of the medicament is to be introduced onto and/or into the subject, and in which at least a portion of the plurality of cells introduced take up residence on or in at least a portion of the organ *in vivo*.
2. The use according to claim 1, in which the one or more biomaterials is selected from one or more synthetic polymers, biodegradable polymers, and biocompatible polymers.
3. The use according to claim 1 or claim 2, in which the one or more biomaterials is selected from one or more of collagens, laminins, fibronectins, nidogen, elastins, proteoglycans, hyaluronans, glycosaminoglycan chains, chitosan, and alginate.
4. The use according to any one of claims 1 to 3, in which the one or more epithelial cells are selected from one or more of pancreatic stem cells, biliary stem cells, committed pancreatic progenitor cells, committed biliary progenitors, and islet cells.
5. The use according to any one of claims 1 to 4, in which the one or more mesenchymal cell partners thereof are selected from one or more of angioblasts, stellate cell precursors, stellate cells, stromal cells, myofibroblasts, endothelial cell precursors, and endothelial cells.
6. The use according to claim 1, in which the mixture further comprises a basal medium, a nutrient medium, lipids, signaling molecules, extracellular matrix components, or combinations thereof.
7. The use according to claim 6, in which the signaling molecules are selected from one or more of cytokines, fibroblast growth factors (FGFs), hepatocyte growth factors (HGFs), stromal cell-derived growth factors (SGFs), epidermal growth factors (EGFs), vascular

endothelial cell growth factors (VEGFs), insulin like growth factor I (IGF I), insulin-like growth factor II (IGF-II), oncostatin-M, leukemia inhibitory factors (LIF), interleukins, transforming growth factor- β (TGF- β), transferrin, insulin, tri-iodothyronine (T3), thyroxine (T4), glucagon, glucocorticoids, growth hormone (GH), estrogens, androgens, and combinations thereof.

8. The use according to any one of claims 1 to 7, in which the plurality of cells are cultured in serum-free medium.

9. The use according to claim 8, in which the serum-free medium comprises insulin, transferrin, lipids, calcium, zinc and selenium.

10. The use according to claim 8 or claim 9, in which the serum-free medium comprises Kubota's medium.

11. The use according to any one of claims 1 to 10, in which at least a portion of the cells is obtained previously from a donor.

12. The use according to claim 11, in which the donor is a non-autologous donor.

13. The use according to claim 11, in which the donor is an autologous donor.

14. The use according to claim 11, in which the donor is a fetus, a neonate, a child, or an adult.

15. The use according to any one of claims 1 to 14, in which the medicament is for introduction via injection, biodegradable covering, or sponge.

16. The use according to claim 15, in which the biodegradable covering forms a patch.

17. Use of a mixture in the manufacture of a medicament for localizing a plurality of cells onto a surface, into an interior portion, or both of a diseased or dysfunctional organ, the mixture comprising:

a plurality of cells and one or more biomaterials, wherein the plurality of cells are not

totipotent cells and are not liver cells;

in which the plurality of cells comprise one or more combinations of one or more epithelial cells and one or more mesenchymal cell partners thereof;

and wherein the one or more biomaterials is capable of forming a hydrogel comprising the plurality of cells on a surface, in an interior portion, or both of the diseased or dysfunctional organ.

18. The use according to claim 17, in which the plurality of cells are not tumor cells, cancer cells, or diseased cells.

19. The use according to claim 17 or claim 18, in which the one or more biomaterials are selected from glycosaminoglycan chains, hyaluronans, proteoglycans, gelatins, collagens, laminins, fibronectins, nidogen, elastins, plant-derived matrix components and combinations thereof.

20. The use according to any one of claims 17 to 19, in which the mixture further comprises a trigger for solidification of the biomaterials.

21. The use according to claim 20, in which the trigger for solidification of the hydro-gel forming biomaterials comprises polyethylene glycol diacrylate or a disulfide-bridgeinducing derivative thereof.

22. The use according to any one of claims 17 to 21, in which the one or more epithelial cells are selected from one or more of pancreatic stem cells, biliary stem cells, committed pancreatic progenitor cells, committed biliary progenitors, and islet cells.

23. The use according to any one of claims 17 to 22, in which the one or more mesenchymal cell partners thereof are selected from one or more of angioblasts, stellate cell precursors, stellate cells, stromal cells, myofibroblasts, endothelial precursors, and endothelial cells.

24. The use according to any one of claims 17 to 23, in which the hydrogel possesses a shear modulus ranging from about 0.1 to about 100 kPa.

25. The use according to any one claims 17 to 24, in which the hydrogel possesses a shear

modulus ranging from about 25 to 520 Pa.

26. The use according to any one of claims 17 to 25, in which the mixture is introduced into a pocket formed on a surface of the organ.

27. The use according to claim 26, in which the pocket is prepared from omentum, spider silk, insect silk, or a combination thereof.

28. The use according to any one of claims 17 to 27, in which the hydrogel forms *in situ*.

29. The use according to any one of claims 17 to 28, in which the hydrogel is allowed to form before the mixture is introduced onto a surface, into an interior portion, or both of the diseased or dysfunctional organ.

30. Use of a mixture in the manufacture of a medicament for engrafting a plurality of cells onto and/or into an organ in a diseased or dysfunctional condition in a subject, the mixture comprising:

a plurality of cells and one or more biomaterials, wherein the plurality of cells are not totipotent cells and are not liver cells;

in which the plurality of cells comprise one or more epithelial stem cells or epithelial progenitor cells;

and wherein the mixture in the form of the medicament is to be introduced onto and/or into the subject, and in which at least a portion of the plurality of cells introduced take up residence on or in at least a portion of the organ *in vivo*.

31. Use of a mixture in the manufacture of a medicament for engrafting a plurality of cells onto and/or into an organ in a diseased or dysfunctional condition in a subject, the mixture comprising:

a plurality of cells and one or more biomaterials, wherein the plurality of cells are not totipotent cells and are not liver cells;

in which the plurality of cells comprise one or more mesenchymal stem cells or mesenchymal progenitor cells,

and wherein the mixture in the form of the medicament is to be introduced onto and/or into the subject, and in which at least a portion of the plurality of cells introduced take

up residence on or in at least a portion of the organ *in vivo*.

32. Use of a mixture in the manufacture of a medicament for localizing a plurality of cells onto a surface, into an interior portion, or both of a diseased or dysfunctional organ, the mixture comprising:

a plurality of cells and one or more biomaterials, wherein the plurality of cells are not totipotent cells and are not liver cells;

in which the plurality of cells comprise one or more epithelial stem cells or epithelial progenitor cells;

and wherein the one or more biomaterials is capable of forming a hydrogel comprising the plurality of cells on a surface, in an interior portion, or both of the diseased or dysfunctional organ.

33. The use according to claim 32, in which the mixture further comprises a trigger for solidification of the biomaterials.

34. Use of a mixture in the manufacture of a medicament for localizing a plurality of cells onto a surface, into an interior portion, or both of a diseased or dysfunctional organ, the mixture comprising:

a plurality of cells and one or more biomaterials, wherein the plurality of cells are not totipotent cells and are not liver cells;

in which the plurality of cells comprise one or more mesenchymal stem cells or mesenchymal progenitor cells;

and wherein the one or more biomaterials is capable of forming a hydrogel comprising the plurality of cells on a surface, in an interior portion, or both of the diseased or dysfunctional organ.

35. The use according to claim 34, in which the mixture further comprises a trigger for solidification of the biomaterials.

36. A mixture comprising liver cells and one or more biomaterials for use in engraftment within a subject wherein the mixture is to be introduced onto or into the diseased or dysfunctional liver of the subject and in which, the mixture comprises one or more combinations of one or more liver epithelial cells and one or more mesenchymal cell partners

thereof, and wherein at least a portion of the mixture to be introduced is intended to take up residence on or in at least a portion of the liver *in vivo*.

37. Use of a mixture comprising liver cells and one or more biomaterials in the manufacture of a medicament for the treatment by engraftment within a subject having a diseased or dysfunctional liver wherein the medicament is to be introduced onto or into the diseased or dysfunctional liver of the subject and in which, the medicament comprises one or more combinations of one or more liver epithelial cells and one or more mesenchymal cell partners thereof, and wherein at least a portion of the medicament to be introduced, is intended to take up residence on or in at least a portion of the liver *in vivo*.

38. The use of claim 37, in which the one or more biomaterials is selected from one or more synthetic polymers, biodegradable polymers, and biocompatible polymers.

39. The use of claim 37, in which the one or more biomaterials is selected from one or more of collagens, laminins, fibronectins, nidogen, elastins, proteoglycans, hyaluronans, glycosaminoglycan chains, chitosan, alginate.

40. The use of claim 37, in which the one or more liver epithelial cells are selected from one or more of hepatic stem cells, hepatoblasts, committed unipotent hepatic progenitor cells, committed unipotent biliary progenitors, hepatocytes, and cholangiocytes.

41. The use of claim 37, in which the one or more mesenchymal cell partners thereof are selected from one or more of angioblasts, hepatic stellate cell precursors, stellate cells, stromal cells, myofibroblasts, endothelial cell precursors, and endothelial cells.

42. The use of claim 37, in which the mixture further comprises a basal medium, a nutrient medium, lipids, signaling molecules, extracellular matrix components, or combinations thereof.

43. The use of claim 42, in which the signaling molecules are selected from one or more of cytokines, fibroblast growth factors (FGFs), hepatocyte growth factors (HGFs), stromal cell-derived growth factors (SGFs), epidermal growth factors (EGFs), vascular endothelial cell growth factors (VEGFs), insulin like growth factor I (IGF I), insulin-like growth factor II

(IGF-II), oncostatin-M, leukemia inhibitory factors (LIF), interleukins, transforming growth factor- β (TGF- β), transferrin/Fe, insulin, tri-iodothyronine (T3), thyroxine (T4), glucagon, glucocorticoids, growth hormone (GH), estrogens, androgens, and combinations thereof.

44. The use of claim 37, in which the liver cells are cultured in serum-free medium.

45. The use of claim 44, in which the serum-free medium comprises insulin, transferrin/Fe, lipids, calcium, zinc and selenium.

46. The use of claim 44, in which the serum-free medium comprises Kubota's medium.

47. The use of claim 37, in which at least a portion of the liver cells is to be obtained from a donor.

48. The use of claim 47, in which the donor is a non-autologous donor.

49. The use of claim 47, in which the donor is an autologous donor.

50. The use of claim 47, in which the donor is a fetus, a neonate, a child, or an adult.

51. The use of claim 37, in which the medicament is to be introduced via injection, biodegradable covering, or sponge.

52. The use of claim 51, in which the biodegradable covering forms a patch.

53. A mixture of liver cells and one or more biomaterials for use in localizing liver cells onto a surface, into an interior portion, or both of a diseased or dysfunctional liver, wherein the liver cells in the mixture comprise one or more combinations of one or more liver epithelial cells and one or more mesenchymal cell partners thereof, and wherein the one or more biomaterials in the mixture is intended to form a hydrogel comprising the liver cells on the surface, in the interior portion, or both of the diseased or dysfunctional liver.

54. Use of a mixture of liver cells and one or more biomaterials in the manufacture of a medicament for localizing liver cells onto a surface, into an interior portion, or both of a

diseased or dysfunctional liver, wherein the liver cells in the mixture comprise one or more combinations of one or more liver epithelial cells and one or more mesenchymal cell partners thereof, and wherein the one or more biomaterials in the mixture is intended to form a hydrogel comprising the liver cells on the surface, in the interior portion, or both of the diseased or dysfunctional liver.

55. The use of claim 54, in which the liver cells are not tumor cells, cancer cells, or diseased cells.

56. The use of claim 54, in which the one or more biomaterials are selected from glycosaminoglycan chains, hyaluronans, proteoglycans, gelatins, collagens, laminins, fibronectins, nidogen, elastins, plant-derived matrix components and combinations thereof.

57. The use of claim 54, in which the mixture further comprises a trigger for solidification of the one or more biomaterials into the hydrogel.

58. The use of claim 57, in which the trigger for solidification of the one or more biomaterials into the hydrogel comprises polyethylene glycol diacrylate or a disulfide-containing derivative thereof.

59. The use of claim 54, in which the one or more liver epithelial cells are selected from one or more of hepatic stem cells, hepatoblasts, committed unipotent hepatic progenitor cells, committed unipotent biliary progenitors, hepatocytes, and cholangiocytes.

60. The use of claim 54, in which the one or more mesenchymal cell partners thereof are selected from one or more of angioblasts, hepatic stellate cell precursors, stellate cells, stromal cells, myofibroblasts, endothelial precursors, and endothelial cells.

61. The use of claim 54, in which the hydrogel possesses a shear modulus ranging from about 0.1 to about 100 kPa.

62. The use of claim 54, in which the hydrogel possesses a shear modulus ranging from about 25 to 520 Pa.

63. The use of claim 54, in which the medicament is to be introduced into a pocket formed on a surface of the liver.

64. The use of claim 63, in which the pocket is prepared from omentum, spider silk, insect silk, or a combination thereof.

65. The use of claim 54, in which the hydrogel forms *in situ*.

66. The use according to claim 54, in which the hydrogel is allowed to form before the medicament is introduced onto a surface, into an interior portion, or both of the diseased or dysfunctional liver.

67. A mixture comprising liver cells and one or more biomaterials for use in engraftment within a subject, wherein the mixture is to be introduced onto or into the diseased or dysfunctional liver of the subject and

in which the liver cells of the mixture comprise one or more liver epithelial stem cells or liver epithelial progenitor cells,

and wherein at least a portion of the liver cells to be introduced is intended to take up residence on or in at least a portion of the liver *in vivo*.

68. Use of a mixture comprising liver cells and one or more biomaterials in the manufacture of a medicament for engraftment within a subject wherein the medicament is to be introduced onto or into the diseased or dysfunctional liver of the subject and in which, the medicament comprises one or more combinations of one or more liver epithelial cells and one or more mesenchymal cell partners thereof, and wherein at least a portion of the medicament to be introduced is intended to take up residence on or in at least a portion of the liver *in vivo*.

69. A mixture comprising liver cells and one or more biomaterials for use in engraftment within a subject, wherein the mixture is to be introduced onto or into the diseased or dysfunctional liver of the subject and

in which the liver cells comprise one or more mesenchymal stem cells or mesenchymal progenitor cells,

and wherein at least a portion of the liver cells to be introduced is intended to take up residence on or in at least a portion of the liver *in vivo*.

70. Use of a mixture comprising liver cells and one or more biomaterials in the manufacture of a medicament for engraftment within a subject wherein the medicament is to be introduced onto or into the diseased or dysfunctional liver of the subject and in which, the liver cells of the medicament comprise one or more mesenchymal stem cells or mesenchymal progenitor cells, and wherein at least a portion of the liver cells to be introduced is intended to take up residence on or in at least a portion of the liver *in vivo*.

71. A mixture of liver cells and one or more biomaterials for use in localizing liver cells onto a surface, into an interior portion, or both of a diseased or dysfunctional liver, wherein, the liver cells comprise one or more liver epithelial stem cells or liver epithelial progenitor cells;

and wherein the one or more biomaterials are intended to form a hydrogel comprising the liver cells on the surface, the an interior portion, or both of the diseased or dysfunctional liver.

72. Use of a mixture of liver cells and one or more biomaterials in the manufacture of a medicament for localizing liver cells onto a surface, into an interior portion, or both of a diseased or dysfunctional liver, wherein, the liver cells comprise one or more liver epithelial stem cells or liver epithelial progenitor cells and wherein the one or more biomaterials are intended to form a hydrogel comprising the liver cells on the surface, in the interior portion, or both of the diseased or dysfunctional liver.

73. The use of claim 72, in which the mixture further comprises and a trigger for solidification of the one or more biomaterials into the hydrogel.

74. A mixture of liver cells and one or more biomaterials for use in localizing liver cells onto a surface, into an interior portion, or both of a diseased or dysfunctional liver, wherein the liver cells comprise one or more mesenchymal stem cells or mesenchymal progenitor cells and wherein the one or more biomaterials are intended to form a hydrogel comprising the liver cells on the surface, in the interior portion, or both of the diseased or dysfunctional liver.

75. Use of a mixture of liver cells and one or more biomaterials in the manufacture of a medicament for the localization of liver cells onto a surface, into an interior portion, or both of a diseased or dysfunctional liver, wherein the liver cells comprise one or more mesenchymal stem cells or mesenchymal progenitor cells and wherein the one or more biomaterials are intended to form a hydrogel comprising the liver cells on the surface, in the interior portion, or both of the diseased or dysfunctional liver.

76. The use of claim 75, in which the medicament further comprises and a trigger for solidification of the one or more biomaterials into the hydrogel.

77. Use of normal angioblasts, endothelial cells, stellate cell precursors, stellate cells, stromal cells, epithelial stem cells, mature parenchymal cells, suspension cells or combinations thereof taken from an internal organ of a subject in the manufacture of a medicament for the treatment of a diseased or dysfunctional internal organ wherein the medicament is formed by the following steps:

- a. obtaining cells of an internal organ from a donor;
 - b. combining the cells with one or more gel-forming biomaterials to form a mixture;
- and
- c. optionally, combining the mixture with nutrient medium (in which the medium comprises insulin, transferrin, lipids, calcium, zinc and selenium), signaling molecules, extracellular matrix proteins, or a combination thereof;
- wherein the resulting medicament formed from step b or step c is to be introduced into the subject in such a manner that a substantial portion of the cells take up residence in or on at least a portion of the internal organ *in vivo*.

78. Normal internal organ cells comprising angioblasts, endothelial cells, stellate cell precursors, stellate cells, stromal cells, epithelial stem cells, mature parenchymal cells, suspension cells or combinations thereof for use in the treatment of a diseased or dysfunctional internal organ, wherein the cells are first:

- a. obtained from a donor;
- b. combined with one or more gel-forming biomaterials to form a mixture; and
- c. optionally, combining the mixture with nutrient medium, signaling molecules, extracellular matrix proteins, or a combination thereof;

whereby the resulting mixture formed from step b or step c is to be introduced into the subject in such a manner that a substantial portion of the cells take up residence in or on at least a portion of the internal organ *in vivo*.

79. The use according to claim 77, in which the normal cells are stem cells, committed progenitors, or mature cells.

80. The use according to claim 77, in which the internal organ is liver, lung, gut, intestine, heart, kidney, biliary tree, thyroid, thymus, thyroid, brain, or pancreas.

81. The use according to claim 79, in which the internal organ is liver.

82. The use according to claim 79, in which the suspension of cells are liver stem cells, hepatoblasts, committed progenitors of biliary epithelia or hepatocytes, or mature hepatocytes or cholangiocytes.

83. The use according to claim 77, in which the donor is the subject having the internal organ in diseased or dysfunctional condition and the normal cells are obtained from a portion of the internal organ that is not diseased or dysfunctional.

84. The use according to claim 77, in which the donor is a non-autologous donor.

85. The use according to claim 77, in which the donor is a foetus, a neonate, a child, or an adult.

86. The use according to claim 77, in which the one or more biomaterials comprise collagens, laminins, adhesion molecules, proteoglycans, hya-luronans, glycosaminoglycan chains, chitosan, alginate, and synthetic, biodegradable and biocompatible polymers, or combinations thereof.

87. The use according to claim 77, in which the signaling molecules comprise fibroblast growth factor, hepatocyte growth factor, epidermal growth factor, vascular endothelial cell growth factor (VEGF), insulin like growth factor I, insulin-like growth factor II (IGF-II), oncostatin-M, leukemia inhibitory factor (LIF), inter-leukins, transforming growth factor-/?

(TGF- β 3), HGF, transferrin, insulin, transferrin/fe, tri-iodothyronine, T3, glucagon, glucocorticoids, growth hormones, estrogens, androgens, thyroid hormones, and combinations thereof.

88. The use according to claim 87, in which the interleukins are/IL-6, IL-11, IL-13, or combinations thereof.

89. The use according to claim 77, in which the cells are cultured in serum-free medium.

90. The use according to claim 77, in which the suspension of cells of the internal organ are solidified *ex vivo* within the biomaterials prior to introducing the cells into the subject.

91. The use according to claim 77, in which the suspension of cells is to be introduced to or in the proximity of the diseased or dysfunctional tissue.

92. The use according to claim 91, in which the suspension of cells is to be introduced directly into a tissue.

93. The use according to claim 92, in which the tissue is omentum or liver.

94. The use according to claim 77, in which the suspension of cells is to be introduced via injection, biodegradable covering, or sponge.

95. The use according to claim 77, in which the one or more biomaterials comprise collagens, laminins, adhesion molecules, proteoglycans, hyaluronans, glycosaminoglycan chains, chitosan, alginate, and synthetic, biodegradable and biocompatible polymers, or combinations thereof.

96. The use according to claim 95, in which the biomaterial comprises hyaluronans.