Claims:

1. An *in vitro* method of producing a transdifferentiated population of cells having a mature pancreatic beta cell-like phenotype and function, said method comprising:

(a) obtaining a primary adult human liver cell population enriched for cells predisposed to transdifferentiation, wherein said cell population comprises at least 30% of cells predisposed to transdifferentiation, and wherein the cells predisposed to transdifferentiation comprise:

(i) an active Wnt signaling pathway; or

(ii) increased expression of GSRE; or

(iii) increased expression of HOMER1, LAMP3, or BMPR2, or any combination thereof; or

(iv) decreased expression of ABCB1, ITGA4, ABCB4, or PRNP, or any combination thereof; or

any combination thereof;

(b) contacting said liver cell population with a pancreatic and duodenal homeobox (PDX-1) polypeptide or a nucleic acid encoding a PDX-1 polypeptide under conditions to allow uptake of said polypeptide or nucleic acid at a first time period;

(c) contacting the population of cells of step (b) with a Pax-4 polypeptide, or a NeuroD1 polypeptide, or a nucleic acid encoding a Pax-4 polypeptide, or a nucleic acid encoding a NeuroDl polypeptide under conditions to allow uptake of said polypeptides or nucleic acids at a second time period; and

(d) contacting the population of cells of step (c) with a MafA polypeptide or a nucleic acid encoding a MafA polypeptide under conditions to allow uptake of said polypeptide or nucleic acid at a third time period;

thereby producing a transdifferentiated population of cells having a mature pancreatic beta cell-like phenotype and function.

2. The method of claim 1, wherein the second time period is at least 24 hours after the first time period or is at the same time as the first time period, and wherein the third time period is at least 24 hours after the second time period.

3. The method of any one of claims 1 or 2 wherein said liver cell population enriched for cells predisposed to transdifferentiation comprises pericentral liver cells.

4. An isolated population of primary adult human liver cells, wherein at least 30% of the cells of said population are transdifferentiated and have a mature pancreatic beta cell-like phenotype and function, produced by a method comprising:

(a) obtaining a primary adult human liver cell population enriched for cells predisposed to transdifferentiation, wherein said cell population comprises at least 30% of cells predisposed to transdifferentiation, and wherein the cells predisposed to transdifferentiation comprise:

(i) an active Wnt signaling pathway; or

(ii) increased expression of GSRE; or

(iii) increased expression of HOMER1, LAMP3, or BMPR2, or any combination thereof; or

(iv) decreased expression of ABCB1, ITGA4, ABCB4, or PRNP, or any combination thereof; or

any combination thereof;

(b) contacting said liver cell population with a pancreatic and duodenal homeobox (PDX-1) polypeptide or a nucleic acid encoding a PDX-1 polypeptide under conditions to allow uptake of said polypeptide or nucleic acid at a first time period;

(c) contacting the population of cells of step (b) with a Pax-4 polypeptide, or a NeuroD1 polypeptide, or a nucleic acid encoding a Pax-4 polypeptide, or a nucleic acid encoding a NeuroDl polypeptide under conditions to allow uptake of said polypeptides or nucleic acids at a second time period; and

(d) contacting the population of cells of step (c) with a MafA polypeptide or a nucleic acid encoding a MafA polypeptide under conditions to allow uptake of said polypeptide or nucleic acid at a third time period.

5. The population of cells of claim 4, wherein said mature pancreatic beta cell-like phenotype and function comprises increased glucose regulated processed insulin secretion, or increased glucose regulated C-peptide secretion, or increased expression of endogenous Nkx6.1, or any combination thereof, compared with control non-transdifferentiated primary adult human

liver cell population.

6. The population of cells of any one of claims 4-5, wherein the second time period is at least 24 hours after the first time period or is at the same time as the first time period, and wherein the third time period is at least 24 hours after the second time period.

7. The population of cells of any one of claims 4-6, wherein the liver cell population enriched for cells predisposed to transdifferentiation comprises pericentral liver cells.

8. Use of a population of primary adult human liver cells, wherein at least 30% of the cells of said population are transdifferentiated and have a mature pancreatic beta cell-like phenotype and function, said population produced by a method comprising:

(a) obtaining a primary adult human liver cell population enriched for cells predisposed to transdifferentiation, wherein said cell population comprises at least 30% of cells predisposed to transdifferentiation, and wherein the cells predisposed to transdifferentiation comprise:
(i) an active Wnt signaling pathway; or
(ii) increased expression of GSRE; or
(iii) increased expression of HOMER1, LAMP3, or BMPR2, or any combination thereof; or
(iv) decreased expression of ABCB1, ITGA4, ABCB4, or PRNP, or any combination thereof; or
any combination thereof;

(b) contacting said liver cell population with a pancreatic and duodenal homeobox (PDX-1) polypeptide or a nucleic acid encoding a PDX-1 polypeptide under conditions to allow uptake of said polypeptide or nucleic acid at a first time period;

(c) contacting the population of cells of step (b) with a Pax-4 polypeptide, or a NeuroD1 polypeptide, or a nucleic acid encoding a Pax-4 polypeptide, or a nucleic acid encoding a NeuroDl polypeptide under conditions to allow uptake of said polypeptides or nucleic acids at a second time period; and

(d) contacting the population of cells of step (c) with a MafA polypeptide or a nucleic acid encoding a MafA polypeptide under conditions to allow uptake of said polypeptide or nucleic acid at a third time period, for preparation of a

medicament for treating a degenerative pancreatic disorder.

9. The use of claim 8, wherein the degenerative pancreatic disorder is diabetes.

10. The use of claim 9, wherein the diabetes is Type I or Type II diabetes.

11. The use of claim 8, wherein the degenerative pancreatic disorder is pancreatic cancer or pancreatitis.

12. A method of isolating a population of cells predisposed to transdifferentiation, said method comprising the steps of:

(a) providing a primary adult human liver cell population;

(b) introducing into the cells of said population a nucleic acid construct comprising a glutamine synthetase response element (GSRE) or a fragment thereof capable of activating glutamine synthetase transcription, wherein said GSRE or fragment thereof is operatively linked to a nucleic acid sequence encoding a reporter protein; and

(c) isolating the cells expressing the reporter protein;

thereby isolating a population of cells predisposed to transdifferentiation.

13. The method of claim 12, wherein the nucleic acid construct further comprises a promoter/enhancer.

14. The method of any one of claims 12-13, wherein the reporter protein provides resistance to selection pressure.

15. The method of any one of claims 12-14, wherein the liver cell population comprises pericentral liver cells.

16. An isolated population of adult human liver cells predisposed to transdifferentiation, said population isolated by a method comprising:

(a) providing a primary adult human liver cell population;

(b) introducing into the cells of said population a nucleic acid construct comprising a glutamine synthetase response element (GSRE) or a fragment thereof capable of activating glutamine synthetase transcription, wherein said GSRE or fragment thereof is operatively linked to a nucleic acid

sequence encoding a reporter protein; and

(c) isolating the cells expressing said reporter protein;

wherein the isolated cells expressing the reporter protein comprise cells predisposed to transdifferentiation.

17. The isolated population of liver cells of claim 16, wherein said cells comprise:

(a) an active Wnt-signaling pathway; or

(b) increased expression of GSRE; or

(c) increased expression of HOMER1, LAMP3 or BMPR2, or any combination thereof; or

(d) decreased expression of ABCB1, ITGA4, ABCB4, or PRNP, or any combination thereof; or

any combination thereof.

18. The population of liver cells of claim 17, wherein said cells comprise at least an active Wnt-signaling pathway and at least one further element selected from (b), (c) and (d).

19. A method of increasing the transdifferentiation capacity of a population of liver cells, said method comprising the steps of:

(a) providing a primary adult human liver cell population;

(b) introducing into the cells of said population a nucleic acid construct comprising a glutamine synthetase response element (GSRE) or a fragment thereof capable of activating glutamine synthetase transcription, wherein said GSRE or fragment thereof is operatively linked to a nucleic acid sequence encoding a reporter protein; and

(c) isolating the cells expressing the reporter protein;

thereby increasing the transdifferentiation capacity of said population of cells.

20. The population of cells of any one of claims 1-7 and 17-18, wherein the cells comprising an active Wnt signaling pathway comprise increased expression of Wnt3a, or beta-catenin, or STAT3 binding elements, or any combination thereof, or decreased expression of DKK1, or DKK3, or APC, or any combination thereof.