CLAIMS

1. A method of producing a pancreatic organoid *in vitro*, comprising:

providing a Mesothelin-positive ($MSLN^+$) and/or protein C receptor-positive ($Procr^+$) endocrine progenitor cell; and

3D culturing *in vitro* the $MSLN^+$ and/or $Procr^+$ endocrine progenitor cell in an organoid medium under conditions suitable to produce a pancreatic organoid comprising functional β-cells and/or β-like cells, wherein preferably the organoid medium further comprises a three-dimensional matrix such as Matrigel™ and hydrogel.

2. The method of claim 1, wherein the $MSLN^+$ and/or $Procr^+$ endocrine progenitor cell is isolated from adult islet cells.

3. The method of claim 1, wherein the $MSLN^+$ and/or $Procr^+$ endocrine progenitor cell is provided within a population of adult islet cells.

4. The method of claim 2 or 3, wherein the adult islet cells are from human and the endocrine progenitor cell is MSLN+, wherein optionally the endocrine progenitor cell further expresses one or more of *UPK1B, S100A6, LGALS4, SDCBP2, SDC1, IGFBP3, HMGA1, ITGB4, ITGB6, HN1, GPRC5A, SLPI, LAMC2, FERMT1, MGLL, SEMA3B, TST, SFN, CDH3* and *PROCR*.

5. The method of claim 4, further comprising contacting, *in vitro*, dissociated adult human islet cells with an anti-MSLN antibody or antigen-binding fragment thereof, followed by fluorescence assisted cell sorting (FACS), to isolate the endocrine progenitor cell.

6. The method of claim 4, wherein the organoid medium comprises a basal medium such as DMEM/F12 supplemented with one or more of: 10-200 (e.g., 50) ng ml^{-1} EGF, 1-50 (e.g., 10) ng ml^{-1} FGF2, 1-10 (e.g., 3) μM Wnt agonist such as CHIR99021 or 1-100 (e.g., 30) ng/ml Wnt surrogate such as NGS (next generation surrogate), 0.1-5 (e.g., 0.5) μM TGF-beta pathway inhibitors such as SB431542 or A83-01, 10-500 (e.g., 100) ng ml^{-1} Bmp inhibitor such as Noggin, 1-10 (e.g., 2.5) μM Rock inhibitor such as Y27632, and 1-10 (e.g., 0.5) μM of p38 inhibitor SB202190; wherein optionally the basal medium is further supplemented with one or more of 1-5% (e.g., 2%) B27, 0.1-5% (e.g., 1%) ITS, 0.1-5 (e.g., 2) μg ml^{-1} heparin, and 1-100 (e.g., 50) ng ml^{-1} VEGFa.

7. The method of claim 2 or 3, wherein the adult islet cells are from mouse and the endocrine progenitor cell is Procr+, wherein the 3D culturing comprises co-

culturing with a plurality of endothelial cells, and wherein optionally the endocrine progenitor cell further expresses one or more of Rspo1, Fgf1, Upk3B, Hoxa5 and Msln.

8. The method of claim 7, further comprising contacting, *in vitro*, dissociated adult mouse islet cells with an anti-Procr antibody or antigen-binding fragment thereof, followed by fluorescence assisted cell sorting (FACS), to isolate the endocrine progenitor cell.

9. The method of claim 7, wherein the culture medium comprises a basal medium such as DMEM/F12 supplemented with one or more of: 10-200 (e.g., 50) ng ml^{-1} EGF, 1-50 (e.g., 10) ng ml^{-1} FGF2, and 1-20 (e.g., 5) ng ml^{-1} VEGFa; wherein optionally the basal medium is further supplemented with one or more of 1-5% (e.g., 2%) B27, 0.1-5% (e.g., 1%) ITS, and 0.1-5 (e.g., 2) μg ml^{-1} heparin.

10. The method of any one of claims 1-9, wherein the culturing step comprises culturing until the endocrine progenitor cell forms a colony of 100-300 μm in diameter, and continuously culturing the colony to form a pancreatic organoid of 150-500 μm in diameter.

11. A method of obtaining pancreatic organoids *in vitro*, comprising:

enriching $MSLN^+$ and/or $Procr^+$ endocrine cells from adult pancreas, preferably by one or more of the following methods: (1) staining dissociated adult pancreas cells with TSQ (6-methoxy-8-*p*-toluenesulfonamido-quilone), followed by FACS; (2) density gradient centrifugation of dissociated adult pancreas cells; and (3) hand-picking and dissociating islets from adult pancreas;

3D culturing the enriched $MSLN^+$ and/or $Procr^+$ endocrine cells in an organoid medium under conditions suitable to produce a pancreatic organoid comprising functional β-cells and/or β-like cells, wherein preferably the organoid medium further comprises a three-dimensional matrix.

12. The method of claim 11, wherein the organoid medium comprises Matrigel™ or hydrogel and a basal medium such as DMEM/F12 supplemented with one or more of: 10-200 (e.g., 50) ng ml^{-1} EGF, 1-50 (e.g., 10) ng ml^{-1} FGF2, 1-10 (e.g., 3) μM Wnt agonist such as CHIR99021 or 1-100 (e.g., 30) ng/ml Wnt surrogate such as NGS (next generation surrogate), 0.1-5 (e.g., 0.5) μM TGF-beta pathway inhibitors such as SB431542 or A83-01, 10-500 (e.g., 100) ng ml^{-1} Bmp inhibitor such as Noggin, 1-10 (e.g., 2.5) μM Rock inhibitor such as Y27632, and 1-10

(e.g., 0.5) μM of p38 inhibitor SB202190; wherein optionally the basal medium is further supplemented with one or more of 1-5% (e.g., 2%) B27, 0.1-5% (e.g., 1%) ITS, 0.1-5 (e.g., 2) μg ml^{-1} heparin, and 1-100 (e.g., 50) ng ml^{-1} VEGFa.

13. The method of claim 11 or 12, wherein the pancreatic organoid is 50-500 or 100-300 μm in diameter.

14. The method of any one of claims 1-13, further comprising expanding the pancreatic organoid through passaging for at least 10 times, at least 20 times, or at least 30 times.

15. The method of claim 14, further comprising culturing the expanded pancreatic organoids for 1-12 or 1-4 or 2-12 weeks to generate mature organoids.

16. The method of claim 15, wherein the mature organoid senses glucose and produces and secretes insulin in response to glucose.

17. A method of obtaining endocrine progenitor cells, comprising:

contacting, *in vitro*, adult human islet cells with an anti-MSLN antibody or antigen-binding fragment thereof; and

isolating a $MSLN^+$ endocrine progenitor cell that binds to the anti-MSLN antibody or fragment thereof, preferably using fluorescence assisted cell sorting (FACS).

18. A method of obtaining endocrine progenitor cells, comprising:

contacting, *in vitro*, adult mouse islet cells with an anti-Procr antibody or antigen-binding fragment thereof; and

isolating a $Procr^+$ endocrine progenitor cell that binds to the anti-Procr antibody or fragment thereof, preferably using fluorescence assisted cell sorting (FACS).

19. A composition comprising a plurality of $MSLN^+$ and/or $Procr^+$ endocrine progenitor cells isolated from adult islet cells, a culture medium and optionally a plurality of endothelial cells.

20. The composition of claim 19, wherein the culture medium further comprises a three-dimensional matrix, preferably Matrigel™ or hydrogel.

21. The composition of claim 19 or 20, wherein the adult islet cells are from human, and the endocrine progenitor cells express MSLN and optionally one or more of *UPK1B, S100A6, LGALS4, SDCBP2, SDC1, IGFBP3, HMGA1, ITGB4, ITGB6, HN1, GPRC5A, SLPI, LAMC2, FERMT1, MGLL, SEMA3B, TST, SFN, CDH3* and *PROCR*.

22. The composition of claim 21, wherein the culture medium comprises a basal medium such as DMEM/F12 supplemented with one or more of: 10-200 (e.g., 50) ng ml^{-1} EGF, 1-50 (e.g., 10) ng ml^{-1} FGF2, 1-10 (e.g., 3) μM Wnt agonist such as CHIR99021 or 1-100 (e.g., 30) ng/ml Wnt surrogate such as NGS (next generation surrogate), 0.1-5 (e.g., 0.5) μM TGF-beta pathway inhibitors such as SB431542 or A83-01, 10-500 (e.g., 100) ng ml^{-1} Bmp inhibitor such as Noggin, 1-10 (e.g., 2.5) μM Rock inhibitor such as Y27632, and 1-10 (e.g., 0.5) μM of p38 inhibitor SB202190; wherein optionally the basal medium is further supplemented with one or more of 1-5% (e.g., 2%) B27, 0.1-5% (e.g., 1%) ITS, 0.1-5 (e.g., 2) μg ml^{-1} heparin, and 1-100 (e.g., 50) ng ml^{-1} VEGFa.

23. The composition of claim 19 or 20, wherein the adult islet cells are derived from mouse, and the endocrine progenitor cells express Procr and optionally one or more of Rspo1, Fgf1, Upk3B, Hoxa5 and Msln.

24. The composition of claim 23, wherein the culture medium comprises a basal medium such as DMEM/F12 supplemented with one or more of: 10-200 (e.g., 50) ng ml^{-1} EGF, 1-50 (e.g., 10) ng ml^{-1} FGF2, and 1-20 (e.g., 5) ng ml^{-1} VEGFa; wherein optionally the basal medium is further supplemented with one or more of 1-5% (e.g., 2%) B27, 0.1-5% (e.g., 1%) ITS, and 0.1-5 (e.g., 2) μg ml^{-1} heparin.

25. A pancreatic organoid comprising functional β-cells and/or β-like cells differentiated *in vitro* from $MSLN^+$ and/or $Procr^+$ endocrine progenitor cells, wherein the $MSLN^+$ and/or $Procr^+$ endocrine progenitor cells are isolated from adult islet cells.

26. The organoid of claim 25, wherein the pancreatic organoid senses glucose and produces and secretes insulin in response to glucose.

27. The organoid of claim 25 or 26, wherein the pancreatic organoid is 50-500 μm in diameter.

28. Use of the pancreatic organoid of any one of claims 25-27 in the manufacture of a medicament for the treatment of diabetes, or use of the pancreatic organoid of any one of claims 25-27 for screening *in vitro* an agent for treating or preventing diabetes.