CLAIMS

1. A method of generating a three-dimensional (3D) cell cluster comprising transdifferentiated mammalian non-pancreatic beta cells having a mature pancreatic beta cell phenotype and a scaffold; wherein at least a subset of said cells are attached to said scaffold, the method comprising:

(a) providing a scaffold;

(b) obtaining primary adult mammalian non-pancreatic cells;

(c) propagating and expanding the cells of step (b) to a predetermined number of cells;

(d) transdifferentiating the cells of step (c) wherein said transdifferentiating comprises:

(i) infecting said expanded cells with an adenoviral vector comprising a nucleic acid encoding a human PDX-1 polypeptide;

(ii) infecting said expanded cells of step (i) with an adenoviral vector comprising a nucleic acid encoding a second human pancreatic transcription factor polypeptide; and

(iii) infecting said expanded cells of step (ii) with an adenoviral vector comprising a nucleic acid encoding a human MafA polypeptide;

and a step of attaching at least a subset of said cells to said scaffold after step (b), (c), or (d);

thereby generating a 3D cell cluster comprising transdifferentiated mammalian non-pancreatic beta insulin producing cells, wherein at least a subset of said cells are attached to said scaffold.

2. The method of claim 1, wherein said second pancreatic transcription factor is selected from NeuroD1 and Pax4.

3. The method of claims 1 or 2, wherein steps (i) and (ii) are concurrent.

4. The method of any of claims 1-3, wherein step (c), step (d), or a combination thereof are executed under non-adherent cell culture conditions.

5. The method of any of claims 1-4, wherein said scaffold is selected from a group comprising: a polyglycerol sebacate (PGS) scaffold, a solid scaffold, a hydrogel, an extracellular matrix, an extracellular matrix hydrogel, a protein hydrogel, a peptide hydrogel, a polymer hydrogel, a wood-based nanocellulose hydrogel, or any combination thereof.

6. The method of claim 5, wherein said PGS is crosslinked with a crosslinking agent.

7. The method of claim 6, wherein said crosslinking agent is selected from a group comprising laminin, fibronectin, fibrin, collagen types I/III, and elastin, and any combination thereof.

8. The method of any of claims 1-7, wherein said scaffold comprises a plurality of microparticles.

9. The method of any of claims 1-8, wherein said scaffold comprises PGS, and wherein said microparticles range from about 1μm to about 1mm in diameter.

10. The method of claims 8 or 9, wherein said microparticles range from about 50μm to about 500μm in diameter.

11. The method of any of claims 1-10, wherein said 3D cell cluster is encapsulated by an encapsulation agent.

12. The method of claim 11, wherein said encapsulation agent comprises a material selected from a group comprising: alginate, cellulose sulphate, collagen, chitosan, gelatin, agarose, polyethylene glycol (PEG), poly-L-lysine (PLL), polysulphone (PSU), polyvinyl alcohol (PVA), polylactic acid (PLA), acrylates, and low molecular weight dextran

sulphate (LMW-DS), or any derivatives thereof, and any combination thereof.

13. The method any of claims 1-12, wherein said scaffold encapsulates said transdifferentiated cells.

14. The method of any of claims 1-13, wherein said transdifferentiated cells comprise

(a) improved glucose-regulated C-peptide or insulin secretion; increased GCG NKX6.1, or PAX6 expression; increased expression of the ectopically expressed transcription factors; or increased insulin content; compared to transdifferentiated non-pancreatic beta insulin producing cells cultured as a monolayer cell culture; or

(b) secretion of at least 20 pm/h*10^6 cells of C-peptide in response to high glucose concentrations; or

(c) any combination thereof.

15. The method of any of claims 1-14, wherein said adult mammalian non-pancreatic beta cells are selected from the group comprising epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes, liver cells, blood cells, stem or progenitor cells, liver stem cells, neural stem cells, mesenchymal stem cells, hematopoietic stem or progenitor cells, bone marrow stem cells, umbilical cord blood stem cells, peripheral blood stem cells, fetal liver stem cells, or adipose tissue stem cells, or any combination thereof.

16. A three-dimensional (3D) cell cluster comprising transdifferentiated adult mammalian non-pancreatic beta cells having a mature pancreatic beta cell phenotype and function and a scaffold, wherein at least a subset of said cells are attached to said scaffold, and wherein said cells are transdifferentiated by a method comprising

(a) obtaining primary adult mammalian non-pancreatic cells;

(b) propagating and expanding the cells of step (b) to a predetermined number of cells;

(c) infecting said expanded cells with an adenoviral vector comprising a nucleic acid encoding a human PDX-1 polypeptide;

(d) infecting the cells of step (c) with an adenoviral vector comprising a nucleic acid encoding a second human pancreatic transcription factor polypeptide; and

(e) infecting the expanded cells of step (d) with an adenoviral vector comprising a nucleic acid encoding a human MafA polypeptide.

wherein said transdifferentiated cells increased insulin secretion; compared to transdifferentiated non-pancreatic beta insulin producing cells cultured as a monolayer cell culture.

17. The 3D cell cluster of claim 16, wherein said scaffold is selected from a group comprising: a polyglycerol sebacate (PGS) scaffold, a solid scaffold, a hydrogel, an extracellular matrix, an extracellular matrix hydrogel, a protein hydrogel, a peptide hydrogel, a polymer hydrogel, a wood-based nanocellulose hydrogel, or any combination thereof.

18. The 3D cell cluster of claim 17, wherein said PGS is crosslinked with a crosslinking agent.

19. The 3D cell cluster of claim 18, wherein said crosslinking agent is selected from a group comprising laminin, fibronectin, fibrin, collagen types I/III, and elastin, and any combination thereof.

20. The 3D cell cluster of any of claims 16-19, wherein said scaffold comprises a plurality of microparticles.

21. The 3D cell cluster of any of claims 16-20, wherein said scaffold comprises PGS, and wherein said microparticles range from about 1μm to about 1mm in diameter.

22. The 3D cell cluster of any of claims 20-22, wherein said microparticles range from about 50μm to about 500μm in diameter.

23. The 3D cell cluster of any of claims 16-22, wherein said 3D cell cluster is encapsulated by an encapsulation agent.

24. The 3D cell cluster of claim 23, wherein said encapsulation agent comprises a material selected from a group comprising: alginate, cellulose sulphate, collagen, chitosan, gelatin, agarose, polyethylene glycol (PEG), poly-L-lysine (PLL), polysulphone (PSU), polyvinyl alcohol (PVA), polylactic acid (PLA), acrylates, and low molecular weight dextran sulphate (LMW-DS), or any derivatives thereof, and any combination thereof.

25. The 3D cell cluster of any of claims 16-24, wherein said transdifferentiated cells comprise

(a) improved glucose-regulated C-peptide or insulin secretion; increased GCG NKX6.1, or PAX6 expression; increased expression of the ectopically expressed transcription factors; or increased insulin content; compared to transdifferentiated non-pancreatic beta insulin producing cells cultured as a monolayer cell culture; or

(b) secretion of at least 20 pm/h*10^6 cells of C-peptide in response to high glucose concentrations;

(c) any combination thereof.

26. The 3D cell cluster of any of claims 16-25, wherein said adult mammalian non-pancreatic beta cells are selected from the group comprising epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes, liver cells, blood cells, stem or progenitor cells, or any combination thereof.

27. The 3D cluster of claim 26, wherein said stem or progenitor cells are obtained from a tissue selected from a group comprising: bone marrow, umbilical cord blood, peripheral blood, fetal liver, adipose tissue, or any combination thereof.

28. A pharmaceutical composition comprising the 3D cell cluster of any of claims 16-27.

29. A composition comprising a 3D cell cluster comprising transdifferentiated mammalian non-pancreatic beta cells having a mature pancreatic beta cell phenotype and function and a scaffold to said subject; wherein at least a subset of said cells are attached to said scaffold, and wherein said 3D cell cluster is produced by a method comprising:

(a) providing a scaffold;

(b) obtaining primary adult mammalian non-pancreatic cells;

(c) propagating and expanding the cells of step (b) to a predetermined number of cells;

(d) transdifferentiating the cells of step (c) wherein said transdifferentiating comprises:

(i) infecting said expanded cells with an adenoviral vector comprising a nucleic acid encoding a human PDX-1 polypeptide;

(ii) infecting said expanded cells of step (i) with an adenoviral vector comprising a nucleic acid encoding a second human pancreatic transcription factor polypeptide; and

(iii) infecting said expanded cells of step (ii) with an adenoviral vector comprising a nucleic acid encoding a human MafA polypeptide;

and a step of attaching at least a subset of said cells to said scaffold after step (b), (c), or (d);

for use in treating a pancreatic disease or disorder in a subject.

30. The composition for use of claim 29, wherein said composition is formulated for intradermal, intraperitoneal, or surgical administration administration.

31. The composition for use of claims 29 or 30, wherein said disease comprises type I diabetes, type II diabetes, gestational diabetes, pancreatic cancer, hyperglycemia, pancreatitis, pancreatic pseudocysts, pancreatic trauma caused by injury, type 3 diabetes or a complication of pancreatectomy, or any combination thereof.