CLAIMS

1. A method of inducing differentiation of stem cells into glucose-sensing insulin-secreting pancreatic beta cells, comprising the steps of:

(a) culturing induced pluripotent stem cells as starting cells under conditions for differentiation;

(b) inducing said starting cells to exit the pluripotent state towards the mesendoderm lineage;

(c) directing the differentiating cells towards endoderm cells through culture cell transfection with ~~a~~ first ~~combination of~~ mRNAs at an effective dose and within specific time windows, wherein the first ~~combination of~~ mRNAs comprise~~s~~ FoxA2 mRNAs or Sox17 mRNAs;

(d) further directing said endoderm cells towards pancreatic progenitor cells through transfection with ~~a~~ second ~~combination of~~ mRNAs, wherein the second ~~combination of~~ mRNAs comprise~~s~~ at least one of PDX1, Hlxb9, Ptf1a, ixl1, HNF1a and b, and Sox9 mRNAs;

(e) further maturing said pancreatic progenitor cells into pancreatic endocrine cells with ~~a~~ third ~~combination of~~ mRNAs, wherein the third ~~combination of~~ mRNAs comprise~~s~~ at least one of PDX1, NKX6.1, NKX2.2, Pax6, Pax4, Hlxb9, and Ngn3 mRNAs; and

(f) collecting clusters enriched with pancreatic beta cells that are responsive to environment glucose and able to secrete insulin in response.

2. The method of claim 1, wherein said first ~~combination of~~ mRNAs comprise~~s~~ FoxA2 mRNAs.

3. The method of claim 1, wherein said first ~~combination of~~ mRNAs comprise~~s~~ Sox17 mRNAs.

4. The method of claim 1, wherein said first ~~combination of~~ mRNAs comprise~~s~~ FoxA2 and Sox17 mRNAs.

5. The method of claim 1, wherein said first ~~combination of~~ mRNAs comprise~~s~~ FoxA2, Sox17, GATA4, and GATA6 mRNAs.

6. The method of claim 1, wherein said second ~~combination of~~ mRNAs comprise~~s~~ at least PDX1 mRNAs.

7. The method of claim 1, wherein said third ~~combination of~~ mRNAs comprise~~s~~ at least PDX1 and NKX6.1 mRNAs.

8. The method of claim 1, further comprising effecting a pancreatic beta cell fate commitment with ~~a~~ fourth ~~combination of~~ mRNAs which comprise~~s~~ at least one of NKX6.1, MAFA, or MAFA mRNAs.

9. The method of claim 1, wherein said starting cells are generated from a body fluid or tissue of a subject.

10. A footprint-free cell obtained by the method of claim 9.

11. A composition for treating diabetes or a diabetes-related condition ~~disease, disorder or malformation~~ comprising the cell of claim 10.

12. A cell of claim 10 or a composition comprising the cell of claim 10 for use in therapy.

13. The cell or composition of claim 12 for use in therapy, wherein the cell of claim 10 is derived from the recipient of the therapy.

14. The cell or composition of claim 12 for use in therapy, wherein the starting cells of claim 10 are generated from the recipient of the therapy.

15. Use of the cell of claim 10 in the manufacture of medicament for treating diabetes or a diabetes-related condition.

16. The use of claim 15, wherein the cell of claim 10 is derived from the recipient of the treatment.

17. The use of claim 15, wherein the cell of claim 10 is harvested from the recipient of the treatment.

18. A method of producing induced glucose-sensing insulin-secreting pancreatic beta cells, comprising the steps of:

(a) culturing induced pluripotent stem cells as starting cells under conditions for differentiation;

(b) inducing said starting cells to exit the pluripotent state towards the mesendoderm lineage;

(c) directing the differentiating cells towards endoderm cells through culture cell transfection with ~~a~~ first ~~combination of~~ mRNAs at an effective dose and within the specific time windows, wherein the first ~~combination of~~ mRNAs comprise~~s~~ FoxA2 mRNAs or Sox17 mRNAs;

(d) further directing said endoderm cells towards pancreatic progenitor cells through transfection with ~~a~~ second combination of mRNAs, wherein the second combination of mRNAs comprise~~s~~ at least one of PDX1, Hlxb9, Ptf1a, ixl1, HNF1a and b, and Sox9 mRNAs;

(e) further maturing said pancreatic progenitor cells into pancreatic endocrine cells with ~~a~~ third ~~combination of~~ mRNAs, wherein the third ~~combination of~~ mRNAs comprise~~s~~ at least one of PDX1, NKX6.1, NKX2.2, Pax6, Pax4, Hlxb9, and Ngn3 mRNAs; and

(f) collecting clusters enriched with pancreatic beta cells that are responsive to environment glucose and able to secrete insulin in response.