Claims

1. An in vitro cell culture comprising (i) a population of human pancreatic endocrine cells, in which at least 10% of the differentiated cells express insulin, PDX1, NKX6.1, and MAFA, and (ii) a differentiation medium supplemented with L-alanyl-glutamine and an inhibitor selected from the group consisting of an aurora kinase inhibitor, an RSK inhibitor, an inhibitor of protein methyltransferase DOT1L, and combinations thereof, wherein the population is obtained by a step-wise differentiation protocol comprising:

(a) culturing human pluripotent stem cells in a medium supplemented with either (i) activin A and wnt3A or (ii) GDF-8 and 14-Prop-2-en-1-yl-3,5,7,14,17,23,27-heptaazatetracyclo[19.3.1.1~2,6~.1~8,12~]heptacosa-1(25),2(27),3,5,8(26),9,11,21,23-nonaen-16-one to obtain definitive endoderm cells;

(b) differentiating the definitive endoderm cells into pancreatic endocrine cells; and (c) culturing the pancreatic endocrine cells in the differentiation medium supplemented with L-alanyl-glutamine and an inhibitor selected from the group consisting of an aurora kinase inhibitor, an RSK inhibitor, an inhibitor of protein methyltransferase DOT1L, and combinations thereof.

2 A method of inducing MAFA expression in cells comprising treating human pancreatic endocrine cells with a medium supplemented with an inhibitor selected from the group consisting of an RSK inhibitor, an inhibitor of protein methyltransferase DOT1L, and combinations thereof, wherein the treatment with the inhibitor induces MAFA expression.

3. The method of claim 2, wherein the inhibitor is an RSK inhibitor.

4. The method of claim 3, wherein the RSK inhibitor is RSK inhibitor II.

5. The method of claim 2, wherein the medium further comprises an antioxidant.

6. The method of claim 2, wherein the inhibitor is an inhibitor of protein methyltransferase DOT1L.

7. The method of claim 6, wherein the inhibitor of protein methyltransferase DOT1L is EPZ-5676.

8 An in vitro cell culture comprising (i) a population human pancreatic endocrine cells, in which at least 10% of the differentiated cells express insulin, PDX1, NKX6.1, and MAFA, and (ii) a differentiation medium supplemented with an RSK inhibitor, wherein the population is obtained by a step-wise differentiation protocol comprising:

(a) culturing human pluripotent stem cells in a medium supplemented with either (i) activin A and wnt3A or (ii) GDF-8 and 14-Prop-2-en-1-yl-3,5,7,14,17,23,27-heptaazatetracyclo[19.3.1.1~2,6~.1~8,12~]heptacosa-1(25),2(27),3,5,8(26),9,11,21,23-nonaen-16-one to obtain definitive endoderm cells;

(b) differentiating the definitive endoderm cells into pancreatic endocrine cells; and

(c) culturing the pancreatic endocrine cells in the differentiation medium supplemented with the RSK inhibitor.

9. The in vitro culture of claim 8, wherein the RSK inhibitor is RSK inhibitor II.

10. An in vitro cell culture comprising (i) a population human pancreatic endocrine cells, in which at least 10% of the differentiated cells express insulin, PDX1, NKX6.1, and MAFA, and (ii) a differentiation medium supplemented with an inhibitor of protein methyltransferase DOT1L, wherein the population is obtained by a step-wise differentiation protocol comprising:

(a) culturing human pluripotent stem cells in a medium supplemented with either (i) activin A and wnt3A or (ii) GDF-8 and 14-Prop-2-en-1-yl-3,5,7,14,17,23,27-heptaazatetracyclo[19.3.1.1~2,6~.1~8,12~]heptacosa-1(25),2(27),3,5,8(26),9,11,21,23-nonaen-16-one to obtain definitive endoderm cells;

(b) differentiating the definitive endoderm cells into pancreatic endocrine cells; and

(c) culturing the pancreatic endocrine cells in the differentiation medium supplemented with L-alanyl-glutamine and an inhibitor selected from the group consisting of an aurora kinase inhibitor, an RSK inhibitor, an inhibitor of protein methyltransferase DOT1L, and combinations thereof.

11. The in vitro culture of claim 10, wherein the inhibitor of protein methyltransferase DOT1L is EPZ-5676.

12. The in vitro culture of claim 1, further comprising an antioxidant.

13. A method for inducing MAFA expression in pancreatic endocrine cells comprising culturing the human foregut endoderm cells with an RSK inhibitor, an inhibitor of protein methyltransferase DOT1L, and combinations thereof to obtain mature pancreatic endocrine cells which express MAFA.

14. An in vitro cell culture comprising (i) a population human pancreatic endocrine cells, in which at least 10% of the differentiated cells express insulin, PDX1, NKX6.1, and MAFA, and (ii) a differentiation medium supplemented with L-alanyl-glutamine and an inhibitor selected from the group consisting of an aurora kinase inhibitor, an RSK inhibitor, an inhibitor of protein methyltransferase DOT1L, and combinations thereof, wherein the population is obtained by a step-wise differentiation protocol which comprises culturing human pancreatic endocrine cells in the differentiation medium.

15. The method of claim 13, wherein the method comprises culturing the human foregut endoderm cells with an RSK inhibitor.

16 The method of claim 15, wherein the RSK inhibitor is RSK inhibitor II.

17. The method of claim 13, wherein the method comprises culturing the human foregut endoderm cells with an inhibitor of protein methyltransferase DOT1L.

18. The method of claim 17, wherein the inhibitor of protein methyltransferase DOT1L is EPZ-5676.

19. The method of claim 2, wherein the method comprises culturing the cells in a suspension culture.

20. The method of claim 2, wherein the method comprises culturing the cells at the air-liquid interface.