What is claimed is:

1. A method to derive a population of pancreatic endocrine precursor cells from pluripotent stem cells comprising the steps of:

    a. Culturing a population of pluripotent stem cells;

    b. Differentiating the pluripotent stem cells into a population of cells expressing markers characteristic of the definitive endoderm lineage;

    c. Differentiating the cells expressing markers characteristic of the definitive endoderm lineage into a population of primitive gut tube cells;

    d. Differentiating the population of primitive gut tube cells into a population of posterior foregut cells; and

    e. Treating the population of posterior foregut cells with a medium supplemented with an agent that degrades retinoic acid.

2. The method of claim 1, wherein the agent that degrades retinoic acid is a CYP26A inhibitor.

3. The method of claim 2, wherein the CYP26A inhibitor is used at a concentration from about 1 nM to about 1000 nM.

4. The method of claim 2, wherein the CYP26A inhibitor is used at a concentration from about 10 nM to about 100 nM.

5. The method of claim 2, wherein the CYP26A inhibitor is N-{4-[2-Ethyl-1-(1H-1, 2, 4-triazol-1-yl)butyl]phenyl}-1, 3-benzothiazol-2-amine.

Claims

1. A method to derive a population of pancreatic endocrine precursor cells from pluripotent stem cells comprising the steps of:

a. Culturing a population of pluripotent stem cells;

b. Differentiating the population of pluripotent stem cells into a population of cells expressing markers characteristic of the definitive endoderm lineage;

c. Differentiating the population of cells expressing markers characteristic of the definitive endoderm lineage into a population of primitive gut tube cells;

d. Differentiating the population of primitive gut tube cells into a population of posterior foregut cells; and

e. Treating the population of posterior foregut cells with a medium supplemented with a CYP26A inhibitor and with no added retinoic acid such that the population of posterior foregut cells differentiates into a population of pancreatic endocrine precursor cells, wherein expression of endocrine precursor markers is increased and wherein the differentiating in steps b., c. and d. comprises treatment in a medium lacking a CPY26A inhibitor.

2. The method of claim 1, wherein the CYP26A inhibitor is used at a concentration from about 1 nM to about 1000 nM.

3. The method of claim 1, wherein the CYP26A inhibitor is used at a concentration from about 10 nM to about 100 nM.

4. The method of claim 1, wherein the CYP26A inhibitor is N-{4-[2-Ethyl-1-(1H-1, 2, 4-triazol-1-yl)butyl]phenyl}-1, 3-benzothiazol-2-amine.

5. The method of claim 1, wherein treatment increases expression of the endocrine precursor markers NGN3, Pax and NeuroD.

6. The method of claim 1, wherein the treatment decreases the expression of CDX2 and albumin.

7. The method of claim 1, wherein the medium supplemented with the CYP26A inhibitor is further supplemented with at least one factor selected from the group consisting of a factor capable of inhibiting BMP, a TGFβ receptor signaling inhibitor, and a PKC activator.

8. The method of claim 7, wherein the factor capable of inhibiting BMP comprises noggin.

9. The method of claim 7, wherein the TGFβ receptor signaling inhibitor comprises an inhibitor of ALK5.

10. The method of claim 9, wherein the inhibitor of ALK5 is ALK5 inhibitor II.

11. The method of claim 7, wherein the PKC activator is selected from the group consisting of (2S, 5S)-(E, E)-8-(5-(4-(Trifluoromethyl)phenyl)-2,4-pentadiemoylamino) benzolactam, Indolactam V (ILV), phorbol-12-myristate-13-acetate (PMA), and phorbol-12,13-dibutyrate (PDBu).

12. A method to derive a population of pancreatic endocrine precursor cells from pluripotent stem cells comprising the steps of:

a. Differentiating pluripotent stem cells into a population of cells expressing markers characteristic of the definitive endoderm lineage (Stage I) by the culturing the pluripotent stem cells in a medium supplemented with activin A;

b. Differentiating the population of cells expressing markers characteristic of the definitive endoderm lineage (Stage I) into a population of primitive gut tube cells (Stage II) by culturing the Stage I cells in a medium supplemented with FGF7;

c. Differentiating the population of primitive gut tube cells (Stage II) into a population of posterior foregut cells (Stage III) by culturing the Stage II cells in a medium supplemented with retinoic acid and a P38 inhibitor; and

d. Differentiating the population of posterior foregut cells (Stage III) into a population of Stage IV cells by treating the Stage III cells with a media supplemented with a CPY26A inhibitor and with no added retinoic acid, wherein the treatment increases the expression of endocrine precursor markers and wherein the differentiating in steps a., b. and c. comprises treatment in a medium lacking a CPY26A inhibitor.

13. The method of claim 12, wherein the Stage IV cells are pancreatic endocrine precursors.

14. The method of claim 12, wherein treatment increases expression of the endocrine precursor markers NGN3, Pax and NeuroD.

15. The method of claim 12, wherein treatment decreases the expression of CDX2 and albumin.

16. The method of claim 12, wherein the CYP26A inhibitor is used at a concentration from about 1 nM to about 1000 nM.

17. The method of claim 12, wherein the medium in step c. is further supplemented with at least one or more of FGF7, activin A or a BMP receptor inhibitor.

18. The method of claim 12, wherein the medium supplemented with a CPY26A inhibitor is further supplemented with at least one factor selected from the group consisting of a factor capable of inhibiting BMP, a TGFβ receptor signaling inhibitor, and a PKC activator.

19. The method of claim 18, wherein the factor capable of inhibiting BMP comprises noggin.

20. The method of claim 18, wherein the TGFβ receptor signaling inhibitor comprises an inhibitor of ALK5.

21. The method of claim 20, wherein the inhibitor of ALK5 is ALK5 inhibitor II.

22. The method of claim 18, wherein the PKC activator is selected from the group consisting of (2S, 5S)-(E, E)-8-(5-(4-(Trifluoromethyl)phenyl)-2,4-pentadiemoylamino) benzolactam, Indolactam V (ILV), phorbol-12-myristate-13-acetate (PMA), and phorbol-12,13-dibutyrate (PDBu).