CLAIMS

1. A method of manufacturing a transdifferentiated population of human non-pancreatic β-like insulin producing cells, the method comprising the steps of:
   (a) obtaining a population of primary human non-pancreatic β-cells;
   (b) propagating and expanding said human cells;
   (c) pre-incubating the expanded cells of step (b) with a Wnt-pathway agonist,
   (d) transdifferentiating said pre-incubated cells of step (c) by a method comprising:
      (i) contacting said pre-incubated cells with a PDX-1 polypeptide or a nucleic acid encoding a PDX-1 polypeptide, and a NeuroD1 polypeptide or nucleic acid encoding a NeuroD1 polypeptide; and
      (ii) contacting the cells of step (i) with a MafA polypeptide or a nucleic acid encoding a MafA polypeptide;
   (e) harvesting said transdifferentiated cells;
   wherein said method further comprises a step of incubating the cells with an epigenetic modifier, either prior to step (c), or prior, concurrent, or after step (d);
   thereby manufacturing a population of transdifferentiated human insulin producing cells.

2. The method of claim 1, wherein said epigenetic modifier comprises a histone deacetylase inhibitor (HDACi), an inhibitor of DNA methylation, a TGFβ inhibitor, suberanilohydroxamic acid (SAHA), sodium butyrate, romidepsin, chidamide, panobinostat, belinostat, SB431542, or 5-Aza-2-deoxycitidine (5-AZA), or any combination thereof; or said Wnt-pathway agonist comprises lithium (Li), Wnt9, Wnt3A, a GSK3b, a Rho Kinase inhibitor, Y27632 (Y2), or any combination thereof.

3. The method of claims 1 or 2, wherein said Wnt-pathway agonist pre-incubation occurs 24, 48, or 72 hours prior to step (d), wherein said addition of the epigenetic modifier occurs 24, 48, or 72 hours prior to the transdifferentiation step (d), or wherein said addition of the epigenetic modifier and said pre-incubation with Wnt-pathway agonist are concurrent.

4. The method of any of claims 1-3, wherein said method further comprises

contacting said pre-incubated cells with an additional pancreatic transcription factor at said first time-point; or

contacting said pre-incubated cells with an additional pancreatic transcription factor at the second time-point; or

contacting said pre-incubated cells with an additional pancreatic transcription factor at both said first time-point and at the second time-point;

and wherein said additional pancreatic transcription factor comprises PAX4, PAX6, ILS-1, NGN3, NKX6.1, RFX6, or FOXA2.

5. The method of any of claims 1-4, further comprising incubating the cells with nicotine amide, epidermal growth factor (EGF), exendin-4, or any combination thereof, during step (d).

6. A method for enriching a population of non-pancreatic β-cells for cells comprising an enriched capacity for transcription factor-induced transdifferentiation into a pancreatic β-cell phenotype and function, said method comprising the steps of:

(a) obtaining a population of primary human non-pancreatic β-cells;

(b) identifying cells within the population of (a) having increased expression of at least one gene of the group comprising a solute carrier family 2, facilitated glucose transporter member 3 (GLUT-3); a vesicle-associated membrane protein 2 (VAMP2); a syntaxin-1A (Stx1a); a tyrosine-protein kinase transmembrane receptor ROR2 (ROR2); Frizzled-4 (FZD4); a pituitary homeobox 2 (PITX2); and a Proto-oncogene Wnt-1 (WNT1); or any combination thereof, wherein said increased expression is compared within the non-pancreatic β-cell population; and

(c) selecting said primary human non-pancreatic β-cells having increased expression of at least one gene recited in (b);

wherein said selected cells comprise an enriched capacity for transcription factor induced transdifferentiation to a pancreatic β-cell like phenotype and function.

7. The method of claim 6, wherein said identifying further comprises identifying cells with increased expression of at least one gene selected from the group comprising vesicle-associated membrane protein 4 (VAMP4); thrombospondin-1; discoidin, CUB and LCCL domain-containing protein 2 (THBS1); integrin alpha-6 (ITGA6); homer protein homolog 1 (HOMER1); lysosome-associated membrane glycoprotein 3 (LAMP3); bone morphogenetic protein receptor type-2 (BMPR2); or with decreased expression of at least one gene selected from the group comprising multidrug resistance protein 1 (ABCB1), integrin alpha-4 (ITGA4), phosphatidylcholine translocator (ABCB4); or any combination thereof.

8. The method of claims 6 or 7, said method further comprising steps of
   (a) propagating and expanding said human cells;
   (b) pre-incubating the expanded cells of step (a) with a Wnt-pathway agonist;
   (c) incubating said pre-incubated cells with at least one epigenetic modifier; and
   (d) collecting said cells.

9. The method of claim 8, wherein said epigenetic modifier comprises a histone deacetylase inhibitor (HDACi), an inhibitor of DNA methylation, a TGFβ inhibitor, suberanilohydroxamic acid (SAHA), sodium butyrate, romidepsin, chidamide, panobinostat, or belinostat, SB431542, 5-Aza-2-deoxycitidine (5-AZA), or any combination thereof; or said Wnt-pathway agonist comprises lithium (Li), Wnt9, Wnt3, a GSK3b antagonist, a Rho Kinase inhibitor, Y27632 (Y2), or any combination thereof.

10. The method of claims 8 or 9, wherein said incubating with said epigenetic modifier occurs before said pre-incubation, at the same time as said pre-incubation, following said pre-incubation and at the same time than a transdifferentiation step, or following a transdifferentiation step.

11. The method of any of claims 8-10, wherein said Wnt-pathway agonist pre-incubation occurs 24, 48, or 72 hours prior to a transdifferentiation step.

12. The method of any of claims 6-11, wherein said non-pancreatic β-cells are adult human liver cells.

13. The method of any of claims 6-12, wherein said identifying comprises incubating cells with a labeled antibody or ligand that binds the protein product of said at least one gene, and wherein said selecting comprises selecting cells bound to said labeled antibody or ligand.

14. The method of any of claims 6-13, wherein following transcription factor induced transdifferentiation of said selected cells, said transdifferentiated selected cell population expresses increased endogenous Nkx6.1, increased insulin content, increased glucagon content, or increased glucose-regulated insulin secretion and C-peptide secretion, or any combination thereof, compared with a control transdifferentiated non-selected population of cells.