THAT WHICH IS CLAIMED:

1. A method for making a population of human induced pluripotent stem cells (hiPSCs), the method comprising culturing *in vitro* a population of non-pluripotent cells, transformed to express a pluripotent state, in a low osmolality medium comprising a base medium and supplements, wherein the low osmolality medium comprises:

(a) a leukemia inhibitory factor (LIF) polypeptide;

(b) a glycogen synthase kinase 3 (GSK3) inhibitor; and

(c) a MEK inhibitor;

wherein the low osmolality medium has an osmolality of 200 mOsm/kg to 250 mOsm/kg.

2. The method of claim 1, wherein the transformed cells are first cultured in a high osmolality medium prior to culturing in the low osmolality medium, wherein the high osmolality medium comprises bFGF, optionally wherein the high osmolality medium has an osmolality of at least about 290 mOsm/kg, and optionally wherein:

(a) the transformed cells are first cultured in the high osmolality medium until they express characteristics of a naïve state;

(b) the transformed cells are first cultured in the high osmolality medium for a period of about two months;

(c) the transformed cells are first cultured in the high osmolality medium until they display a morphology characterized by three-dimensional cell clumps; or

(d) a combination thereof.

3. A method for maintaining a population of human induced pluripotent stem cells (hiPSCs) in an *in vitro* culture, the method comprising culturing the population of hiPSCs in a low osmolality medium comprising a base medium and supplements, wherein the low osmolality medium comprises:

(a) a leukemia inhibitory factor (LIF) polypeptide;

(b) a glycogen synthase kinase 3 (GSK3) inhibitor; and

(c) a MEK inhibitor;

wherein the low osmolality medium has an osmolality of 200 mOsm/kg to 250 mOsm/kg.

4. The method of any one of claims 1-3, further comprising enzymatically dissociating the hiPSCs into a single-cell suspension and subculturing the enzymatically dissociated hiPSCs.

5. The method of claim 4, wherein the enzymatic dissociation:

(a) is performed using trypsin;

(b) is performed in the absence of a ROCK inhibitor; or

(c) a combination thereof; and

wherein the subcultured hiPSCs:

(a) continue to express one or more pluripotency markers;

(b) maintain a naïve state and display a morphology characterized by compact dome-shaped colonies; or

(c) a combination thereof; and

wherein the subcultured hiPSCs maintain a normal karyotype.

6. A method for modifying a target genomic locus in a human induced pluripotent stem cell (hiPSC), comprising:

(a) introducing into hiPSCs a targeting vector comprising an insert nucleic acid flanked by 5’ and 3’ homology arms corresponding to 5’ and 3’ target sites at the target genomic locus; and

(b) identifying a genetically modified hiPSC comprising in its genome the insert nucleic acid integrated at the target genomic locus;

wherein the hiPSCs are cultured in a low osmolality medium comprising a base medium and supplements, wherein the low osmolality medium comprises:

(i) a leukemia inhibitory factor (LIF) polypeptide;

(ii) a glycogen synthase kinase 3 (GSK3) inhibitor; and

(iii) a MEK inhibitor;

wherein the low osmolality medium has an osmolality of 200 mOsm/kg to 250 mOsm/kg.

7. The method of claim 6, wherein the targeting vector is a large targeting vector (LTVEC), wherein the sum total of the 5' and 3' homology arms is at least 10 kb.

8. The method of claim 6 or 7, wherein the targeted genetic modification comprises:

(a) deletion of an endogenous human nucleic acid sequence;

(b) insertion of an exogenous nucleic acid sequence, optionally wherein the exogenous nucleic acid sequence comprises one or more of the following:

(i) a nucleic acid sequence that is homologous or orthologous to the endogenous human nucleic acid sequence;

(ii) a chimeric nucleic acid sequence;

(iii) a conditional allele flanked by site-specific recombinase target sequences; and

(iv) a reporter gene operably linked to a promoter active in the hiPSC; or

(c) replacement of the endogenous human nucleic acid sequence with the exogenous nucleic acid sequence,

optionally wherein the targeted genetic modification is biallelic.

9. The method of any one of claims 6-8, wherein introducing step (a) further comprises introducing a nuclease agent that promotes homologous recombination between the targeting vector and the target genomic locus in the hiPSC.

10. The method of claim 9, wherein the nuclease agent comprises:

(a) a zinc finger nuclease (ZFN);

(b) a Transcription Activator-Like Effector Nuclease (TALEN);

(c) a meganuclease; or

(d) a Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) associated (Cas) protein and a guide RNA (gRNA) comprising a CRISPR RNA (crRNA) that recognizes a genomic target sequence and a trans-activating CRISPR RNA (tracrRNA).

11. The method of claim 10, wherein the nuclease agent comprises the Cas protein and the guide RNA, wherein the Cas protein is Cas9.

12. The method of any one of claims 6-11, wherein prior to step (a), the hiPSCs are enzymatically dissociated into a single-cell suspension and subcultured.

13. The method of claim 12, wherein the enzymatic dissociation:

(a) is performed using trypsin;

(b) is performed in the absence of a ROCK inhibitor; or

(c) a combination thereof, and

wherein the subcultured hiPSCs:

(a) continue to express one or more pluripotency markers;

(b) maintain a naïve state and display a morphology characterized by compact dome-shaped colonies; or

(c) a combination thereof, and

wherein the subcultured hiPSCs maintain a normal karyotype.

14. The method of any one of claims 1-13, wherein the hiPSCs have a normal karyotype, and wherein the hiPSCs:

(a) comprise naïve hiPSCs;

(b) express one or more pluripotency markers, optionally wherein the pluripotency markers comprise NANOG, alkaline phosphatase, or a combination thereof;

(c) display a morphology characterized by compact dome-shaped colonies;

(d) can differentiate into cells of any one of the endoderm, ectoderm, or mesoderm germ layers;

(e) have a doubling time of between about 16 hours and about 24 hours; or

(f) any combination of (a) to (e).

15. The method of any one of claims 1-14, wherein the hiPSCs are derived from non-pluripotent cells transformed to express a pluripotent state, wherein the transformed cells express reprogramming genes comprising Oct4, Sox2, Klf4, Myc, or any combination thereof, and optionally wherein the transformed cells comprise primed hiPSCs.

16. The method of any one of claims 1-15, wherein the base medium has an osmolality of about 180 mOsm/kg to about 250 mOsm/kg, optionally wherein the base medium comprises sodium chloride at about 3 mg/mL, sodium bicarbonate at about 2.2 mg/mL, and has

an osmolality of about 200 mOsm/kg, and optionally wherein the base medium comprises glucose at about 4.5 mg/mL.

17. The method of any one of claims 1-16, wherein the low osmolality medium has an osmolality of about 220-240 mOsm/kg, optionally wherein the low osmolality medium has an osmolality of about 225-235 mOsm/kg, and optionally wherein the low osmolality medium has an osmolality of about 233 mOsm/kg.

18. The method of any one of claims 1-17, wherein:

(a) the supplements comprise:

(i) F-12 medium;

(ii) N2 supplement;

(iii) NEUROBASAL medium;

(iv) B-27 supplement;

(v) L-glutamine;

(vi) 2-mercaptoethanol; or

(vii) any combination of (i) to (vi);

(b) the LIF polypeptide is a human LIF (hLIF) polypeptide;

(c) the GSK3 inhibitor comprises CHIR99021;

(d) the MEK inhibitor comprises PD0325901; or

(e) any combination of (a) to (d),

optionally wherein the hiPSCs are cultured on MATRIGEL, newborn human foreskin fibroblast (NuFF) feeder cells, or GELTREX.

19. The method of any one of claims 1-18, wherein the low osmolality medium comprises F-12 medium and NEUROBASAL medium.

20. The method of any one of claims 1-19, wherein the low osmolality medium comprises inhibitors consisting essentially of a glycogen synthase kinase 3 (GSK3) inhibitor and a MEK inhibitor.

21. The method of any one of claims 1-20, wherein the low osmolality medium comprises base medium at about 24.75% (v/v), F-12 medium at about 24.75% (v/v), N2

supplement at about 0.5% (v/v), NEUROBASAL medium at about 49% (v/v), B-27 supplement at about 1% (v/v), L-glutamine at about 2 mM, 2-mercaptoethanol at about 0.1 mM, hLIF at about 100 units/mL, CHIR99021 at about 3 μM, and PD0325901 at about 0.5 μM, optionally wherein the hiPSCs are cultured on MATRIGEL, newborn human foreskin fibroblast (NuFF) feeder cells, or GELTREX.

22. The method of any one of claims 1-21, wherein the low osmolality medium does not comprise one or more of the following: bFGF supplement; TGF-β1 supplement; JNK inhibitor; p38 inhibitor; ROCK inhibitor; and PKC inhibitor.

23. The method of claim 22, wherein the low osmolality medium does not comprise bFGF supplement.

24. The method of any one of claims 1-23, wherein the hiPSCs are naïve hiPSCs that display a morphology characterized by compact, dome-shaped colonies.