CLAIMS

What is claimed is:

1. A method of inducing formation of a human colon organoid (HCO), comprising the steps of
    a. contacting a definitive endoderm (DE) with an FGF signaling pathway activator and a WNT signaling pathway activator for a period of time sufficient for said DE to form a mid-hindgut spheroid;
    b. contacting the mid-hindgut spheroid of step (a) with a BMP activator and an EGF signaling pathway activator for about 1 day to about 3 days; and
    c. contacting the mid-hindgut spheroid of step (b) with an EGF signaling pathway activator without a BMP activator for a period of time sufficient to form said human colon organoid, wherein said human colon organoid expresses SATB2.
2. The method of claim 1, wherein said DE is derived from a precursor cell selected from an embryonic stem cell, an induced pluripotent stem cell, a mesoderm cell, a definitive endoderm cell, a posterior endoderm cell, a hindgut cell or combinations thereof.
3. The method of claim 1 or 2, wherein said FGF signaling pathway activator is selected from a small molecule FGF signaling pathway activator, a protein-based FGF signaling pathway activator, FGF1, FGF2, FGF3, FGF4, FGF10, FGF11, FGF12, FGF13, FGF14, FGF15, FGF16, FGF17, FGF18, FGF19, FGF20, FGF21, FGF22, FGF23, or combinations thereof.
4. The method of any one of claims 1 to 3, wherein said WNT signaling pathway activator is selected from a protein Wnt signaling pathway activator, a small molecule Wnt signaling pathway activator or combinations thereof.
5. The method of cany one of claims 1 to 4, wherein said BMP activator is selected from BMP2, BMP4, BMP7, BMP9, a small molecule that activates

the BMP pathway, a protein that activates the BMP pathway, ventromorphins, and combinations thereof.

6. The method of any one of claims 1 to 5, wherein said period of time sufficient for said DE to form a mid-hindgut spheroid is determined by expression of CDX2 by said mid-hindgut spheroid of step (a).
7. The method of any one of claims 1 to 6, wherein said period of time sufficient for said mid-hindgut spheroid to form said human colon organoid is determined by expression of SATB2 and CDX2 by a cell of said human colon organoid.
8. The method of any one of claims 1 to 7, wherein said HCO comprises colonic enteroendocrine cells (EEC).
9. The method of any one of claims 1 to 8, wherein said HCO comprises of crypts and is free of villi.
10. The method of any one of claims 1 to 9, wherein said HCO comprises colon-specific goblet cells.
11. The method of any one of claims 1 to 10, wherein said HCO is substantially free of Paneth cells.
12. The method of any one of claims 1 to 11, wherein said HCO secretes colon-specific hormone INSL5.
13. The method of any one of claims 1 to 12, wherein the WNT signaling pathway activator is selected from Lithium Chloride; 2-amino-4,6-disubstituted pyrimidine (hetero) arylpyrimidines; IQ1; QS11; NSC668036; DCA beta-catenin; 2-amino-4-[3,4-(methylenedioxy)-benzyl-amino]-6-(3-methoxyphenyl) pyrimidine; Wnt1, Wnt2, Wnt2b, Wnt3, Wnt3a, Wnt4, Wnt5a, Wnt5b, Wnt6, Wnt7a, Wnt7b, Wnt8a, Wnt8b, Wnt9a, Wnt9b, Wnt10a, Wnt10b, Wnt11, Wnt16, a GSK3 inhibitor, and CHIR99021.
14. The method of any one of claims 1 to 13, wherein the WNT signaling pathway activator is CHIR99021.

15. The method of any one of claims 1 to 14, wherein said contacting the mid-hindgut spheroid of step (b) with a BMP activator and an EGF signaling pathway activator is for about 3 days.
16. The method of any one of claims 1 to 15, wherein said FGF signaling pathway activator is FGF4.
17. The method of claim 16, wherein said FGF4 is provided at a concentration of about 200-1000 ng/mL.
18. The method of claim 16 or claim 17, wherein said FGF4 is provided at a concentration of about 500 ng/mL.
19. The method of any one of claims 14 to 18, wherein said CHIR99021 is provided at a concentration of about 1-50 μM.
20. The method of any one of claims 14 to 19, wherein said CHIR99021 is provided at a concentration of about 3 μM.
21. The method of any one of claims 1 to 20, wherein said BMP activator is BMP2.
22. The method of claim 21, wherein said BMP2 is provided at a concentration of about 50-500 ng/mL.
23. The method of claim 21, wherein said BMP2 is provided at a concentration of about 100 ng/mL.
24. The method of any one of claims 1 to 23, wherein said EGF signaling activator is selected from EGF, TGF alpha, HB-EGF, Amphiregulin, Epigen, Betacellulin, and small molecules such as db-cAMP, and combinations thereof.
25. The method of claim 24, wherein said EGF signaling pathway activator is EGF.
26. The method of claim 25, wherein said EGF is provided at a concentration of about 50-500 ng/mL.
27. The method of claim 25 or claim 26, wherein said EGF is provided at a concentration of about 100 ng/mL.

28. The method of claim 15, wherein the FGF signaling pathway activator is FGF4, the WNT signaling pathway activator is CHIR99021, the BMP activator is BMP2, and the EGF signaling pathway activator is EGF.
29. The method of claim 28, wherein the DE is derived from an induced pluripotent stem cell.
30. The method of claim 28, wherein the FGF4 is provided at a concentration of about 500 ng/mL, the CHIR99021 is provided at a concentration of about 3 μM, the BMP2 is provided at a concentration of about 100 ng/mL, and the EGF is provided at a concentration of about 100 ng/mL.
31. The method of claim 30, wherein the DE is derived from an induced pluripotent stem cell.