

**Supplementary Fig. 1:**

- (A) Genotyping analysis of the NOD-*scid Il2rg*<sup>-/-</sup> EPS or cEPS cells. ICR: ICR strain EPS cell lines.
- (B) Karyotyping analysis of ES cell lines under 2i/LIF condition (passage 22 and 23). Red boxes indicate abnormal chromosome. Each cell line counts 30 cells.
- (C) qRT-PCR analysis of pluripotent gene expression in NOD-*scid Il2rg*<sup>-/-</sup> EPS and cEPS cells. Error bars indicate SEM (n = 2).
- (D) Schematic of *Tdtomato* reporter knock-in to label NOD-*scid Il2rg*<sup>-/-</sup> EPS and cEPS cells.
- (E) Representative images of TD<sup>+</sup> EPS and cEPS colonies after nucleofection with pX330 plasmid and targeting vector. Scale bar, 50 μm.
- (F) The bar chart showing the percentage of chimeras with NOD-*scid Il2rg*<sup>-/-</sup> EPS or cEPS cells contributing to the embryo, yolk sac and placenta in vivo at E13.5. n indicates numbers of E13.5 fetuses.
- (G) Images of primary colonies of ICR and 129×OG strains at the end of the chemical induction (day 40) and the cEPS colonies for P9 and P7 passages respectively.

**Supplementary Fig. 2:**

- (A) Schematic of human *IL-6* expression cassette targeting mouse *IL-6* in NOD-*scid Il2rg*<sup>-/-</sup> EPS cells.
- (B) Genomic PCR of human *IL-6* inserted NOD-*scid Il2rg*<sup>-/-</sup> EPS cells to identify correct targeted colonies. HDR5 and HDR3: homologous arm fragments; Human *IL-6*: human *IL-6* fragments.
- (C) Phase-contrast images of human *IL-6* inserted NOD-*scid Il2rg*<sup>-/-</sup> EPS cells for 15 passages in LCDM medium. Scale bars, 100 μm.
- (D) Postnatal chimeras generated by injection of human *IL-6* inserted NOD-*scid Il2rg*<sup>-/-</sup> EPS cells into C57BL/6 8-cell embryo.
- (E) ELISA analysis of human IL-6 level in chimera after LPS stimulation.