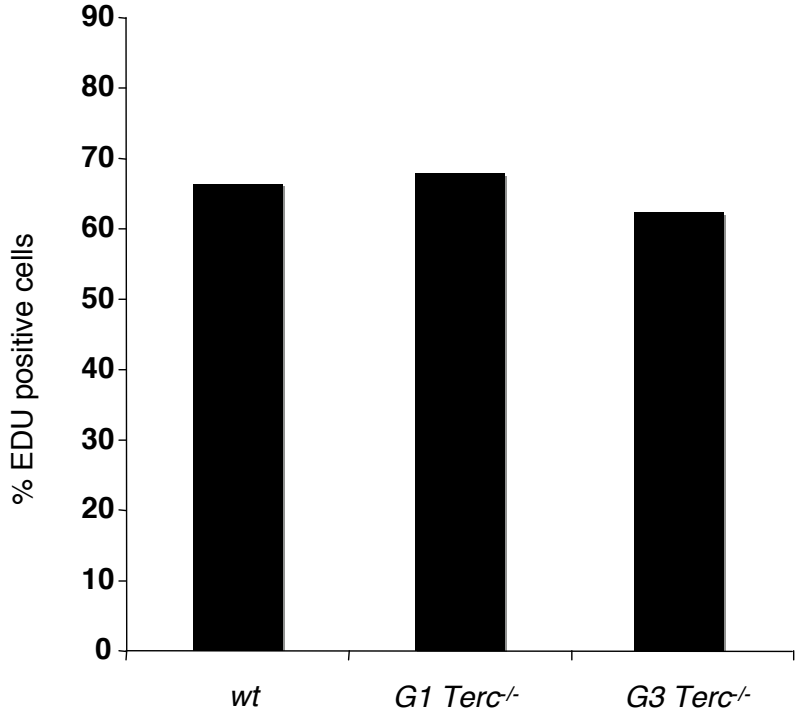
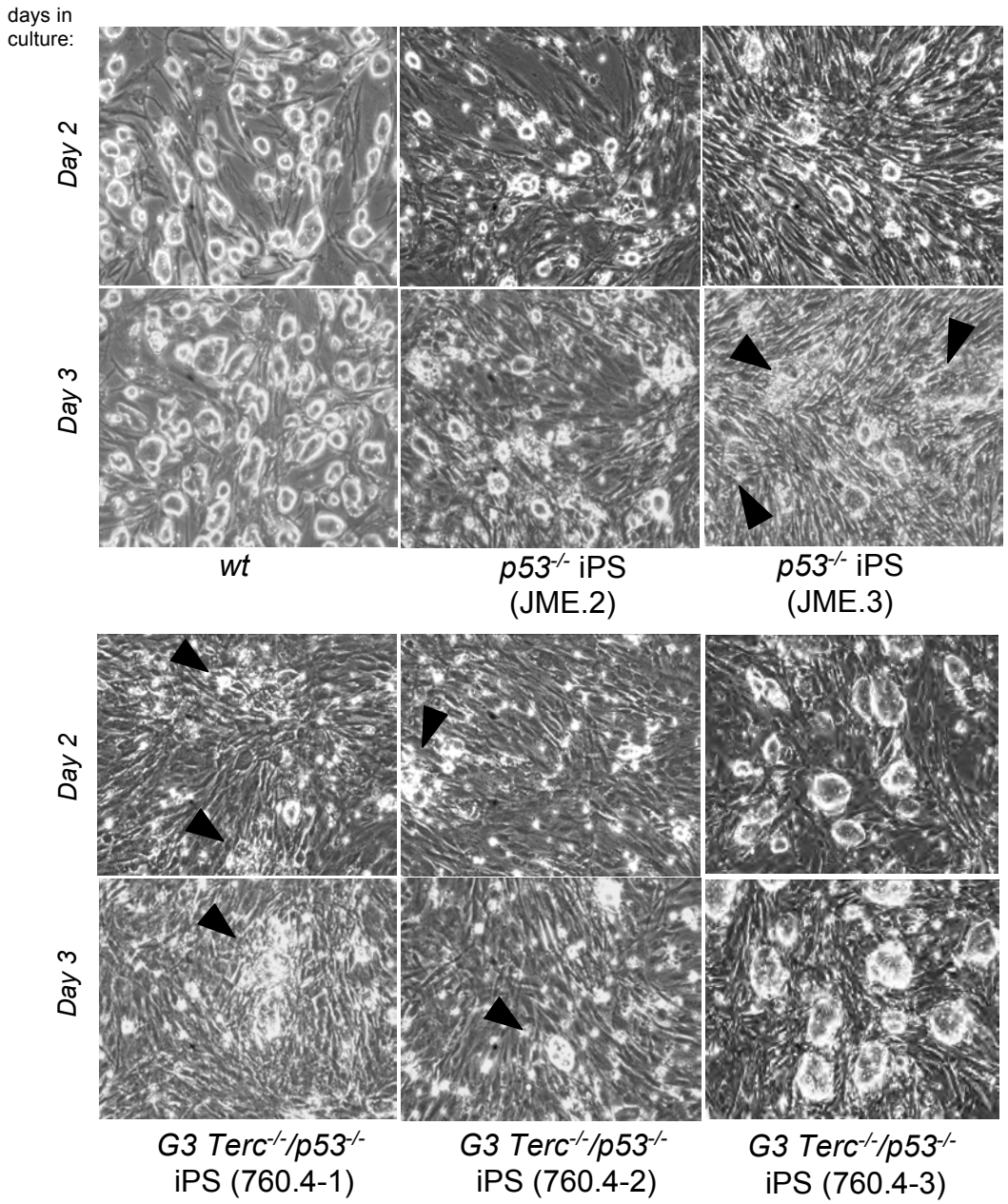
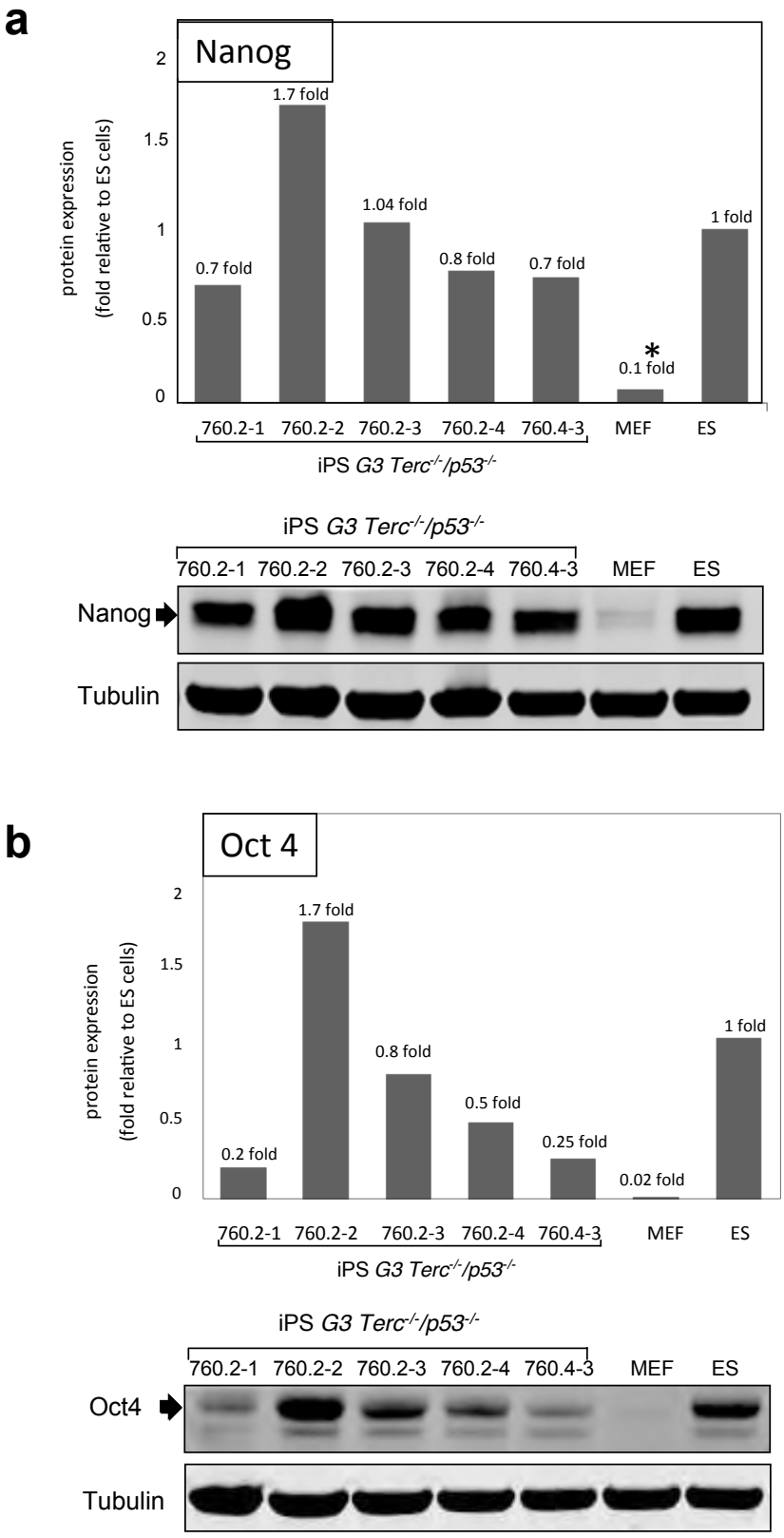
SUPPLEMENTARY INFORMATION



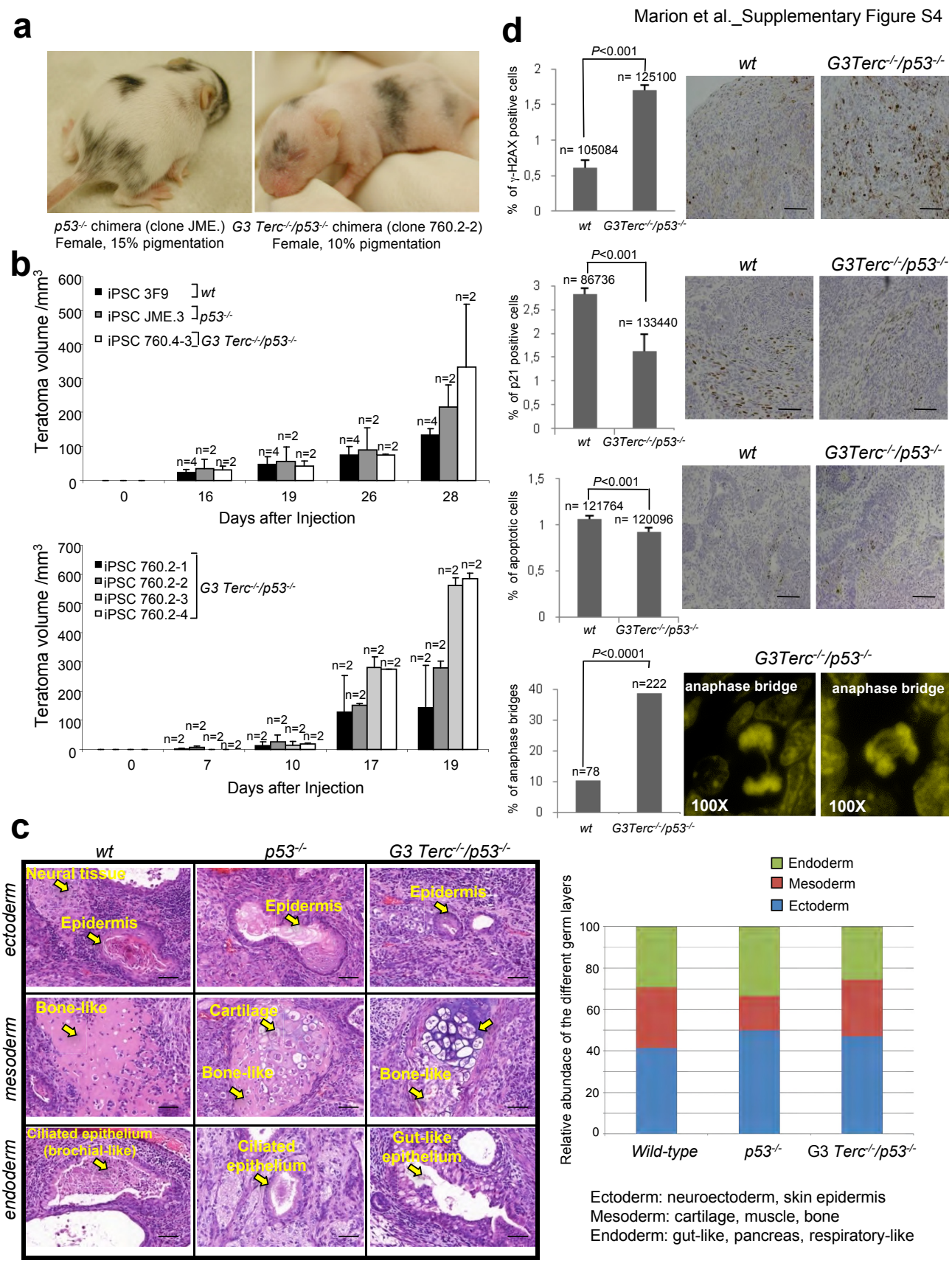
Supplementary Figure S1. Proliferation rates in G1 and G3 Terc-deficient MEF. *Wild-type*, G1 *Terc*$^{-/-}$ and G3 *Terc*$^{-/-}$ MEFs were incubated with EdU (5-ethynyl-2'-deoxyuridine) overnight. The cells were then fixed and stained to detect the incororated EdU by FACS. Bars represent percentage of cells that had incorporated EdU for each genotype.



Supplementary Figure S2. Decreased stability upon expansion of p53$^{-/-}$ and G3 *Terc*$^{-/-}$ */p53*$^{-/-}$ iPSC clones. Representative images of iPSC of the indicated genotypes cultured on feeder layers. Note that in contrast to wild-type iPSC colonies with a typical rounded morphology, *p53*-null genotypes show iPSC colonies surrounded by fibroblast-looking cells, which appear to differentiate from them. Furthermore, some *p53*-null iPSC colonies show a flat appearance (arrow heads). Numbers in brackets identify individual iPSC clones. Days 2 and 3 indicate days of culturing.



Supplementary Figure S3. Robust expression of Nanog and Oct-4 in G3 *Terc*$^{-/-}$/*p53*$^{-/-}$ iPSC clones used for chimera generation and teratoma formation. ***a,b***. Expression of endogenous pluripotency markers Nanog and Oct-4 in iPSC of the indicated genotypes. Quantification was performed after correcting by tubulin levels. Numbers in identify individual iPSC clones. Asterisk indicates that detectable Nanog expression MEF is the consequence of well-leakage in the gel.



Supplementary Figure S4. Chimeras and teratomas from *p53*$^{-/-}$ and G3 *Terc*$^{-/-}$/*p53*$^{-/-}$ iPSC. ***a.*** Chimeras from the indicated iPSC. ***b***. Teratoma growth from the indicated iPSC. n= teratomas analyzed per iPSC clone. ***c***. Left, teratomas show tissues from the three germ layers (ectoderm, mesoderm & endoderm). Scale bar, 50μm. Right, relative abundance of

tissues derived from each of the three germ layers (ectoderm, mesoderm & endoderm) in iPSC-derived teratomas of the indicated genotypes. The microscopic examination revealed ectodermal derivatives (brain, epidermis and associated structures), mesoderm (cartilage, bone, smooth and striated muscle) and endoderm (gastrointestinal tract and respiratory like tissues, pancreas). ***d***. Left, percentage of teratoma cells positive for γH2AX, p21, and apoptosis out of total cells analyzed (n). Percentage of anaphase bridges out of total anaphases observed (n). Chi-square test was used for statistics. Error bars, standard error. Right, images of teratoma stainings. Scale bar, 200μm.

Reprogramming efficiencies

Cell type	Reprogramming Efficiency (average)	n	St. Error
wt (MEF)	0.00724129	3	0.0005013
p53$^{-/-}$ (MEF)	0.02715027	3	0.0102065
G3 *Terc$^{-/-}$/p53$^{-/-}$ (MEF)*	0.04391208	3	0.0101065
G3 *Terc$^{-/-}$ (MEF)*	0.00081474	3	0.0003859
BJ (human primary)	0.00685564	2	0.0000659
BJ/shp53 (human primary)	0.06935798	2	0.0016537
3F *ctrl. (wt MEF*)	0.00592718	2	0.0002822
3F + UV *(wt MEF*)	0.00422289	2	0.0003491
3F + IR *(wt MEF*)	0.00323670	2	0.0004624
3F + shp53.*ctrl (wt MEF*)	0.00842741	2	0.0006360
3F + shp53 + UV *(wt MEF*)	0.00845060	2	0.0000660
3F + shp53 + IR *(wt MEF*)	0.00791164	2	0.0000783
3F + Bcl2.*ctrl (wt MEF*)	0.00720988	2	0.0001975
3F + Bcl2 + UV *(wt MEF*)	0.00663076	2	0.0003529
3F + Bcl2 + IR *(wt MEF*)	0.00689157	2	0.0001446
wt (MEF)	0.00221687	2	0.0001747
53BP1$^{-/-}$ (MEF)	0.00091783	1	
ATM$^{-/-}$ (MEF)	0.00051399	2	0.0002037

Supplementary Table 1. Summary of reprogramming efficiencies. Reprogramming efficiency is calculated as the number of alkaline phosphatase (AP) positive colonies normalized by infection efficiency and divided by the initial number of cells.

Infection efficiency is measured by GFP expression level in assays with the 3 Factors plus GFP, all in equal proportions of retroviral supernatants, and using FACS analysis (for details see Methods).

"n" refers to independent number of cultures and at least 2-4 independent reprogramming experiments were carried out for each culture.

Microinjection in B6-*tyr*$^{C-2J}$ blastocysts

Genotype (iPS clone)	Blastocysts Injected	Cells injected	Blastocysts Transferred	Pups born	Chimeras Sex (% pigmentation)
***p53-/-* iPSC (JME.3)**	33	5-8	33	8 +11 reabsortions	1F(15%)* 2M(<1%) 3F(<1%)
G3 *Terc-/-/p53-/-* iPSC (760.2-2)	49	5-7	49	7	1F(10%) died at 14 days
G3 *Terc-/-/p53-/-* iPSC (760.2-3)	27	5-7	27	33	No chimeras

Supplementary Table 2. Generation of chimeras from *p53*$^{-/-}$ and *Terc*$^{-/-}$/*p53*$^{-/-}$ iPSC clones. All the iPSC used for microinjection expressed Nanog and Oct-4 (see Supplementary Figure S3).

*Germ-line transmission.