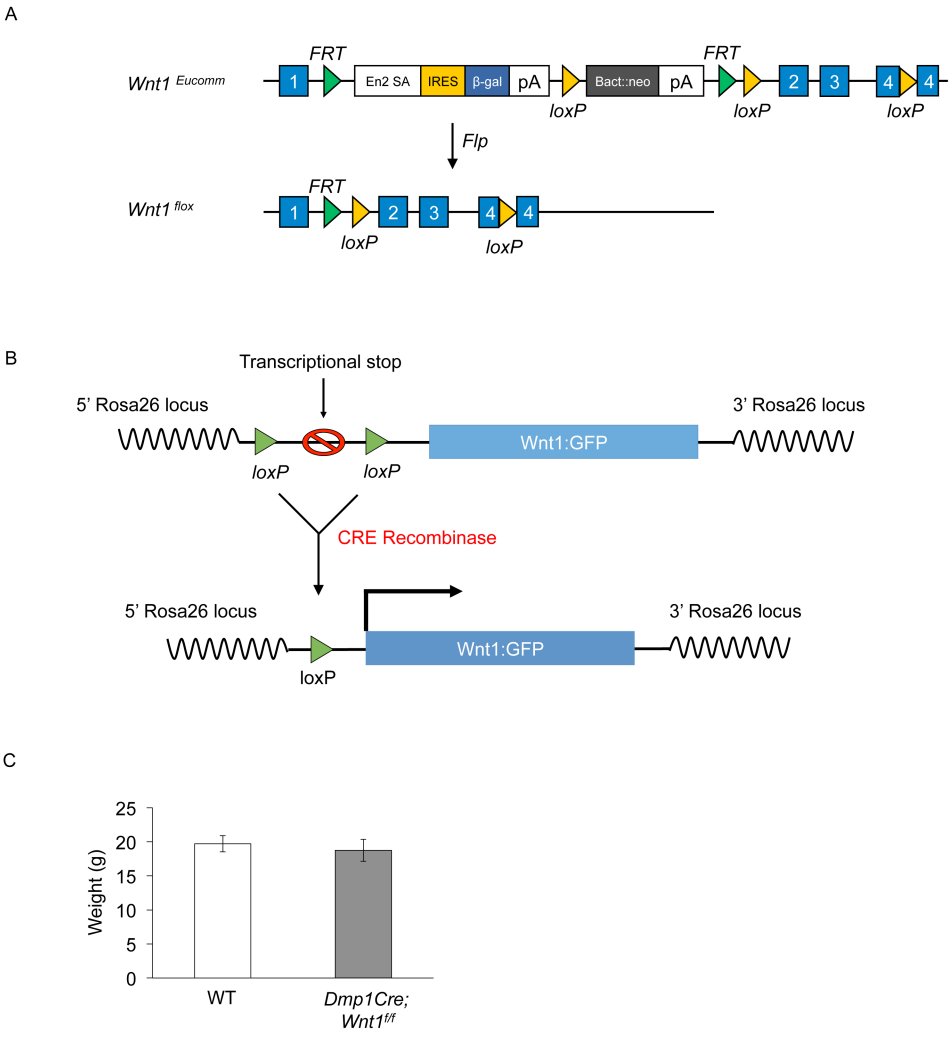
Supplementary Table1. Serum CTX assay of all genetic mouse models

Table S1. Bone resorption parameter- serum CTX-I

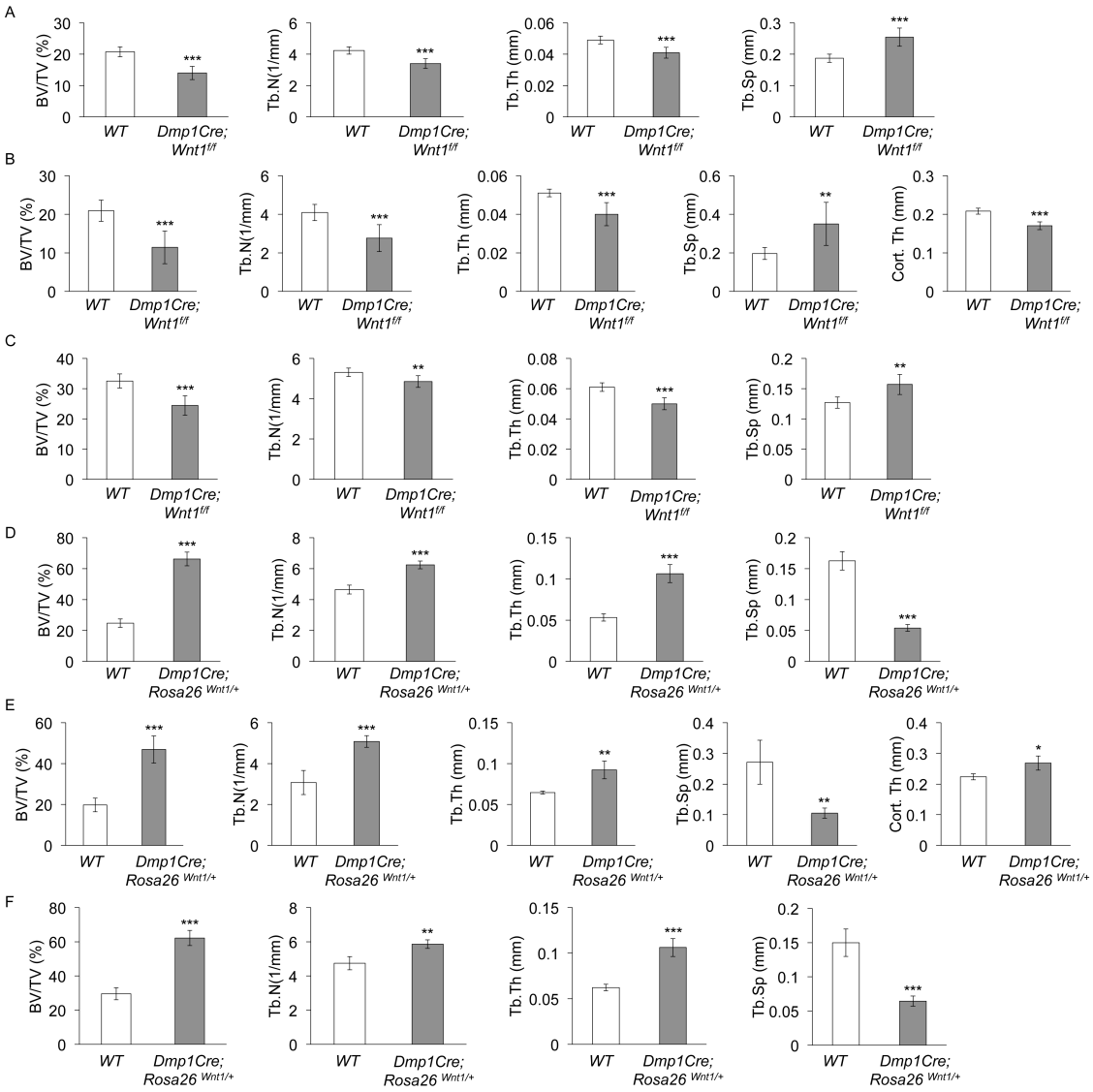
Groups	CTX-I	
WT (n=5)	25.74±6.77	
Dmp1Cre; Wnt1$^{f/f}$ (n=5)	23.75±4.2	
WT (n=4)	16.97±8.48	**
Dmp1Cre; Rosa26 $^{Wnt1/+}$ (n=4)	37.83±7.2	
WT (Vehicle treated) (n=5)	41.47±14.9	
Dmp1Cre; Rosa26 $^{Wnt1/+}$ (Vehicle treated) (n=4)	40.31±15.93	
WT (Rapamycin treated) (n=5)	61.33±23.51	
Dmp1Cre; Rosa26 $^{Wnt1/+}$ (Rapamycin treated) (n=4)	68.87±26.41	
WT (n=5)	25.49±11.74	
Dmp1Cre; Tsc1 $^{f/f}$ (n=4)	36.69±10.9	
Wnt1 $^{sw/sw}$ (n=5)	33.52±10	
Dmp1Cre; Tsc1 $^{f/f}$; Wnt1 $^{sw/sw}$ (n=5)	28.48±8.57	
WT (Vehicle treatment) (n=7)	19.85±6.97	**
WT (Scl-Ab treatment) (n=4)	35.48±6.83	
Wnt1 $^{sw/sw}$ (Vehicle treatment) (n=8)	35.02±6.66	
Wnt1 $^{sw/sw}$ (Scl-Ab treatment) (n=8)	33.34±5.46	

Data is presented as mean±standard deviation. *P<0.05, **P<0.01, ***P<0.001



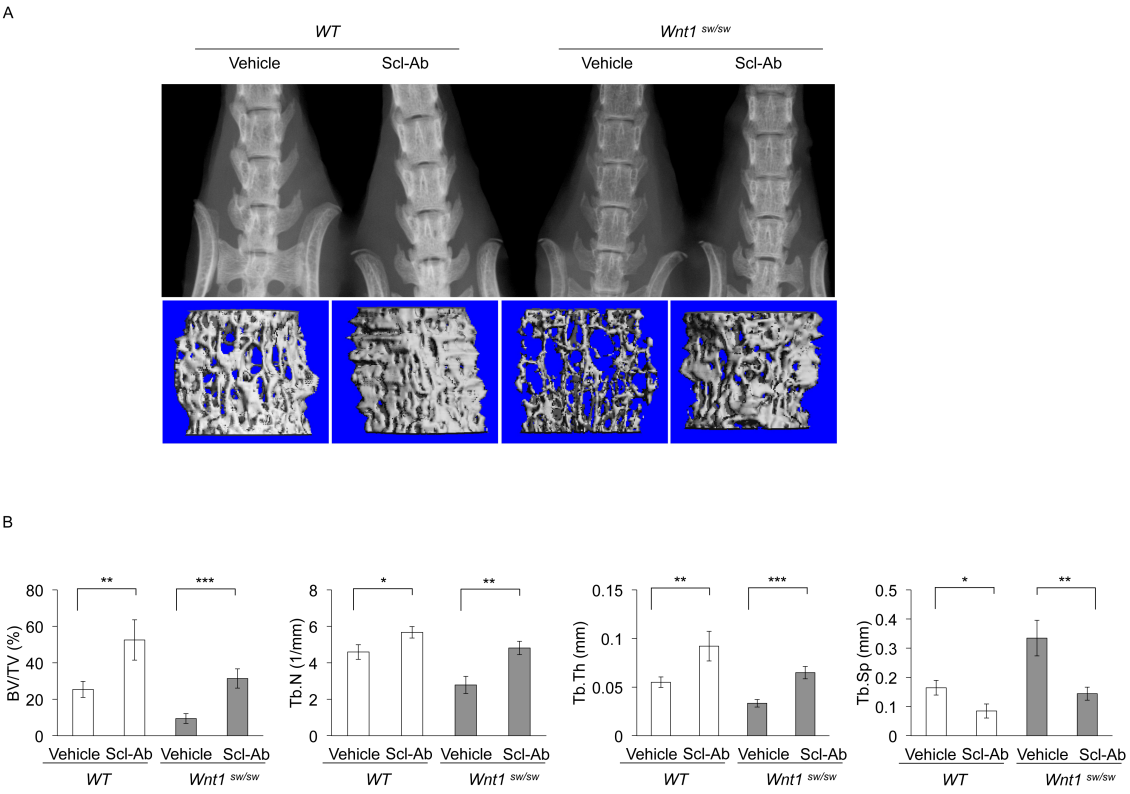
Supplementary Figure 1. Generation of a *Wnt1* conditional knockout mouse model and the construct of the *Rosa26-Wnt1* mouse model. (A) First, a knockout-first mouse carrying European Conditional Mouse Mutagenesis (EUCOMM) allele (*Wnt1*^{EUCOMM}) was generated. Then, *Wnt1*^{EUCOMM} was crossed with Rosa26-Flippase (*Flp*) mice to delete β-gal and the neo cassette, which results in generation of conditional knockout allele (*Wnt1*$^{f/f}$). (B) In *Rosa26*$^{Wnt1/+}$ mice, the *Wnt1::GFP* construct was knocked in *Rosa26* locus with transcriptional stop signal flanked by *loxP* site. (C) Body weight of female WT and *Dmp1Cre; Wnt1*$^{f/f}$ mice at two months old. Results are shown as

means±SDs (n=9 per group). The comparison between WT versus mutant mouse is determined by Student's *t*-test. *P<0.05, **P<0.01, ***P<0.001



Supplementary Figure 2. The phenotypes of bone-specific *Wnt1* loss-of-function (*Dmp1Cre; Wnt1$^{f/f}$*) and gain-of-function (*Dmp1Cre; Rosa26$^{Wnt1/+}$*) mouse models. (A) μCT analysis of female WT and *Dmp1Cre; Wnt1$^{f/f}$* mice; L4 vertebrae for bone volume/total volume (BV/TV), trabecular number (Tb. N), trabecular thickness (Tb. Th), trabecular space (Tb. Sp), and cortical bone for cortical thickness (Cort. Th). Results are shown as means±SDs (n=8 per group). (B) μCT analysis of male WT and *Dmp1Cre; Wnt1$^{f/f}$* mice; femoral trabecular bone for bone volume/total volume (BV/TV), trabecular number (Tb. N), trabecular thickness (Tb. Th), trabecular space (Tb. Sp), and cortical

bone for cortical thickness (Cort. Th). Results are shown as means±SDs (n=7 per group). (C) μCT analysis of male WT and *Dmp1Cre; Wnt1*$^{f/f}$ mice; L4 vertebrae for bone volume/total volume (BV/TV), trabecular number (Tb. N), trabecular thickness (Tb. Th), trabecular space (Tb. Sp), and cortical bone for cortical thickness (Cort. Th). Results are shown as means±SDs (n=7 per group). (D) μCT analysis of female WT and *Dmp1Cre; Rosa26*$^{Wnt1/+}$ mice; L4 vertebrae for bone volume/total volume (BV/TV), trabecular number (Tb. N), trabecular thickness (Tb. Th), trabecular space (Tb. Sp), and cortical bone for cortical thickness (Cort. Th). Results are shown as means±SDs (n=6 per group). (E) μCT analysis of male WT and *Dmp1Cre; Rosa26*$^{Wnt1/+}$ mice; femoral trabecular bone for bone volume/total volume (BV/TV), trabecular number (Tb. N), trabecular thickness (Tb. Th), trabecular space (Tb. Sp), and cortical bone for cortical thickness (Cort. Th). Results are shown as means±SDs (n= 4 per group). (F) μCT analysis of male WT and *Dmp1Cre; Rosa26*$^{Wnt1/+}$ mice; L4 vertebrae for bone volume/total volume (BV/TV), trabecular number (Tb. N), trabecular thickness (Tb. Th), trabecular space (Tb. Sp), and cortical bone for cortical thickness (Cort. Th). Results are shown as means±SDs (n= 4 per group). The comparison between WT versus mutant mouse is determined by Student's *t*-test. *P<0.05, **P<0.01, ***P<0.001



Supplementary Figure 3. Phenotypic corrections of *Wnt1*$^{sw/sw}$ mice after treatment with Sclerostin-neutralizing antibody (Scl-Ab) in L4 vertebrae. (A) X-ray radiograph and μCT image of L4 vertebrae of WT and *Wnt1*$^{sw/sw}$ mice treated with vehicle control or Scl-Ab. (B) μCT analysis of L4 vertebrae for bone volume/total volume (BV/TV), trabecular number (Tb.N), trabecular thickness (Tb.Th) and trabecular space (Tb.Sp) in WT and *Wnt1*$^{sw/sw}$ mice treated with vehicle control or Scl-Ab. Results are shown as means±SDs (n=7 for WT, n=3 for WT with Scl-Ab, n=8 for *Wnt1*$^{sw/sw}$, n=7 for *Wnt1*$^{sw/sw}$ with Scl-Ab). The comparisons between WT mice with vehicle versus Scl-Ab treatment and *Wnt1*$^{sw/sw}$ mice with vehicle versus Scl-Ab treatment are determined by Mann-Whitney U test. *P<0.05, **P<0.01, ***P<0.001