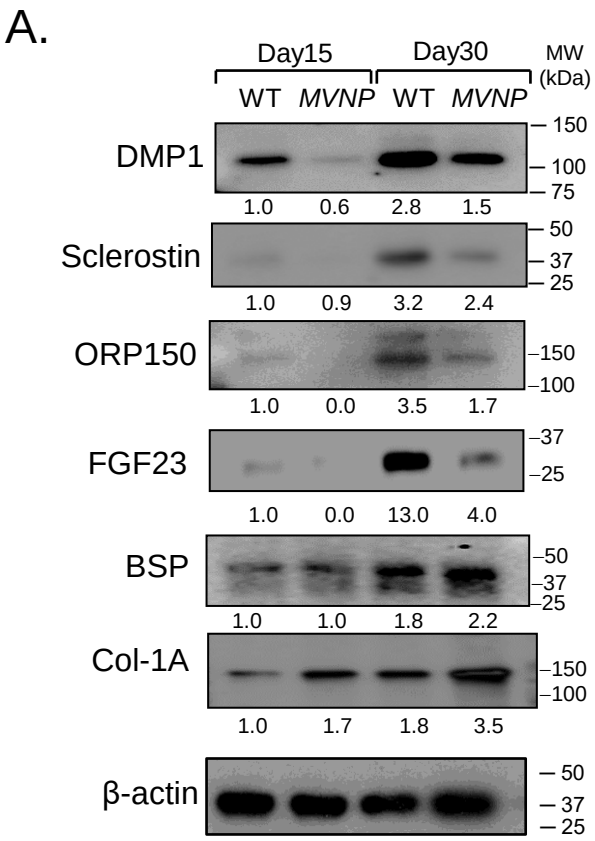
**Supplemental Methods:**

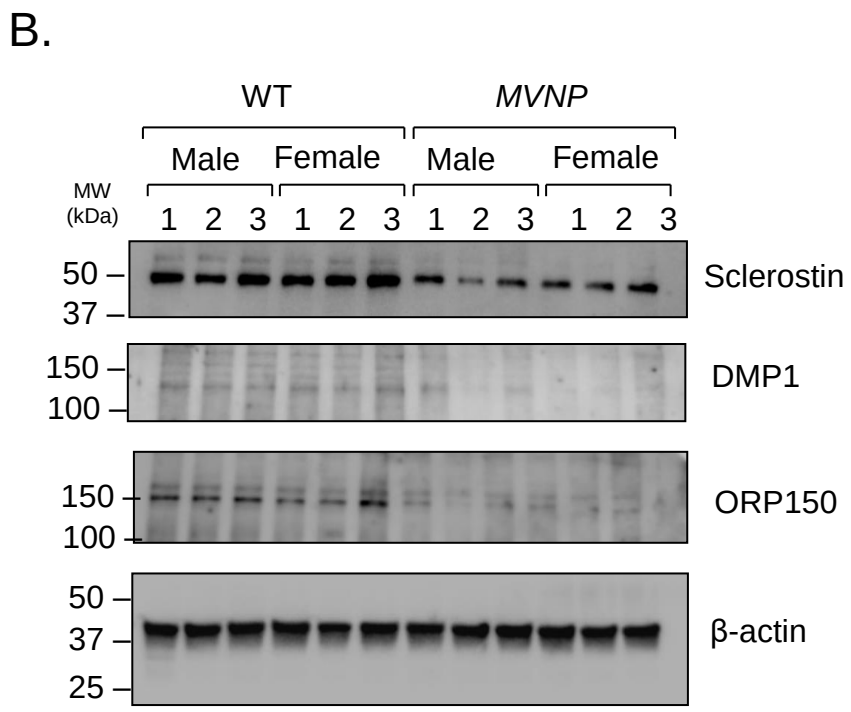
To distinguish osteocytic from osteoblastic cells (OBL), a series of marker genes were examined (Robling and Bonewald, 2020; Guo et al., 2010). OBL-selective ones were bone sialoprotein (BSP) and collagen 1a1 (Col-1a). OCy-selective ones were sclerostin (Sost), hypoxia-upregulated-1 (oxygen-regulated protein, ORP150), fibroblast growth factor 23 (FGF23) and dentinal matrix protein-1 (DMP-1). Osteocalcin is expressed in both late OBL and in OCys. Immunoblotting. Total proteins were extracted from OCLs, OBs, or OCys with RIPA buffer, and the cell lysates (10μg/lane) loaded onto Bio-Rad Mini-PROTEAN Precast Gels. The resolved proteins were transferred onto nitrocellulose membranes (TGX Membrane; Bio-Rad) using the Trans-Blot Turbo Transfer System (Bio-Rad). The membranes were stained with Ponceau S and cut into strips based on the molecular weight markers. Membranes were then exposed to primary antibodies overnight at 4°C and incubated with anti-IgG antibodies conjugated to horseradish peroxidase (HRP) for 1 hour. The blots were washed and specifically bound HRP was visualized by a Super Signal West Dura Extended Duration System (Cell Signaling). The following antibodies were used for detection of IGF1 (Abcam ab63926), IGF1R (Abcam ab39398), RANKL (Santa Cruz sc-59982), OPG (Abcam ab65943), BSP (Abcam ab125227), Col-1A (Millipore-Sigma AB765P), DMP1 (Novus Biological NRP1-45525), sclerostin (Abcam ab63097), ORP150 (Santa Cruz sc-398224), FGF23 (R&D Systems MAB2628), IIL-6 ( Santa Cruz sc-7920), β-actin (Abcam ab49900) and GAPDH (Cell Signaling Technology 3683). Secondary antibody-HRP conjugates were used an anti-rabbit Alexa488 (Invitrogen A11008). IGF1 ELISA assay. Serum IGF1 was measured using an ELISA kit for murine IGF1 (R&D system MG100) according to the manufacturer's instructions.

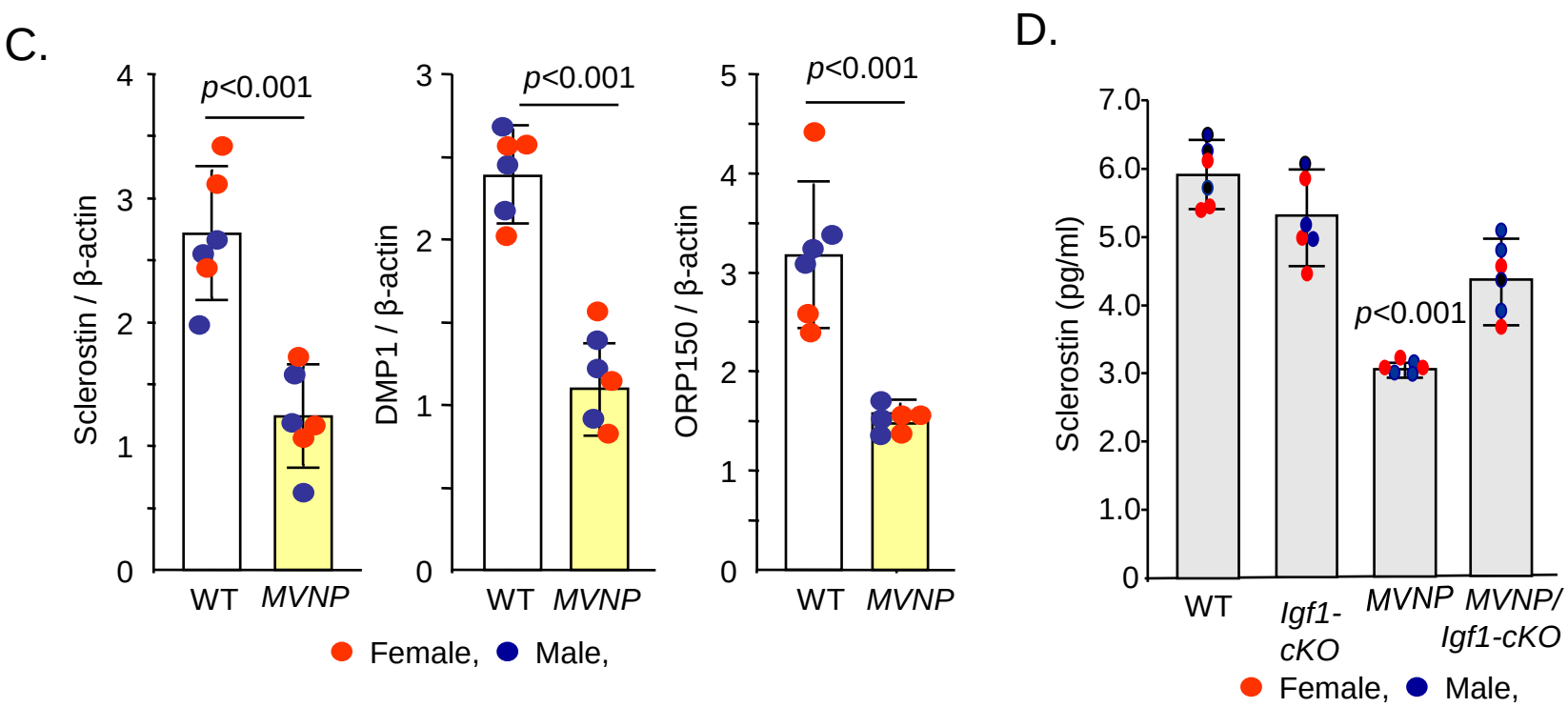
**Supplemental References:**

Guo D, Keightley A, Guthrie J, Veno PA, Harris SE, Bonewald LF. Identification of osteocyte-selective proteins. Proteomics. 2010 Oct;10(20):3688-98. doi: 10.1002/pmic.201000306. PMID: 20845334

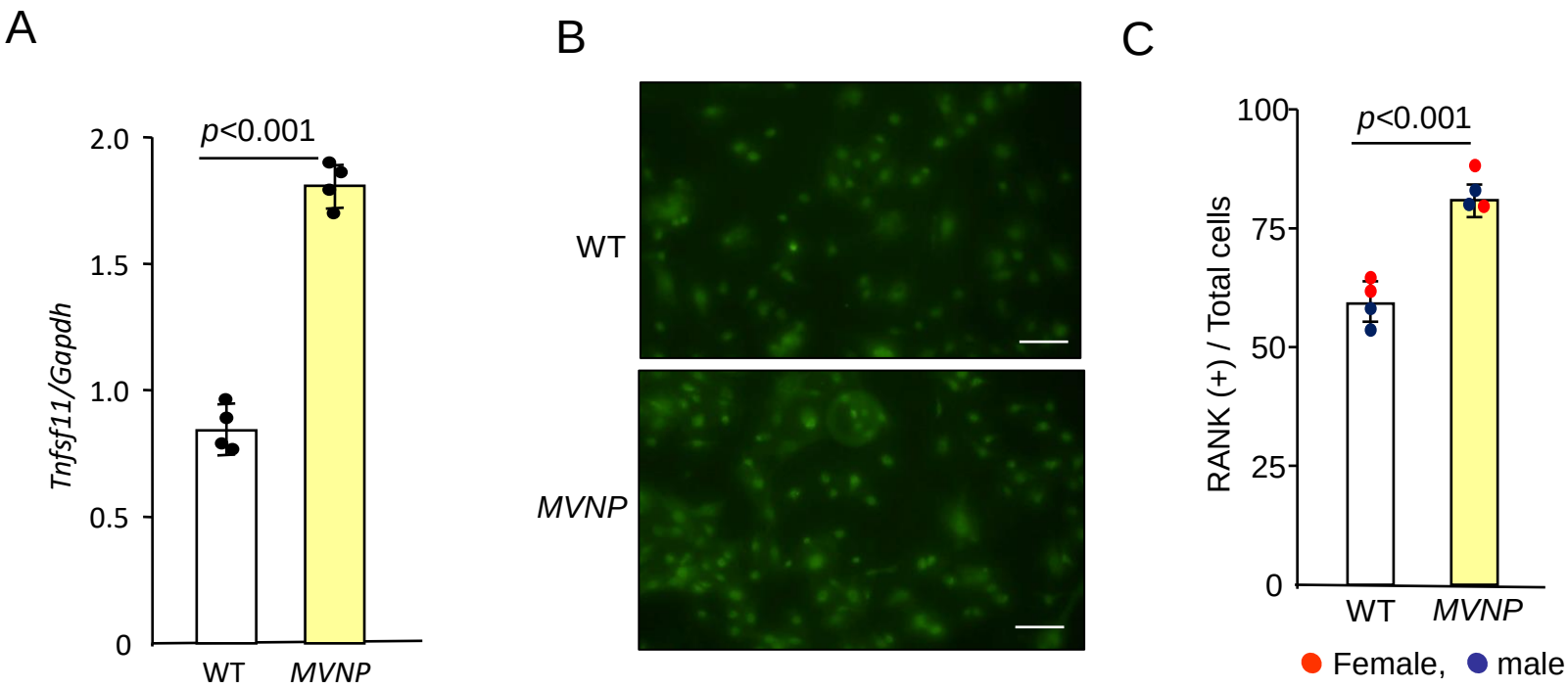
Robling AG, Bonewald LF. The Osteocyte: New Insights. Annu Rev Physiol. 2020 Feb 10;82:485-506. doi: 10.1146/annurev-physiol-021119-034332. PMID: 32040934



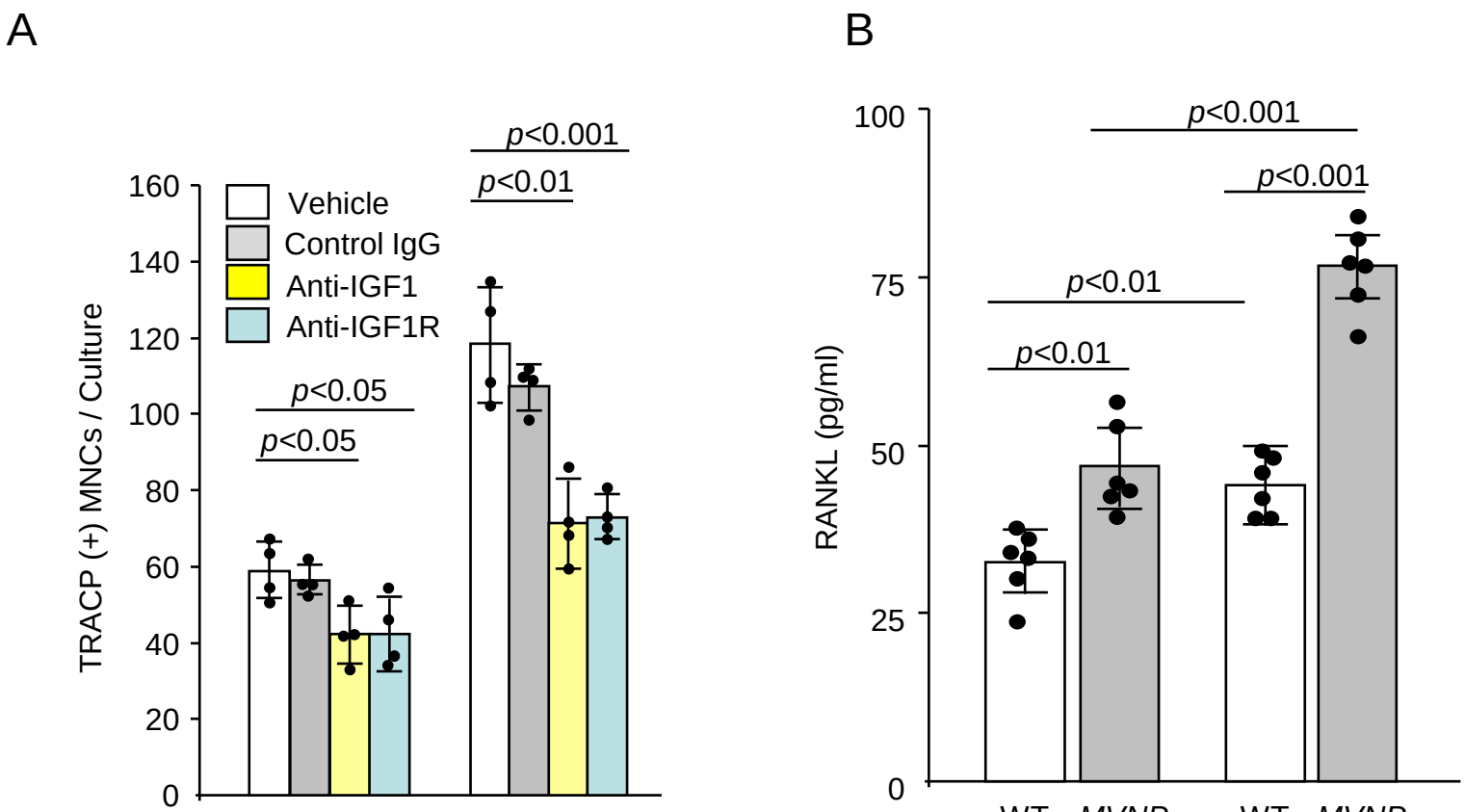



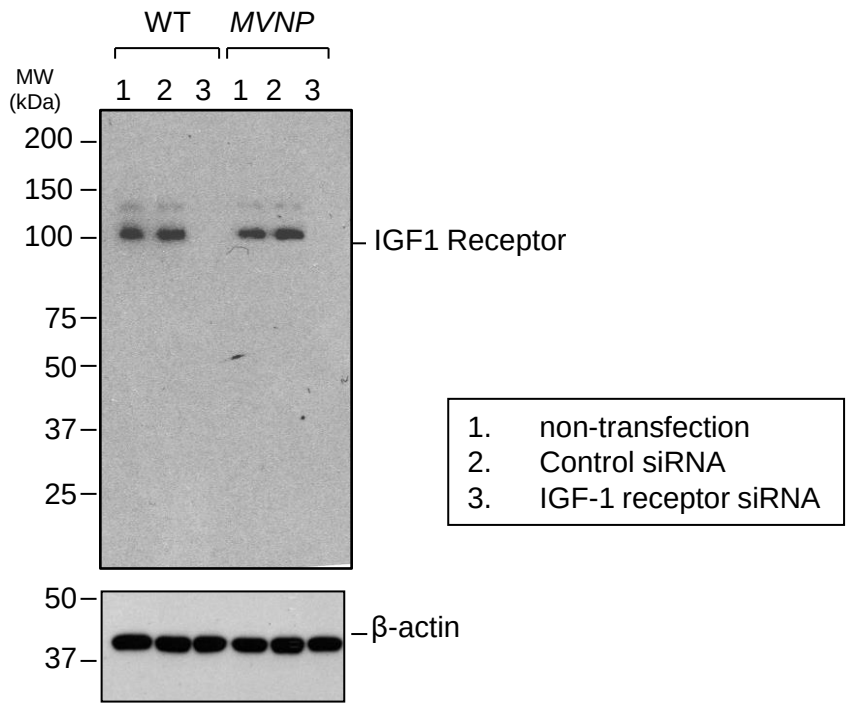

**Supplemental Figure 1.** The Characteristics of isolated OBs and OCys derived from bone outgrowth cells of 20 months old WT and *MVNP* mice. (**A**) The expression of OB (day 15 culture) and OCy (day 30 culture) markers in outgrowth cells. $1\times10^5$ cells /well were cultured with 10%FCS in αMEM for 72 hours. Cell lysates were collected with RIPA buffer. Protein expression was visualized by Western blotting using anti-DMP1, anti-sclerostin, anti-ORP150, anti-FGF23, anti-BSP and anti-Col-1A antibodies. β-actin was the loading control. (**B**) OCy markers in 30-day outgrowth cultures of bones from male and female WT and *MVNP* mice grown as in A. (**C**) Expression ratios for each protein/β-actin were quantitated by densitometric scanning the blots shown in B and analyzing with ImageJ software (NIH). This experiment was performed three times with different biological replicates. The results show mean ± SEM; red = female, and blue = male, analyzed by Mann-Whitney U-test. No statistical difference between male and female. (**D**) Sclerostin in conditioned media. OCy-like cells ($1\times10^5$ cells /ml) from 30-day outgrowth cells were cultured for 72 hours and assayed by ELISA. The results suggest that the 15-day outgrowth cells retain osteoblastic characteristics, while the 30-day ones display a more osteocytic phenotype




**Supplemental Figure 2**. RANKL mRNA and protein from primary OCys and OCy-Like cells. (**A**) *RANKL (Tnfsf11)* mRNA in primary OCys isolated by collagenase digestion form long bones of WT and *MVNP* 18-month-old and RNA isolated from $2\times10^6$ primary OCys. *Tnfsf11* expression was measured by TaqManTM PCR as describe in Methods. Data were shown the mean ± SEM (4 technical replicates from these mice) analyzed by Mann-Whitney U-test. (**B**) RANKL expression in primary OCys. Primary OCys were stained with anti-RANKL antibody and examined by immunofluorescence microscopy. Scale bars;10μm. (**C**) Percent of cells expressing RANKL: RANKL-positive/total OCys in equal squares ($700\times1050$ $\mu m^2$) from B. Representative data for male- (blue) and female- (red) derived cells, analyzed as in A. No statistical difference between male and female in each group. (**D**) RANKL protein in OCy-like cells from bone. $1\times10^5$ cells /ml were cultured with 10%FCS in αMEM for 72 hours and Western blotted using anti-RANKL antibody. β-actin was used as loading control. (**E**) Quantification of D, analysis as In C. There was no statistical difference between male and female groups.

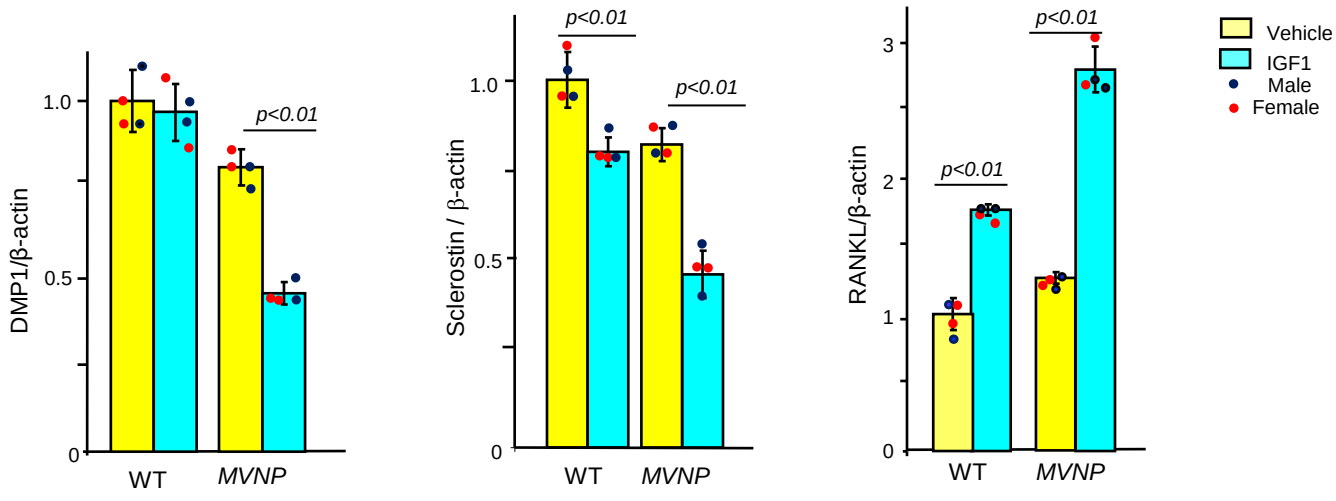



**Supplemental Figure 3**. (**A**) Autocrine stimulation of OCL formation by IGF1. OCL-precursors from CD11b-positive osteoclast precursors from 22-month-old male WT and *MVNP* mice ($5x10^4$ cells/well; 96 well plate) were treated with M-CSF (10 ng/ml) for 72 hours and cultured with RANKL (50 ng/ml) plus vehicle, rabbit IgG (20 ng/ml), anti-IGF1 (10 µg/ml) or anti-IGF1-receptor (0.5 µg/ml) for 72 hours. The cells were then stained for TRACP. The results were showed the mean ± SEM (n=4). The data were analyzed using a 1-way ANOVA with Tukey test. NS; not significant different. The assay was performed in triplicate and with cells from female mice; results were similar. (**B**) RANKL in conditioned media from OBs and OCy-like cells. Outgrowth cells ($1×10^5$ cells/ml; 12 well plate) were as in Supplemental Figure 1, cultured for 72 hours and conditioned media collected. RANKL ELISA results are shown as mean ± SEM (n=6) analyzed as in (A). The assay was performed on 2 biological replicates with similar results.

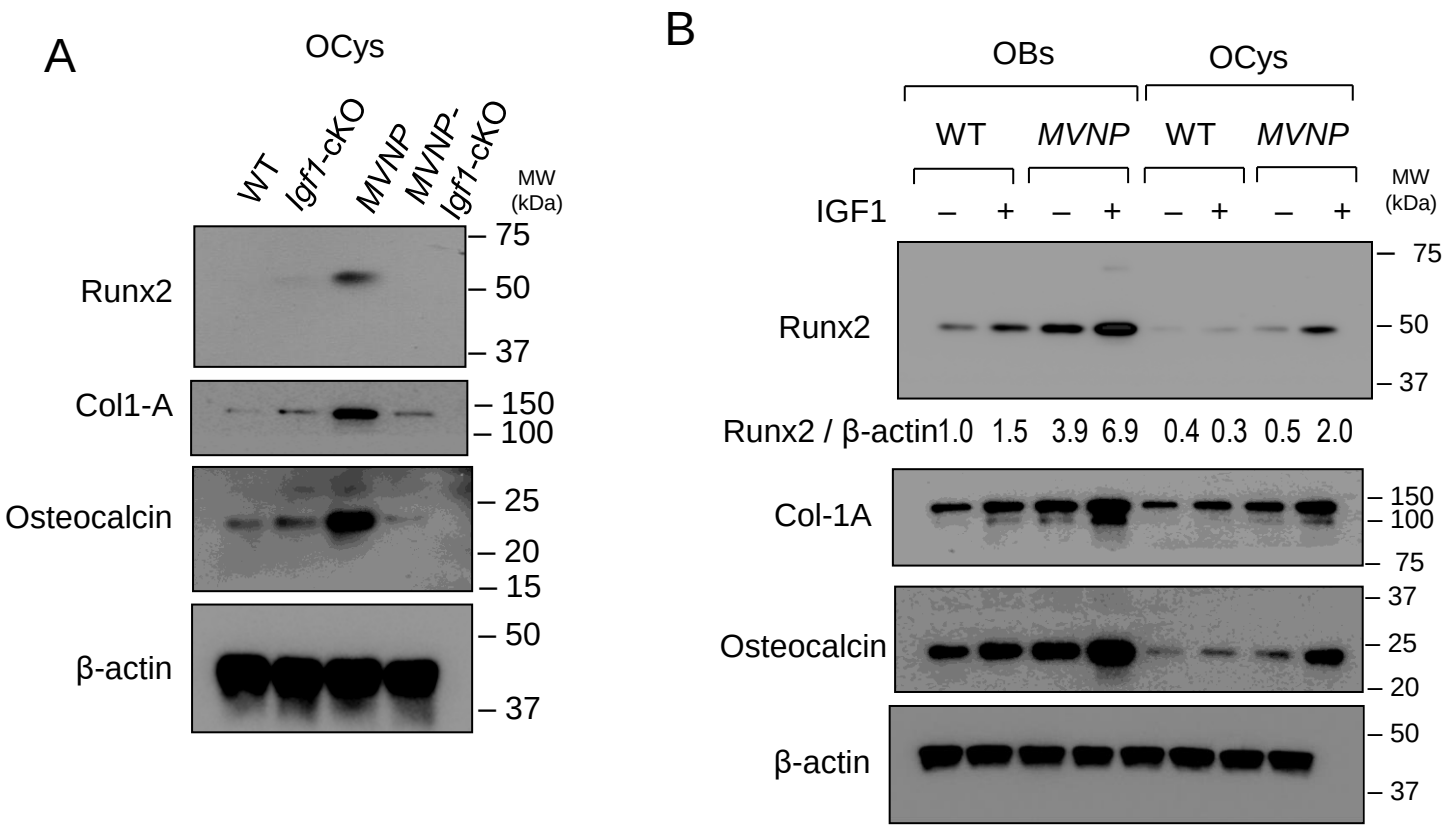



**Supplemental Figure 4.** Knockdown of IGF1 receptor. OCy-like cells from 18-month-old WT or *MVNP* mice were treated over 48hrs with 100nM control or mouse IGF1 receptor-specific siRNA (Cell Signaling, #6568 or #12482). IGF1R expression was detected by Western blotting using rabbit anti-IGF1R antibody (Cell Signaling, D23H3,) as described in Methods. The experiment was performed three times using different biological replicates with similar results.

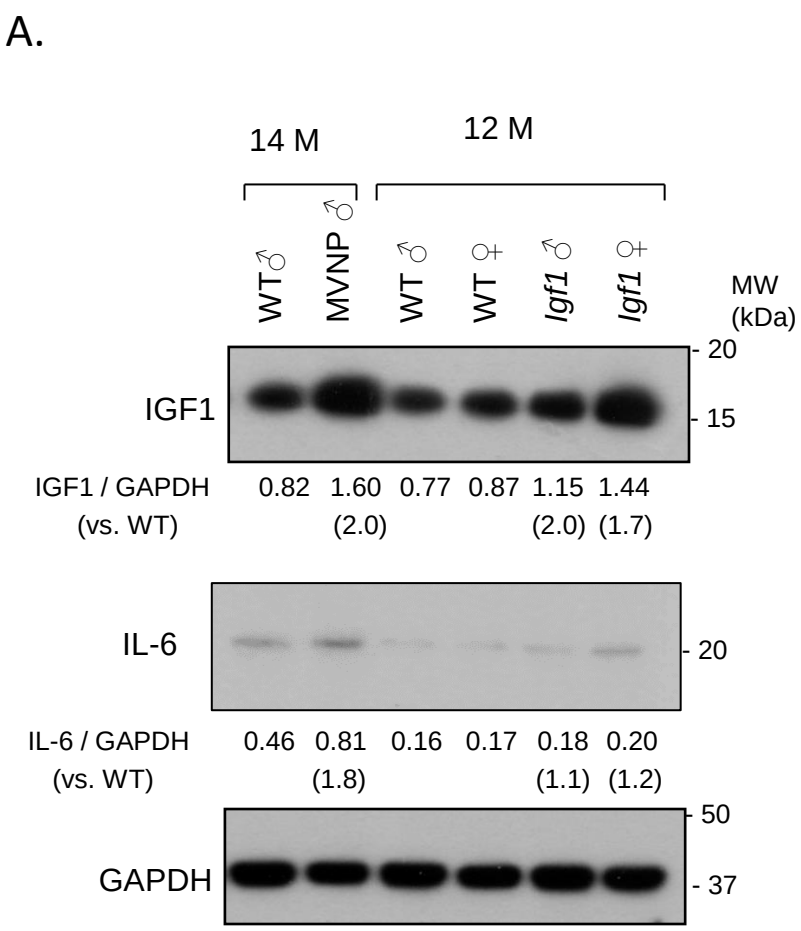
# Supplemental Figure 5

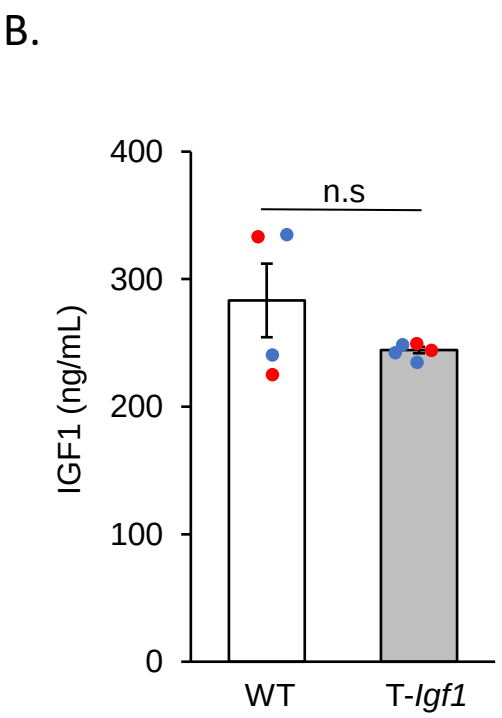



**Supplemental Figure 5.** IGF1 reduced DMP1 and sclerostin and increased RANKL in osteocyte-like cells. OCy-like cells ($1x10^4$/well) derived from bone in WT and *MVNP* mice at 15-19 months old were cultured with 10% FCS in αMEM for 3 days, then treated ± 10 ng/ml IGF1 in αMEM + 2% FCS for 3 days. Cell lysates were collected with RIPA buffer and Western blotted using anti-DMP1, anti-sclerostin, anti-RANKL, and anti-β-actin as loading control. The blots were analyzed as in Supplemental Figure 1, with n=4 and plotted with normalization to the level in vehicle-treated WT OCy-like cells as 1. The assay was performed three times using different biological replicates, with similar results.




**Supplemental Figure 6.** Expression of Runx2 by bone cells derived from 20-month-old WT, *Igf1-cKO*, *MVNP* and *MVNP/Igf1-cKO* mice. (**A**) OCy-like cells ($1\times10^5$ cells/well, from day 30 cultures) were grown in αMEM + 10% FCS for 72 hours, then cell lysates were collected with RIPA buffer. The expressions of Runx2, Col-1A and osteocalcin were measured by Western blotting using anti-Runx2, anti-Col-1A and anti-osteocalcin antibodies. β-actin was used as loading control. (B) Runx2 responses to IGF1. Cells from WT or *MVNP* mice as in A from 15-day and 30-day cultures were treated with IGF-1, and Western blots were analyzed for Runx2 as in Supplemental Figure 1.




**Supplemental Figure 7** (A) IGF1 and IL-6 expression in OCLs formed in mouse BM cultures. IGF1 and IL-6 expression was assayed by Western blotting using anti–IGF1 or -IL-6 antibodies as described in Methods. GAPDH was used as the loading control. The expression levels of IGF1 and IL-6 were quantitated by ImageJ software. The basal ratio for each protein/loading control for OCLs from WT mice cocultured with WT-OCLs was set at 1.0. (B) Serum IGF1 in 16 months of age of T-*Igf1* and WT mice. ELISA assay for IGF1 was described in Methods. Results are expressed as the mean ± SEM for WT (2 male, 2 female, 16 months) and T-Igf1 mice (3 male, 2 female, 16 months). The data were analyzed using a 1-way ANOVA with Tukey test. The blue circles represent results from male mice; red circles represent results from female mice.