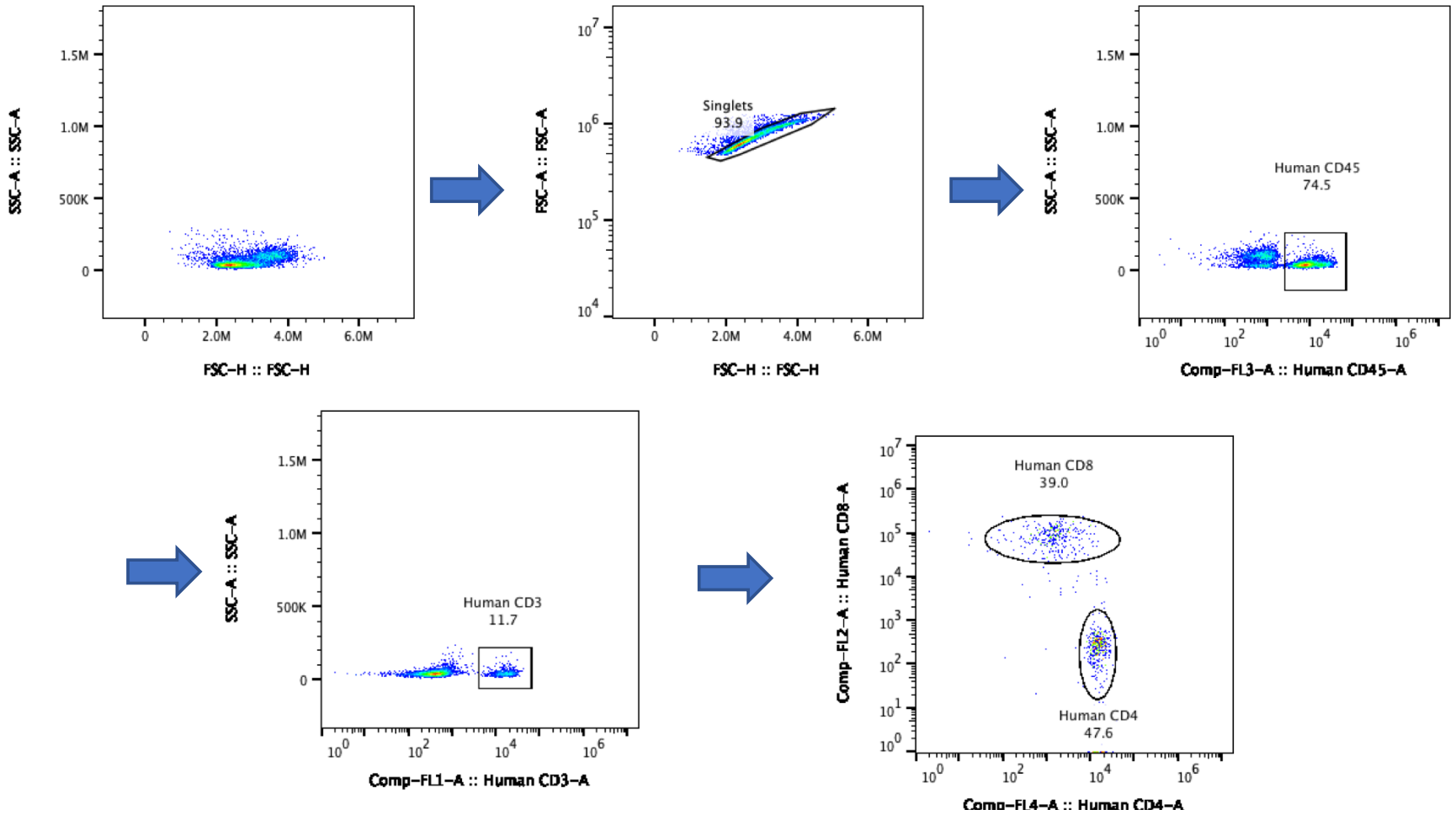
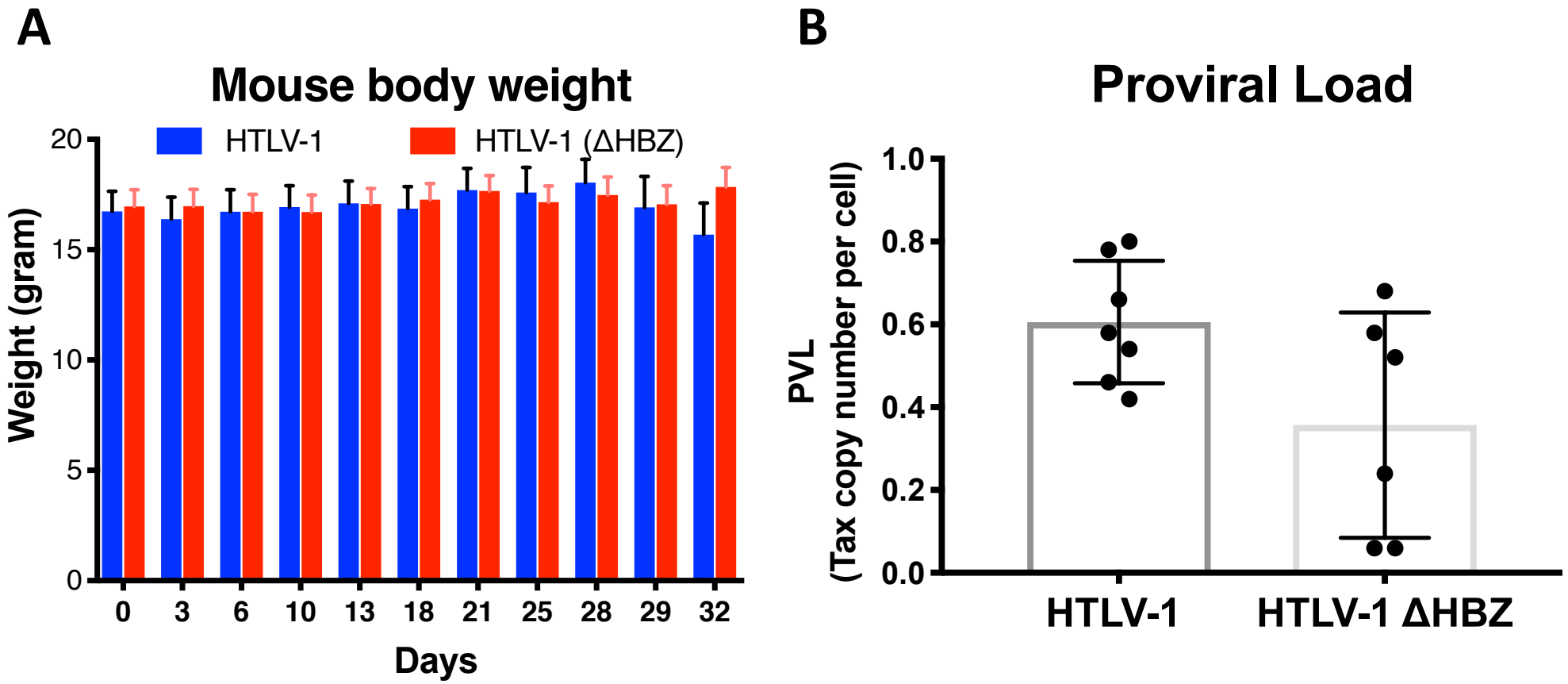
Supplemental Figure 1



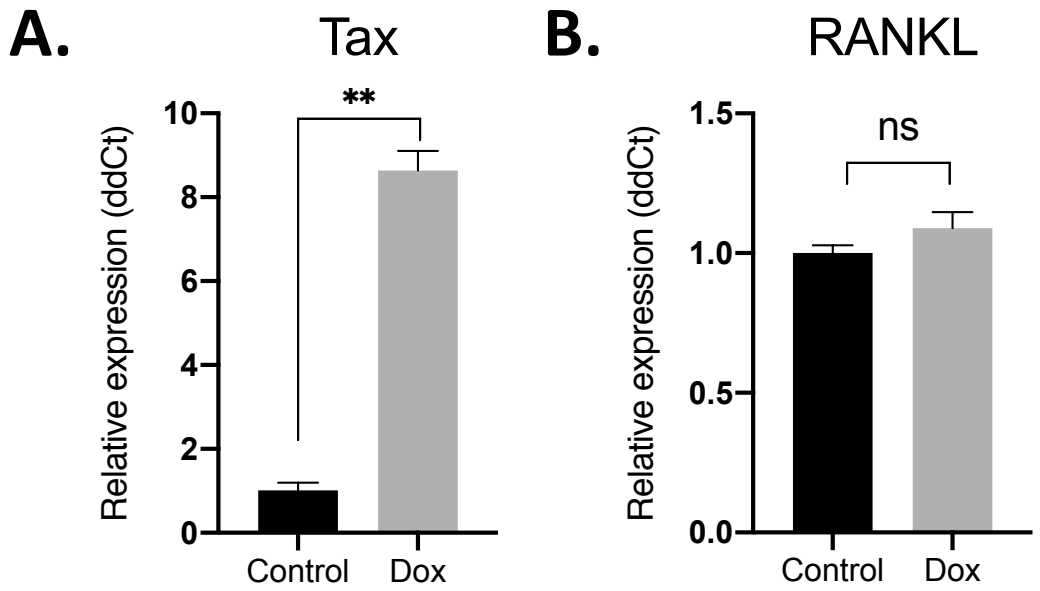
S. Figure 1. Flow cytometry gating strategy. Doublets were first excluded. Human CD45$^+$ cells were then gated followed by gating the CD3$^+$ T cell population. The human CD45$^+$CD3$^+$ population were then gated for CD4$^+$ and CD8$^+$ T cells.

Supplemental Figure 2



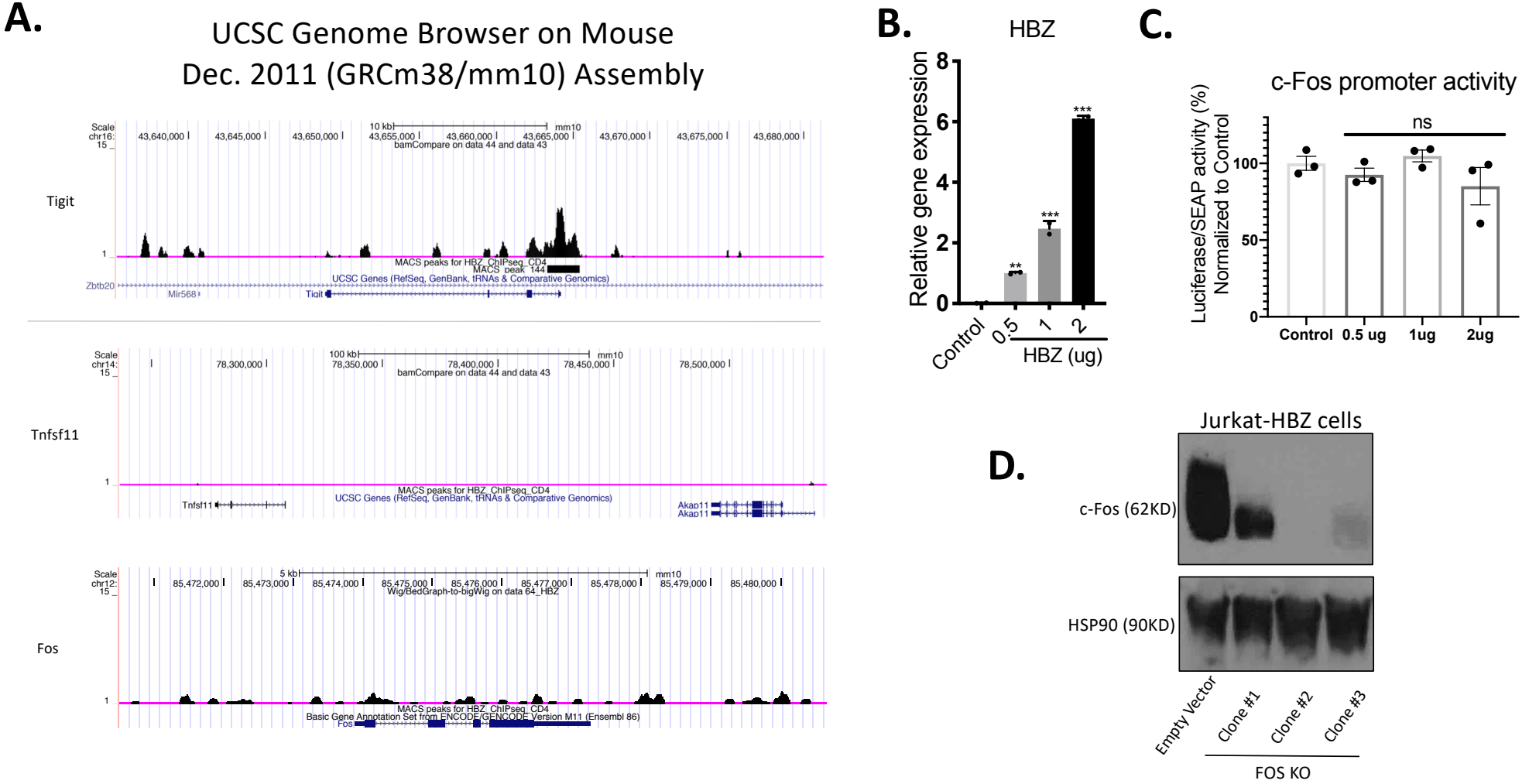
S. Figure 2. (A) Whole body weight of mice infected with HTLV-1 and HTLV-1 ΔHBZ; **(B)** Proviral load measurement by digital droplet PCR of the Tax gene from DNA isolated from the spleen of infected mice (n=6-7 per group). Error bars in this figure represent SEM.

Supplemental Figure 3



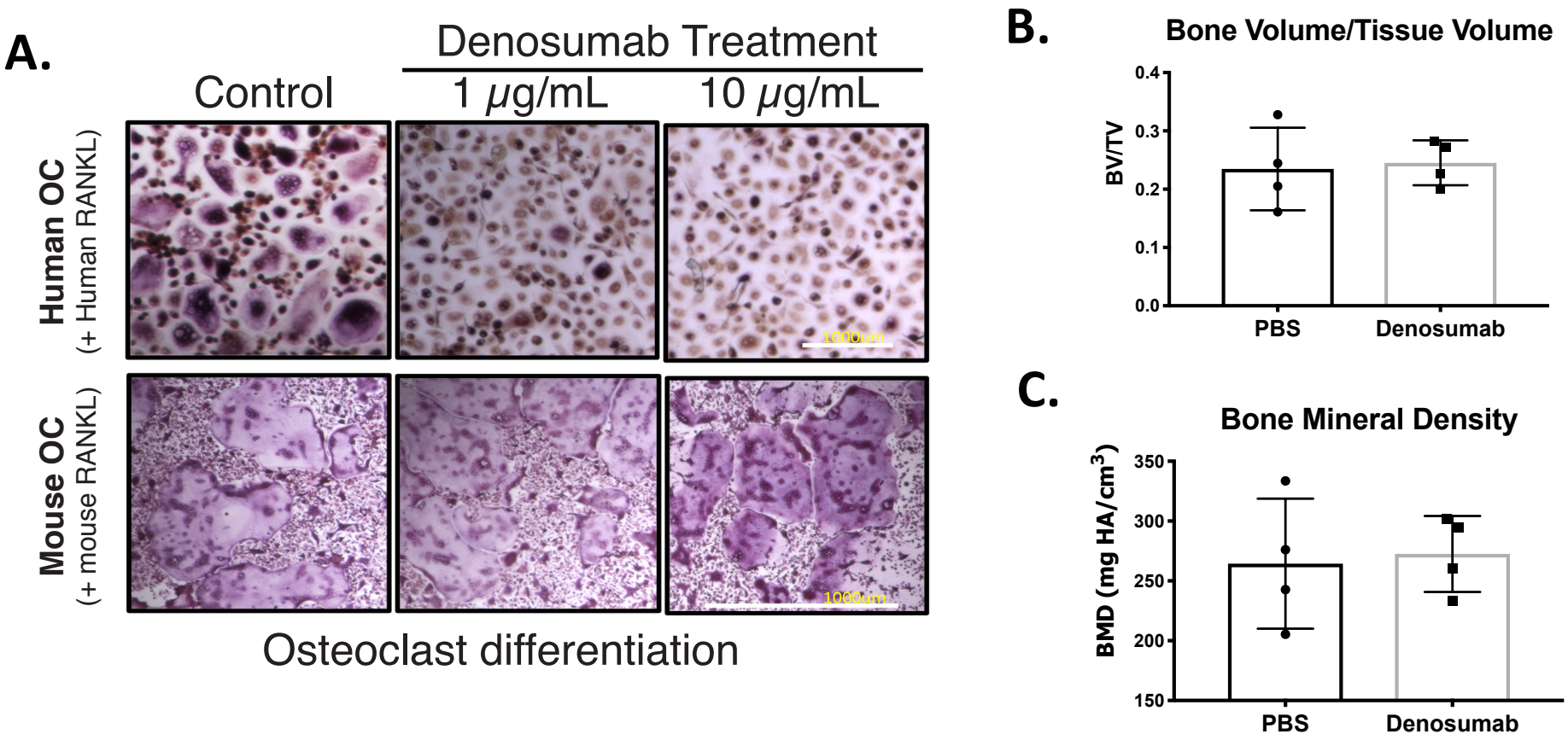
S. Figure 3. Inducible Tet-on Tax1 Jurkat cells were cultured with or without 1 µg/ml doxycycline (Dox) for 48 hours. **A)** Tax and **B)** RANKL gene expression were examined by qRT-PCR post Tax induction. Data is representative of 2 biological replicates. Error bars in this figure represent SEM and ** indicates p-value (2-tailed distribution, homoscedastic students t-test) of $p < 0.01$.

Supplemental Figure 4



S. Figure 4. **(A)** Visualization of HBZ ChIP-seq data in UCSC genome browser. **Top** is a positive control, showing the peaks of the region, at the *Tigit* gene promoter region, that HBZ was confirmed to interact with (PMID: 26735971); **Middle** & **Bottom** are the regions within and upstream Tnfsf11 (RANKL) and Fos genes, showing no significant peaks in this region. **B)** Co-transfection of c-Fos promoter luciferase reporter DNA (1ug, GeneCopoeia) and various amount of HBZ expression plasmid DNA (0.5, 1, 2ug) in Jurkat T-cell line via Nucleofection (Lonza). 72 hours post nucleofection, RNA was harvested to evaluate HBZ transcription level; supernatant was collected to evaluate c-Fos promoter activity measured by secreted luciferase activity and normalized to the internal control SEAP (secreted Alkaline Phosphatase) level. **D)** Western blog showing the efficiency of deletion of c-Fos protein in three Jurkat-HBZ cells clones, after stimulation with PMA (10 ng/mL) for 6 hours. Clones were obtained by standard limiting dilution assay.

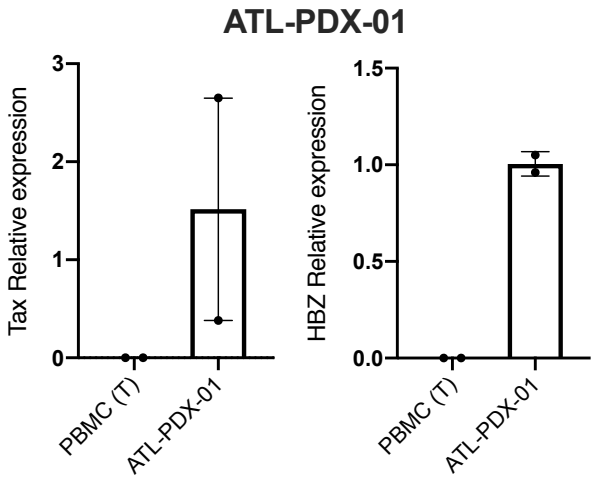
Supplemental Figure 5



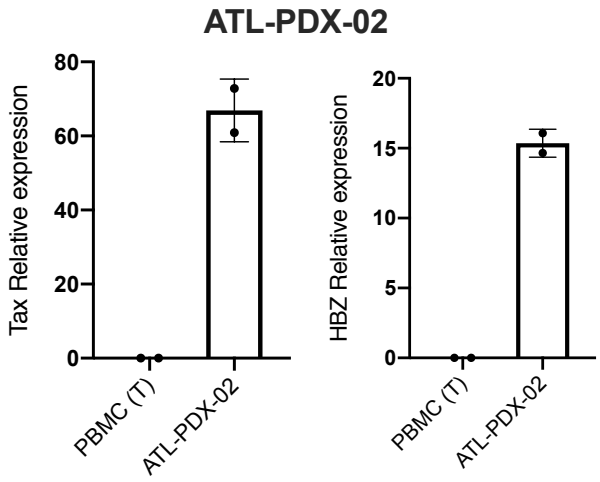
S. Figure 5. **(A)** Tartrate-resistant acid phosphatase (TRAP) staining of human and mouse osteoclast (OC) with denosumab treatment in vitro. Human CD14+ monocyte-derived and mouse bone marrow-derived macrophages were cultured in the presence of mouse MCSF (50 ng/mL) and RANKL (50 ng/mL) or human MCSF (20 ng/mL) and RANKL (40 ng/mL), with or without the treatment of denosumab (final concentration: 1μg/mL, 10μg/mL) for 5 days. TRAP staining was performed to stain the TRAP positive osteoclast. Bar represents 1000 μm); **(B)** Non-tumor bearing NSG mice were treated with denosumab from day 3 for 3 weeks twice weekly before sacrifice. Tibiae were collected for μCT analysis for calculation of trabecular bone to tissue volume ratio (BV/TV) and **(C)** bone mineral density (BMD), n=4 bones per group. Error bars in this figure represent SEM.

Supplemental Figure 6

A.



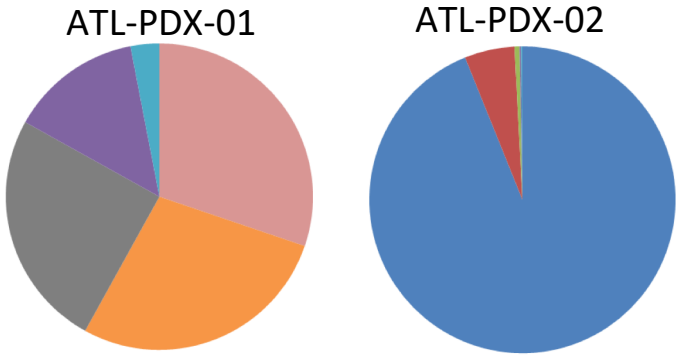
B.



C.

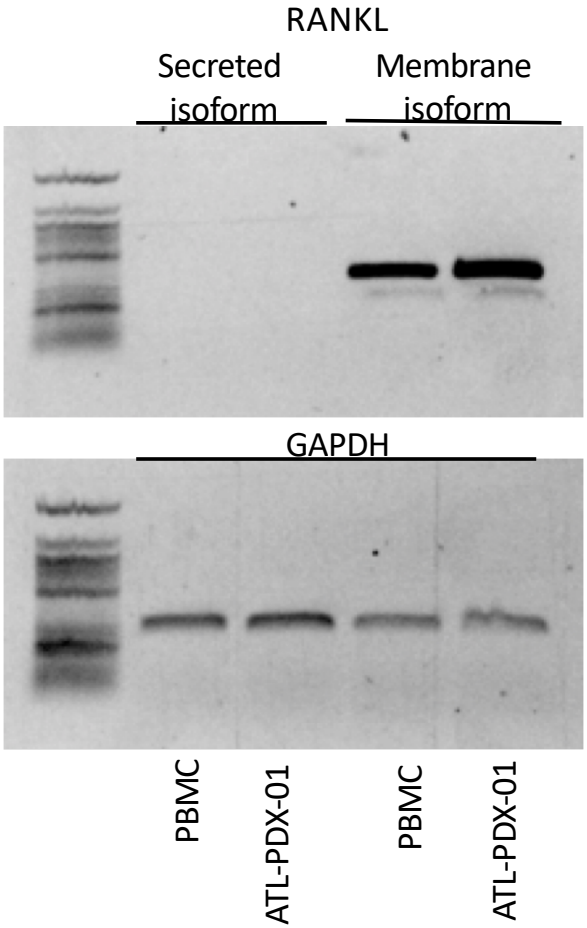
	ATL-PDX-01	ATL-PDX-02
CARD11	N686K	
TP53		I251N
NOTCH1		E2460*
VAV1		Y174C
CCR4	G33D	

D.



S. Figure 6. Tax and HBZ gene expression were examined by qRT-PCR in **A)** ATL-PDX-01 and **B)** ATL-PDX-02 cells . **C)** ATL cells from ATL-PDX-01 and ATL-PDX-02 patients carry different mutations. ATL genes with previously described activating mutations are shown in red; **D)** Clonal analysis based on proviral integration sites reveals that HTLV infected cells in PBMC from ATL-PDX-01 patient revealed oligoclonal expansion, whereas HTLV-1 infected cells in PBMC from ATL-PDX-02 were predominantly one clone. Top 5 clones shown for each patient.

Supplemental Figure 7



S. Figure 7. Membrane-bound RANKL isoform is detected in PBMC and ATL-PDX-01 cells.
cDNA from PBMC or ATL-PDX-01 cells were synthesized using Quanta cDNA RT kit. PCR amplification of secreted or membrane-bound RANKL was as previously described in Walsh et al. *Gene and Immunity*, 2013: primers RANKL-EST-F-248 (5'-AGAAACTGCTGAAATATTGAACACA-3') and sRANKL-R-450 (5'-CCCCGATCATGGTACCAAGAGGAC-3') were used to amplify the secreted RANKL isoform; primers hRANKL-F-315 (5'-AGCGTCGCCCTGTTCTTCTA-3') and EC-R-744 (5'-TGTCGGTGGCATTAATAGTGAGA-3') were used to amplify the membrane-bound RANKL isoform.

Sample **PBMC from HTLV-1 infected humanized mouse**
TRB (T-cell receptor beta)
Total count **384,262**

CLONAL

Rank	Sequence	Length	Merge count	V-gene	J-gene	% total reads	Cumulative %	CDR3 Sequence
1	CCTTCCCATTTTAATTCACTGCCTTTGTCTT TTCCAAGCCCCACACAGTCAGACTAACCT CTGCCACCTGCGCTTCCTGCCGCTGCCCA GTGGTTGGGGGAGGGGGACTAGCAGGG AGGAAACATTTTTGTATCATGGTGTAACAT TGTGGGGACTAGCGGTCTAACACCGGGG AGCTGTTTTTTGGAGAAGGCTCTAG	199	25835	Db2	Jb2-2	6.7	6.7	not found
2	GGAGGTGAGAAGGAAGCCCCCGGCCTG GTCCATACCCCACCACCAACTTGCATAAT GGGGGGTGATGTCACCCACCCTCCACTCC CCTCAAAGGAGCAGCTGCTCTGGTGGTCT CTCCCAGGCTCTGGGGGCGGACCCATGG GAGGGGCTGTTTTTGTACAAAGCTGTAAC ATTGTGGGGACAGGGAAGGAGCTATAAT TCACCCCTCCACTTTGGGAAT	220	21026	Db1	Jb1-6	5.5	12.2	not found
3	GACTGAGGCTGATTTATTACTCAGCTTCTG AGGGTACCACTGACAAAGGAGAAGTCCC CAATGGCTACAATGTCTCCAGATTAAACA AACGGGAGTTCTCGCTCAGGCTGGAGTC GGCTGCTCCCTCCCAGACATCTGTGTACT TCTGTGCCAGCAGTCCCCCCGCGACCCAC ACCCGCTCTGGGGCCAACGTCCTGACTTT CGGGGCCGGCAGCAG	217	14354	Vb6-1	Jb2-6	3.7	15.9	GCCAGCAGTCCCC CCGCGACCCACAC CCGCTCTGGGGCC AACGTCCTGACT
4	ATGGGCTGAGGCTGATCTATTACTCAGCA GCTGCTGATATTACAGATAAAGGAGAAGT CCCCGATGGCTATGTTGTCTCCAGATCCA AGACAGAGAATTTCCCCCTCACTCTGGAG TCAGCTACCCGCTCCCAGACATCTGTGTA TTTCTGCGCCAGCAGACCGGGACAGGGT AATTCACCCCTCCACTTTGGGAAT	197	9532	Vb10-2	Jb1-6	2.5	18.4	GCCAGCAGACCG GGACAGGGTAATT CACCCCTCCAC
5	CCTTCCCATTTTAATTCACTGCCTTTGTCTT TTCCAAGCCCCACACAGTCAGACTAACCT CTGCCACCTGCGCTTCCTGCCGCTGCCCA GTGGTTGGGGGAGGGGGACTAGCAGGG AGGAAACATTTTTGTATCATGGTGTAACAT TGTGGGGACCCGGAGGCTCCTACAATGA GCAGTTCTTCGGGCCAGGG	193	8326	Db2	Jb2-1	2.2	20.6	not found

TRG (T cell receptor gamma)
Total count **533,190**

NON-CLONAL

Rank	Sequence	Length	Merge count	V-gene	J-gene	% total reads	Cumulative %	CDR3 Sequence
1	TGGGTAAGACAAGCAACAAAGTGGAGGC AAGAAAGAATTCTCAAACTCTCACTTCAAT CCTTACCATCAAGTCCGTAGAGAAAGAAG ACATGGCCGTTTACTACTGTGCTGCGTGG GGTGGTTGGTTCAAGATATTTGCTG	141	58130	Vg10	JgP1	10.9	10.9	GCTGCGTGGGGT GGTTGGTTCAAGA TA
2	GGAATCAGTCGAGAAAAGTATCATACTTA TGCAAGCACAGGGAAGAGCCTTAAATTTA TACTGGAAAATCTAATTGAACGTGACTCT GGGGTCTATTACTGTGCCACCTGGGACCT ACCGCAAGAGTTGGGCAAAAAAATCAAG	144	38445	Vg8	JgP	7.2	18.1	not found
3	GGAATCAGTCGAGAAAAGTATCATACTTA TGCAAGCACAGGGAAGAGCCTTAAATTTA TACTGGAAAATCTAATTGAACGTGACTCT GGGGTCTATTACTGTGCCACCTGGGTCCC TCCCTAACACTGGTTGGTTCAAGATATTTG CTG	149	34536	Vg8	JgP1	6.5	24.6	not found
4	GGAGTCAGTCCAGGGAAGTATTATACTTA CGCAAGCACAAGGAACAACTTGAGATTGA TACTGCGAAATCTAATTGAAAATGACTCTG GGGTCTATTACTGTGCCACCTGGGACGGC TTCGGTTCTGATTGGATCAAGACGTTTGC AA	148	17476	Vg2	JgP2	3.3	27.9	GCCACCTGGGACG GCTTCGGTTCTGA TTGGATCAAGACG
5	GGAATCAGTCGAGAAAAGTATCATACTTA TGCAAGCACAGGGAAGAGCCTTAAATTTA TACTGGAAAATCTAATTGAACGTGACTCT GGGGTCTATTACTGTGCCACCTGGGATAG GTAAGAGTTGGGCAAAAAAATCAAG	141	15502	Vg8	JgP	2.9	30.8	not found

Supplemental Table 1. Genomic DNA harvested from PBMC was submitted to Invivoscribe (https://www.invivoscribe.com/) for TRB (T cell receptor beta) and TRG (T cell receptor gamma) gene rearrangement analysis and quantitation.