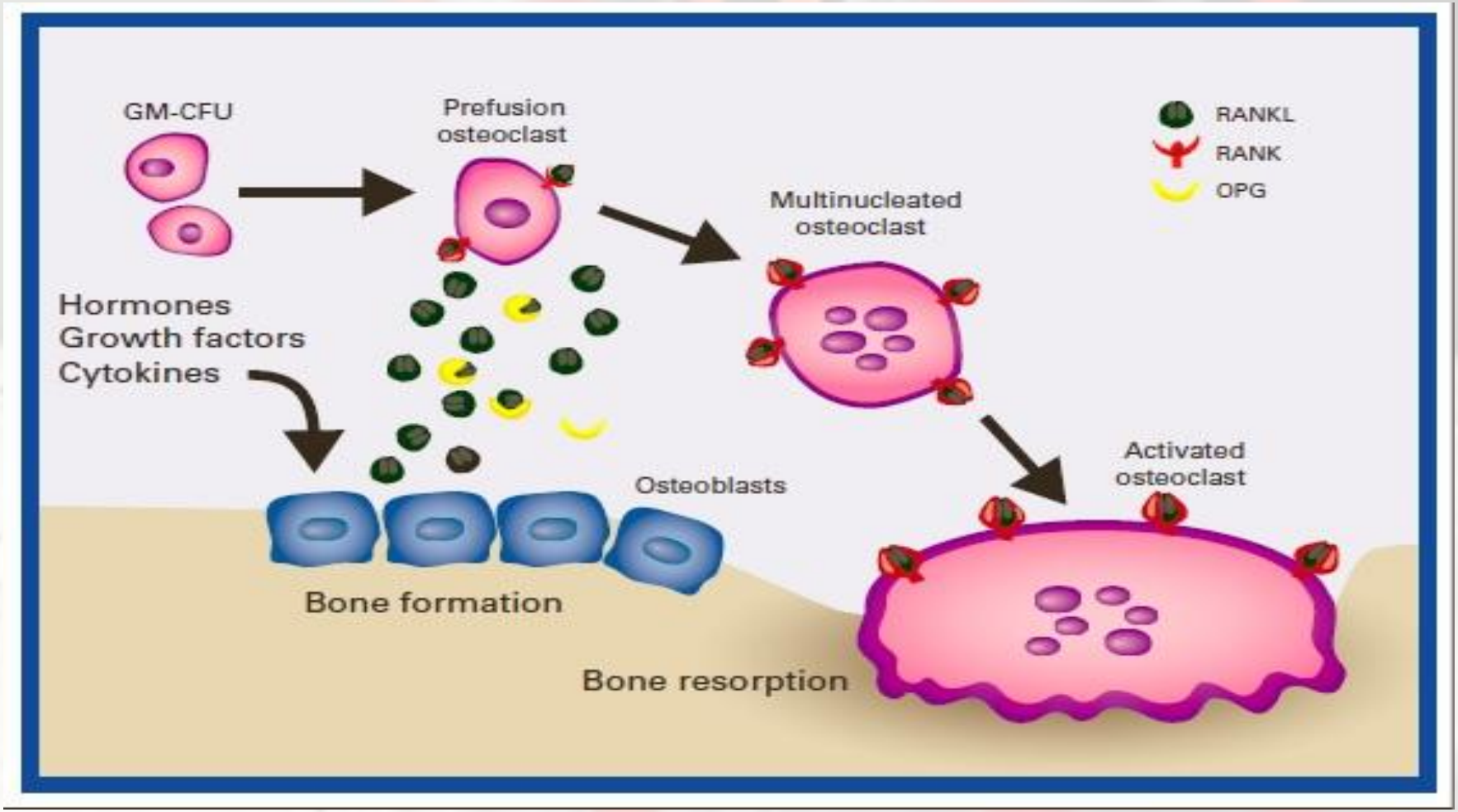
Semmelweis University
Faculty of Dentistry
Department of Community Dentistry
Head of Department: Dr. Peter Kivovics
associate professor
DMD, BDS, MDSc, PhD,

RANK ligand the state of knowledge, biology, clinical and oral surgical implications

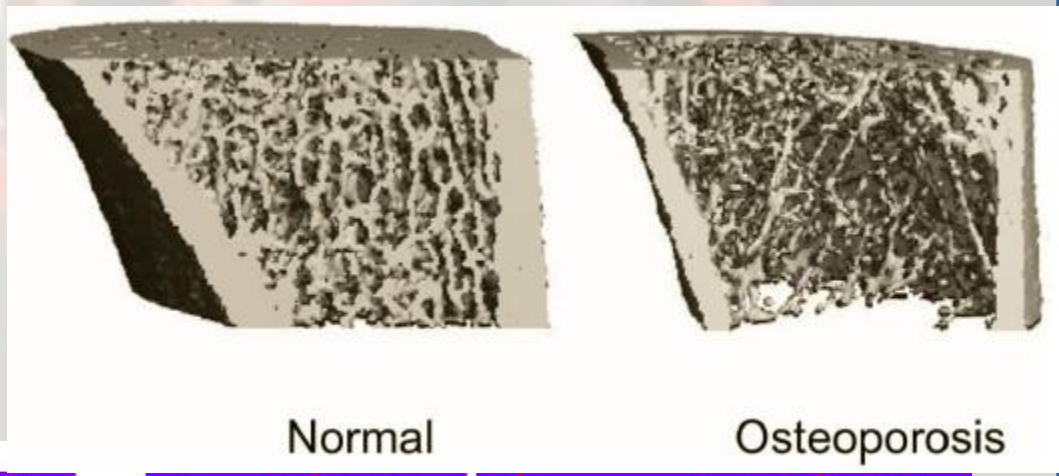
By Deraghme Alex
Consultant Dr. Lőrincz Ádám
Department of Community Dentistry

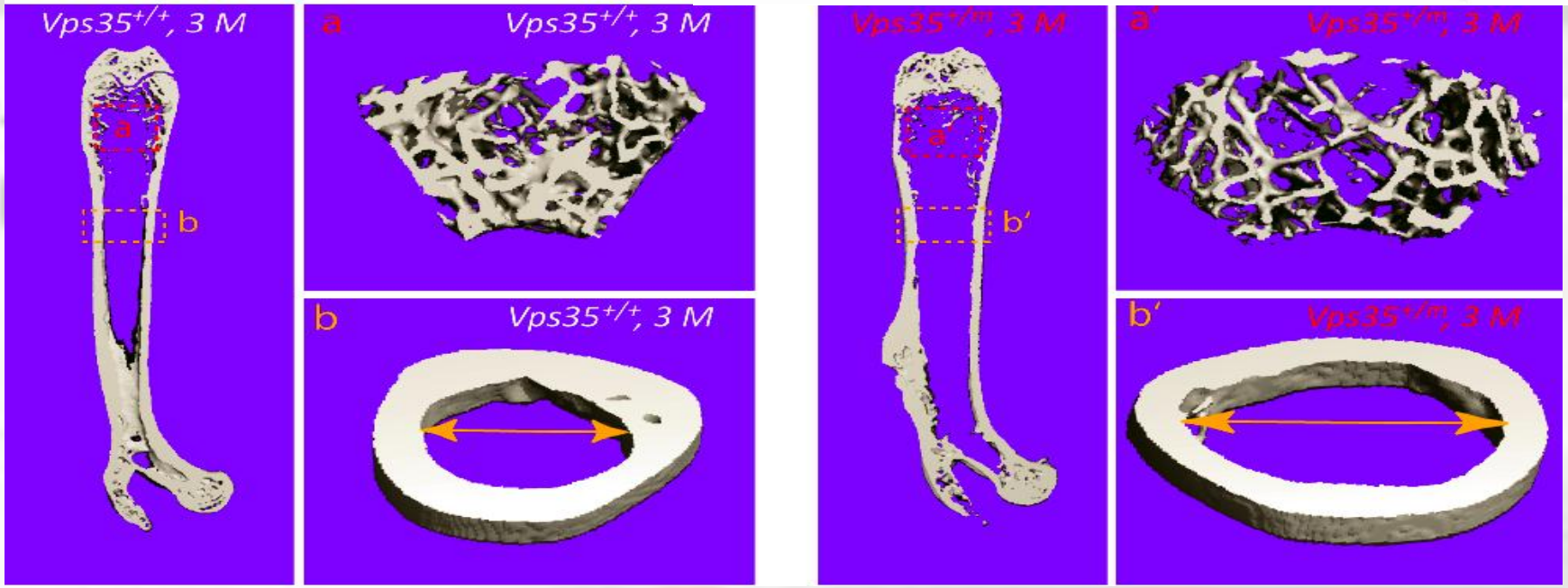
RANKL:Receptor Activator of Nuclear factor Kappa B Ligand



Saylor, P.J., R.J. Lee, and M.R. Smith, *Emerging Therapies to Prevent Skeletal Morbidity in Men With Prostate Cancer.* J Clin Oncol, 2011. **29**(27): p. 3705-14.

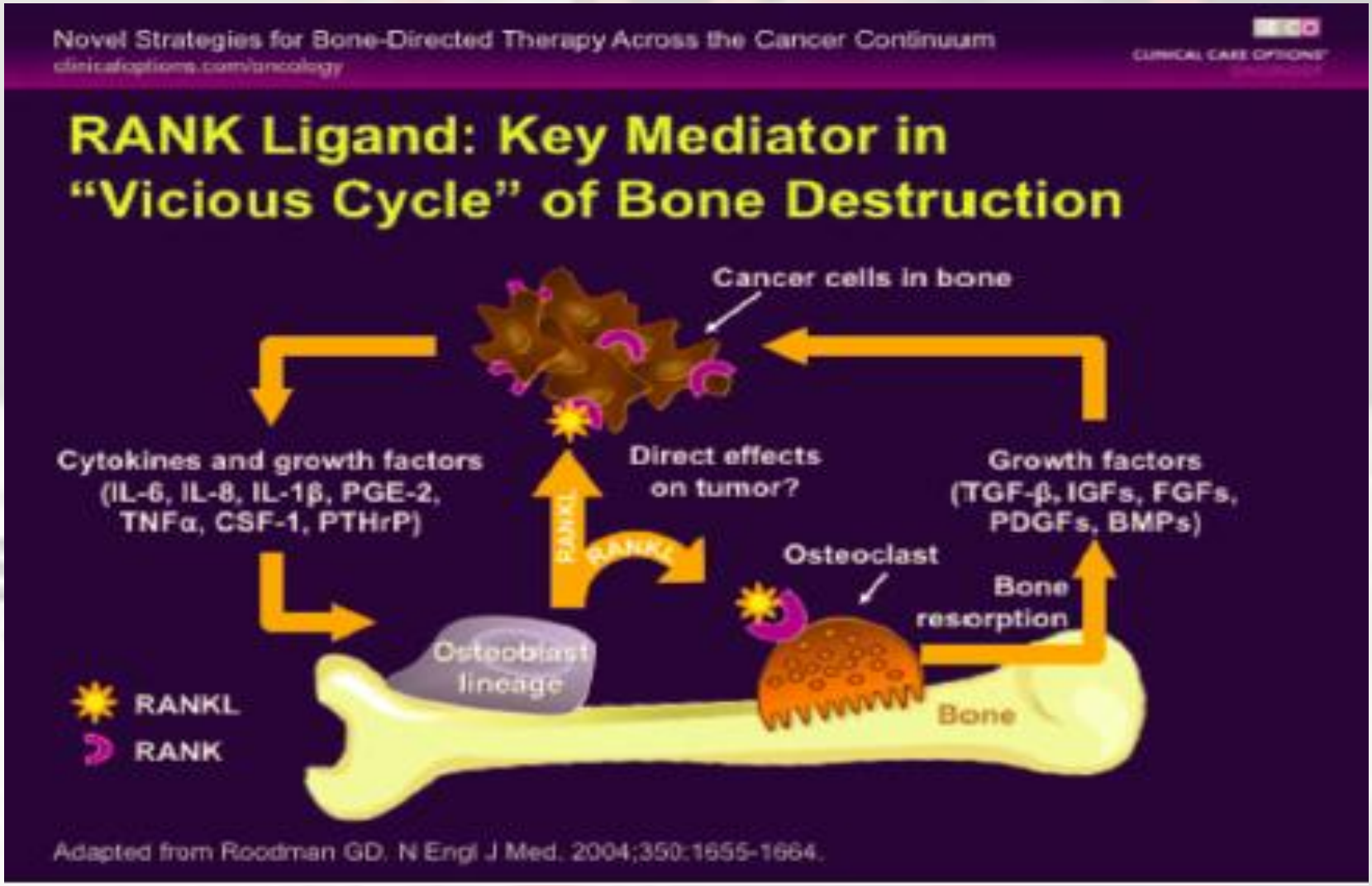
Osteoporosis





Xia, W.F., et al., *Vps35 loss promotes hyperresorptive osteoclastogenesis and osteoporosis via sustained RANKL signaling.* J Cell Biol, 2013. **200**(6): p. 821-37.

Tumors



Castellano, D., et al., *The Role of RANK-Ligand Inhibition in Cancer: The Story of Denosumab.* Oncologist, 2011. **16**(2): p. 136-45.

Further roles

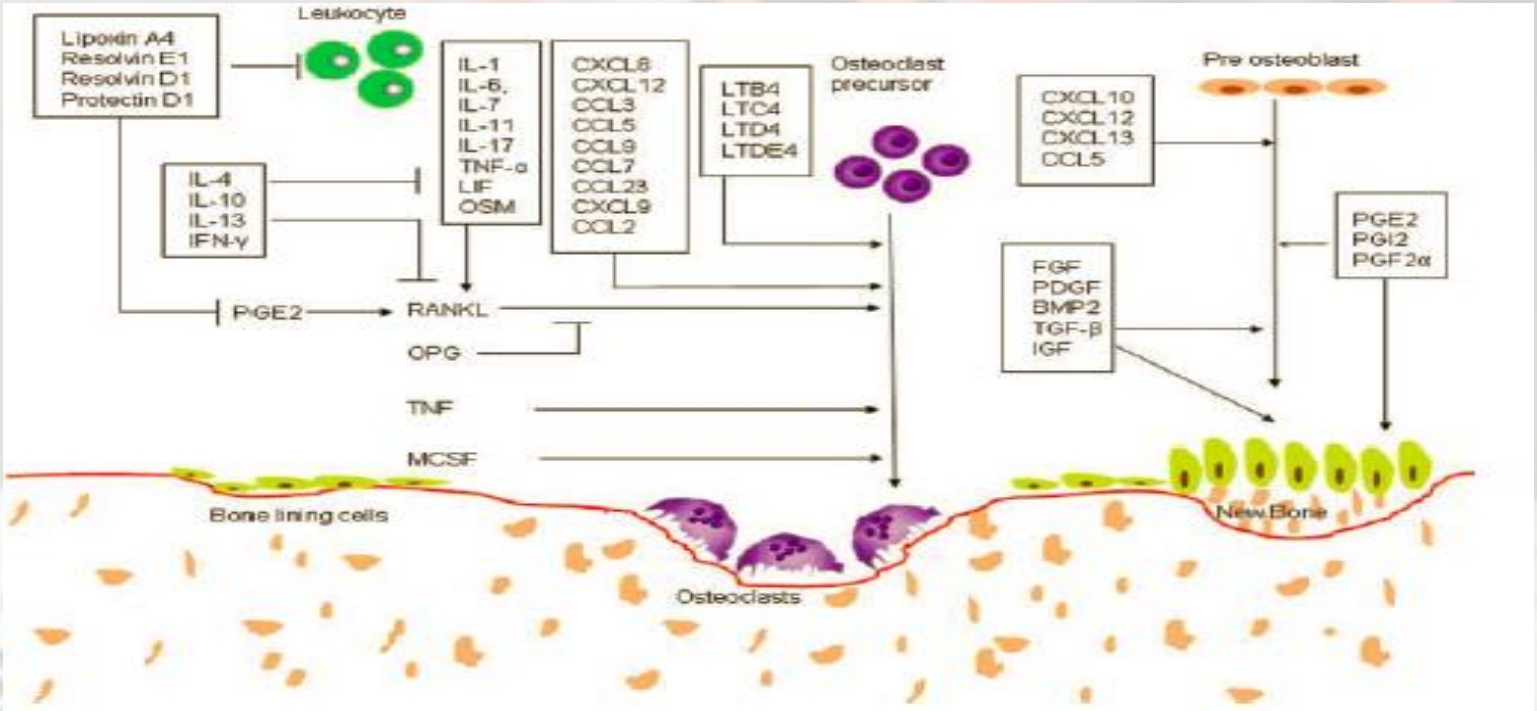


Figure 1. Stimulation of osteoclastogenesis, bone resorption, and coupled bone formation. RANKL, M-CSF, and TNF directly stimulate the formation of osteoclasts, other cytokines or lipid-based mediators such as prostaglandins or leukotrienes indirectly stimulate osteoclastogenesis by effects on RANKL, M-CSF, or TNF-α, and chemokines affect resorption by stimulating recruitment of osteoclast precursors or osteoclast activity. In periodontitis, inflammatory cytokines IL-1, IL-6, IL-7, IL-11, IL-17, TNF-α, LIF, OSM, and RANKL are thought to be primarily produced by leukocytes. Growth factors such as FGF, PDGF, BMP-2, TGF-β, and IGF are released from bone matrix or synthesized locally by various cell types after bone resorption and stimulate proliferation of osteoblast precursors, osteoblast differentiation, or synthesis of bone matrix. Some chemokines, such as CXCL10, CXCL12, CXCL13, and CCL5, may affect bone formation by effects on osteoblast precursors or osteoblasts.

Graves, D., J. Li, and D. Cochran, *Inflammation and Uncoupling as Mechanisms of Periodontal Bone Loss.* J Dent Res, 2011. **90**(2): p. 143-53.

Regulation of hair follicle

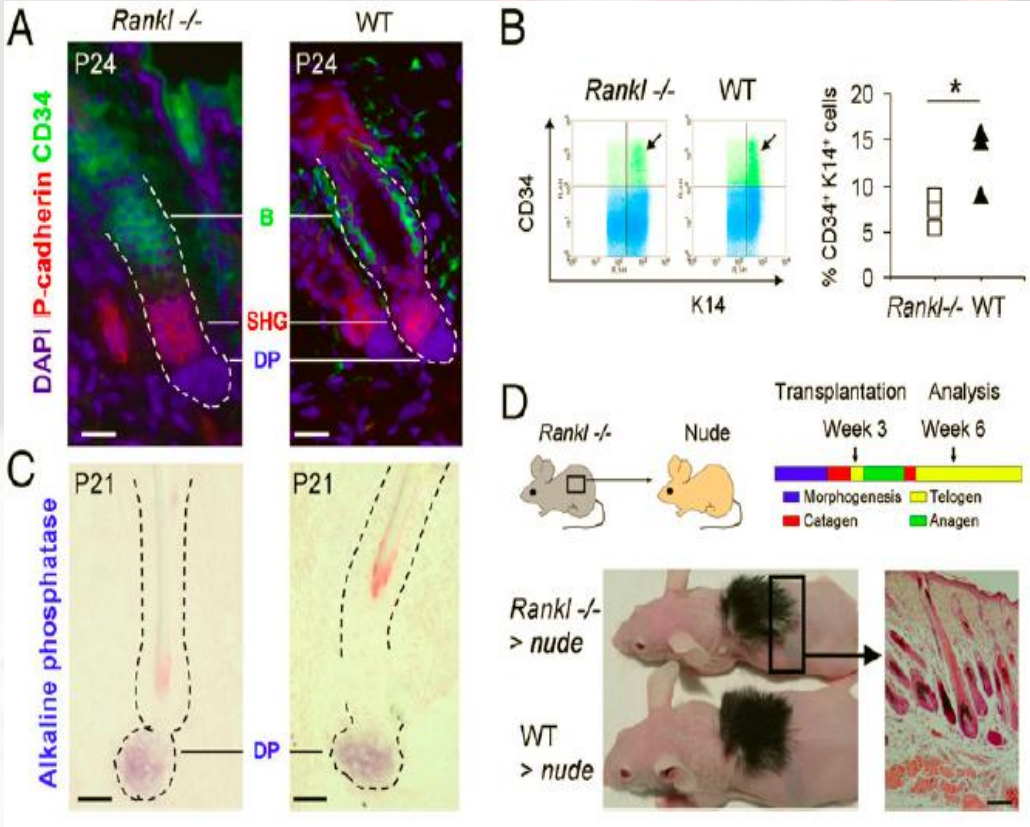
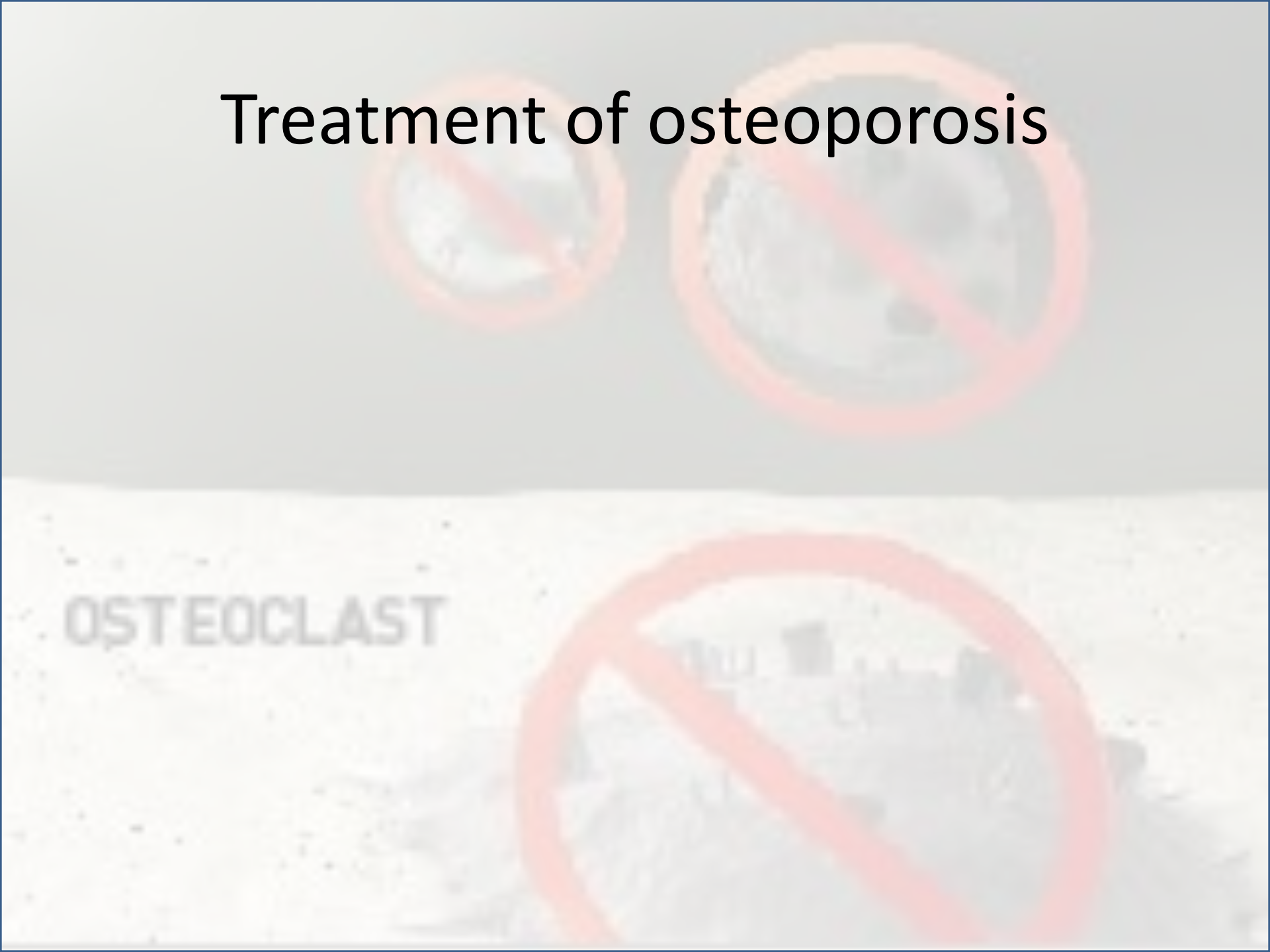


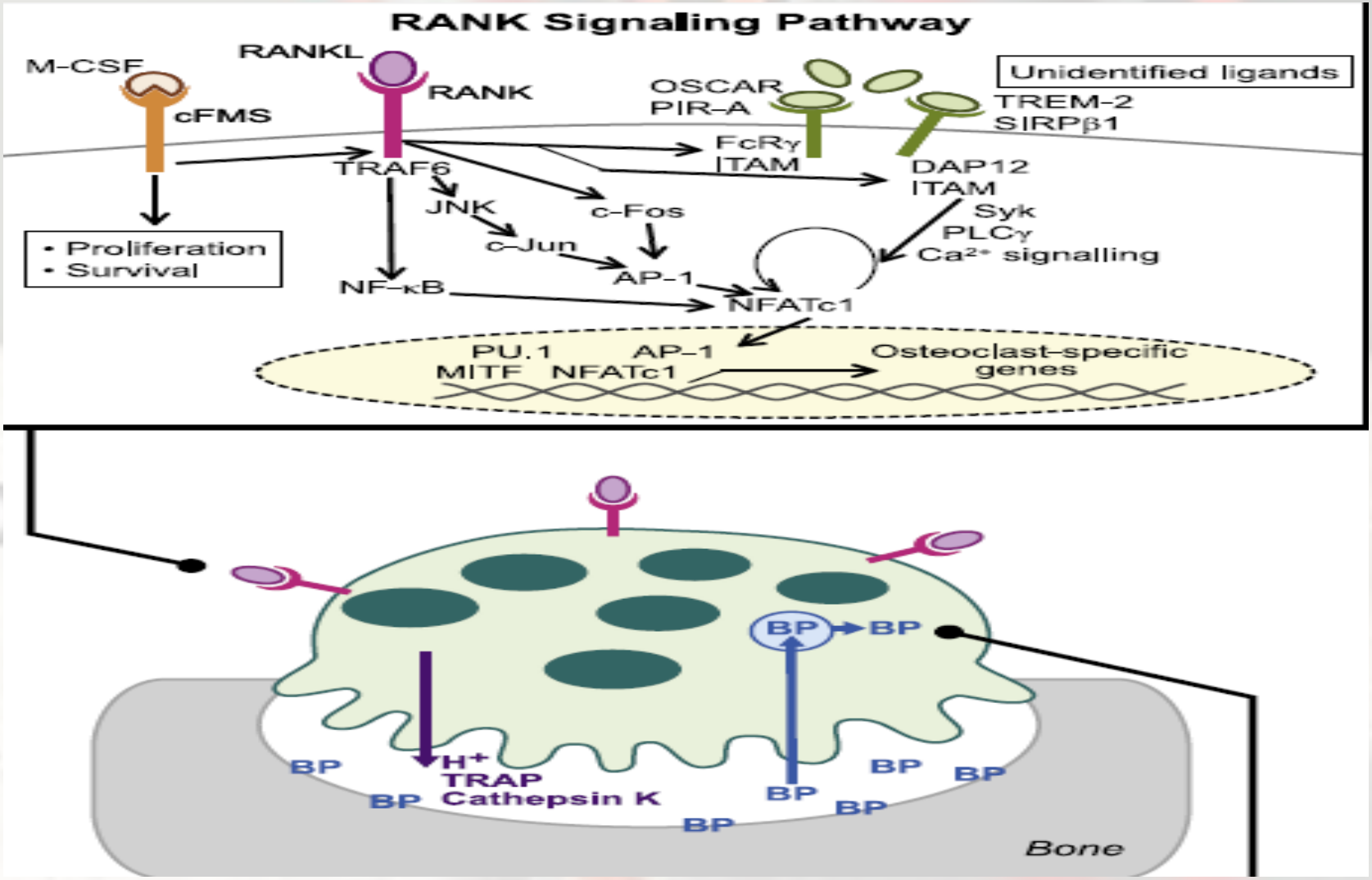
Fig. 2. The HF stem cell and the mesenchymal cell compartment is RANK-signaling independent. (*A*) Identification of CD34$^+$ bulge (B) and P-cadherin$^+$ SHG cells in *Rankl*$^{-/-}$ and control telogen HFs by immunofluorescence. Nuclei were colored with DAPI. (Scale bars, 20 μm.) (*B Left*) Flow cytometry of CD34$^+$ bulge cells among keratin 14$^+$ keratinocytes in *Rankl*$^{-/-}$ and WT telogen HFs. Arrows point to CD34$^+$ keratin 14$^+$ cells. (*Right*) Graph depicts the percentage of CD34$^+$ and keratin 14$^+$ cells in three KO mice and littermate controls (*$P < 0.05$). (*C*) Identification of follicular DP by their alkaline phosphatase activity. (Scale bars, 20 μm.) (*D*) Restored *Rankl*$^{-/-}$ hair renewal after transplantation onto *nude* mice at week 3 and analysis at week 6. A *Rankl*$^{-/-}$ skin section shows HFs in anagen. Image is representative for five transplantation experiments. (Scale bar, 100 μm.) The paraffin-embedded section was stained with hematoxylin/eosin.

Duheron, V., et al., *Receptor activator of NF-?B (RANK) stimulates the proliferation of epithelial cells of the epidermo-pilosebaceous unit.* Proc Natl Acad Sci U S A, 2011. **108**(13): p. 5342-7.

Treatment of osteoporosis



Bisphosphonates



Baron, R., S. Ferrari, and R.G. Russell, *Denosumab and bisphosphonates: different mechanisms of action and effects.* Bone, 2011. **48**(4): p. 677-92.

Denosumab

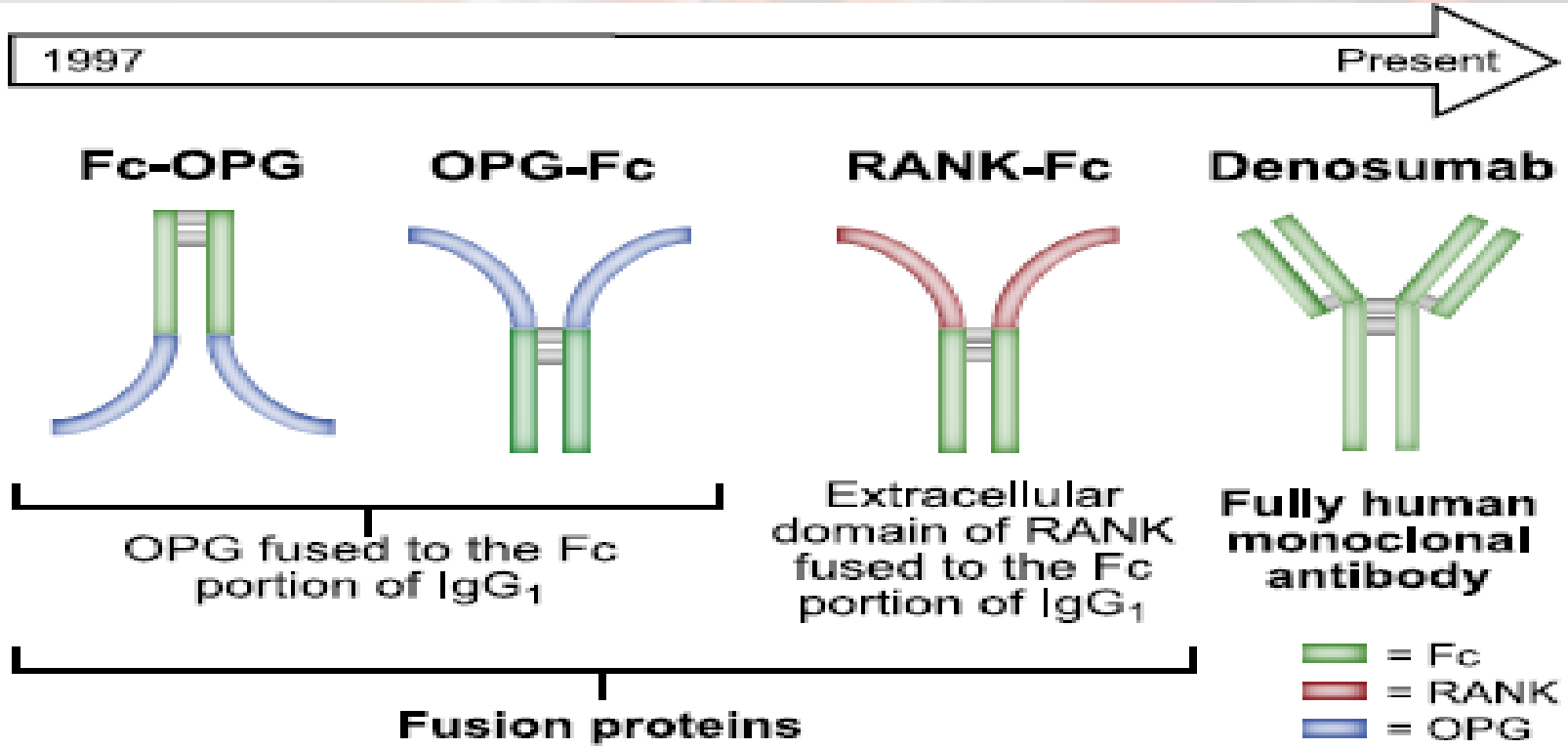
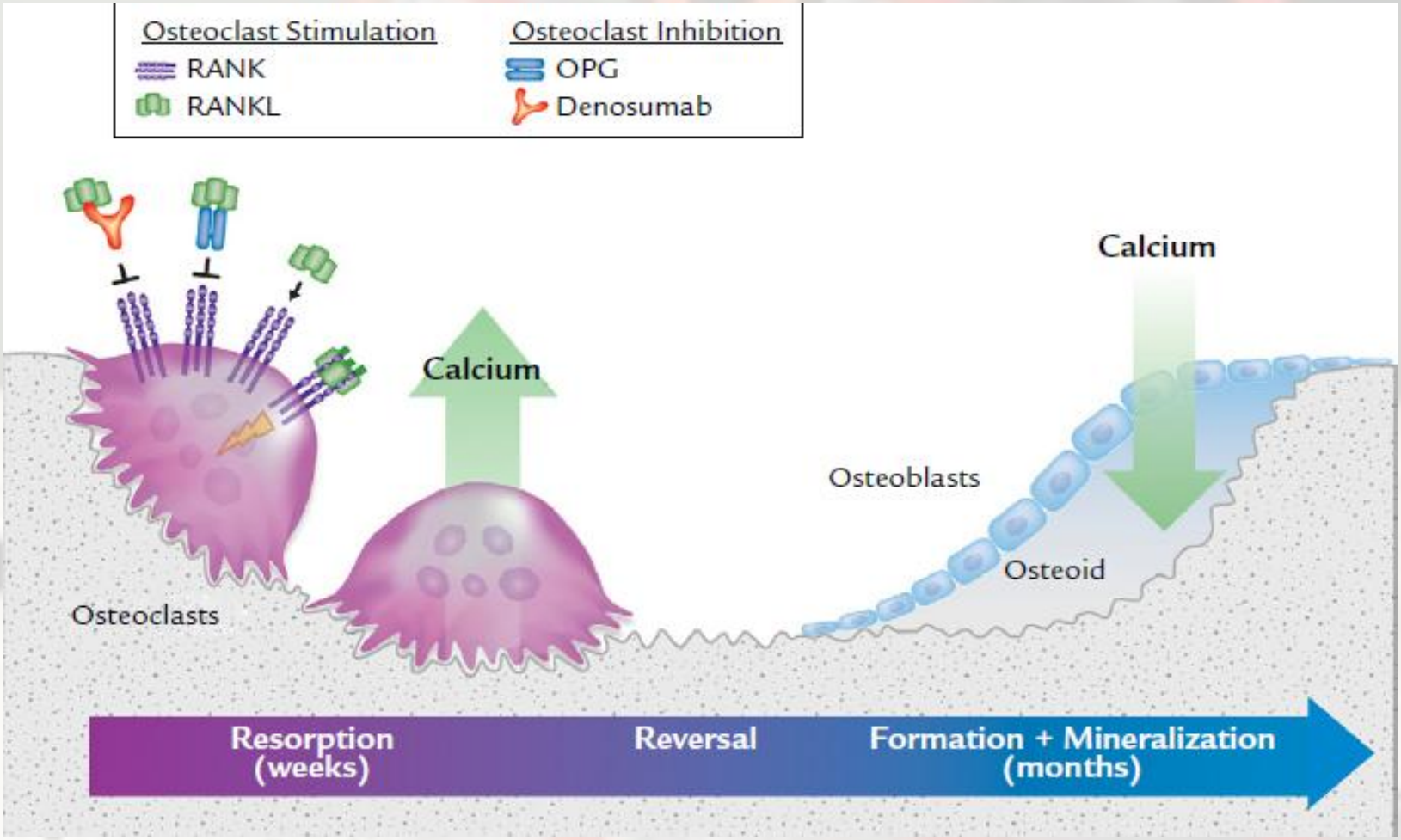


Fig. 3. History of the development of RANKL antagonists.

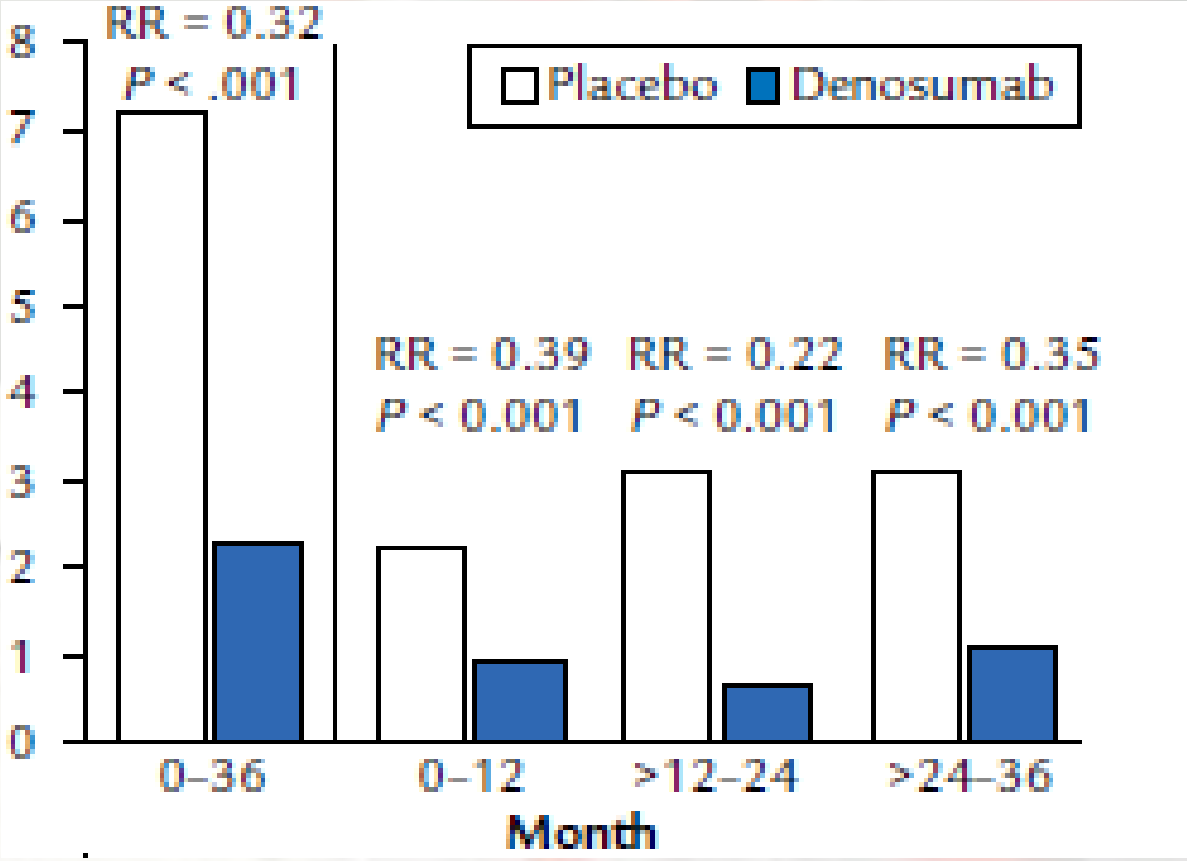
Baron, R., S. Ferrari, and R.G. Russell, *Denosumab and bisphosphonates: different mechanisms of action and effects.* Bone, 2011. **48**(4): p. 677-92.

The mechanism of action of denosumab



Dempster, D.W., et al., *Role of RANK ligand and denosumab, a targeted RANK ligand inhibitor, in bone health and osteoporosis: a review of preclinical and clinical data.* Clin Ther, 2012. **34**(3): p. 521-36.

The effectiveness of denosumab



Dempster, D.W., et al., *Role of RANK ligand and denosumab, a targeted RANK ligand inhibitor, in bone health and osteoporosis: a review of preclinical and clinical data.* Clin Ther, 2012. **34**(3): p. 521-36.

Denosumab vs bisphosphonate

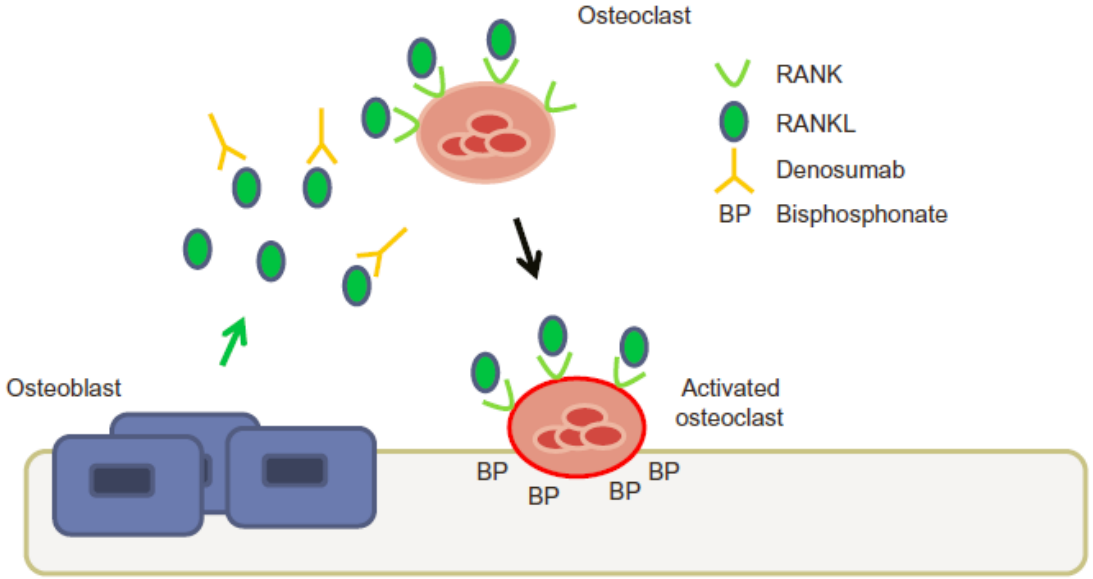


Figure 1 Mechanism of action of denosumab compared to zoledronic acid.
Notes: RANKL is secreted by bone marrow stromal cells and osteoblasts. RANKL binds to the RANK receptor on osteoclasts and promotes osteoclast differentiation and activity. Denosumab is a fully human monoclonal antibody that binds to RANKL and thereby inhibits the activation of osteoclasts by RANKL. Bisphosphonates (for example, zoledronic acid) bind to bone, enter, and inhibit bone resorption by osteoclasts.
See review by Baron et al[17] for details.
Abbreviations: RANK, receptor activator of nuclear factor κB; RANKL, RANK ligand.

Yee, A.J. and N.S. Raje, *Denosumab, a RANK ligand inhibitor, for the management of bone loss in cancer patients.* Clin Interv Aging, 2012. **7**: p. 331-8.

Comparison of there effectiveness

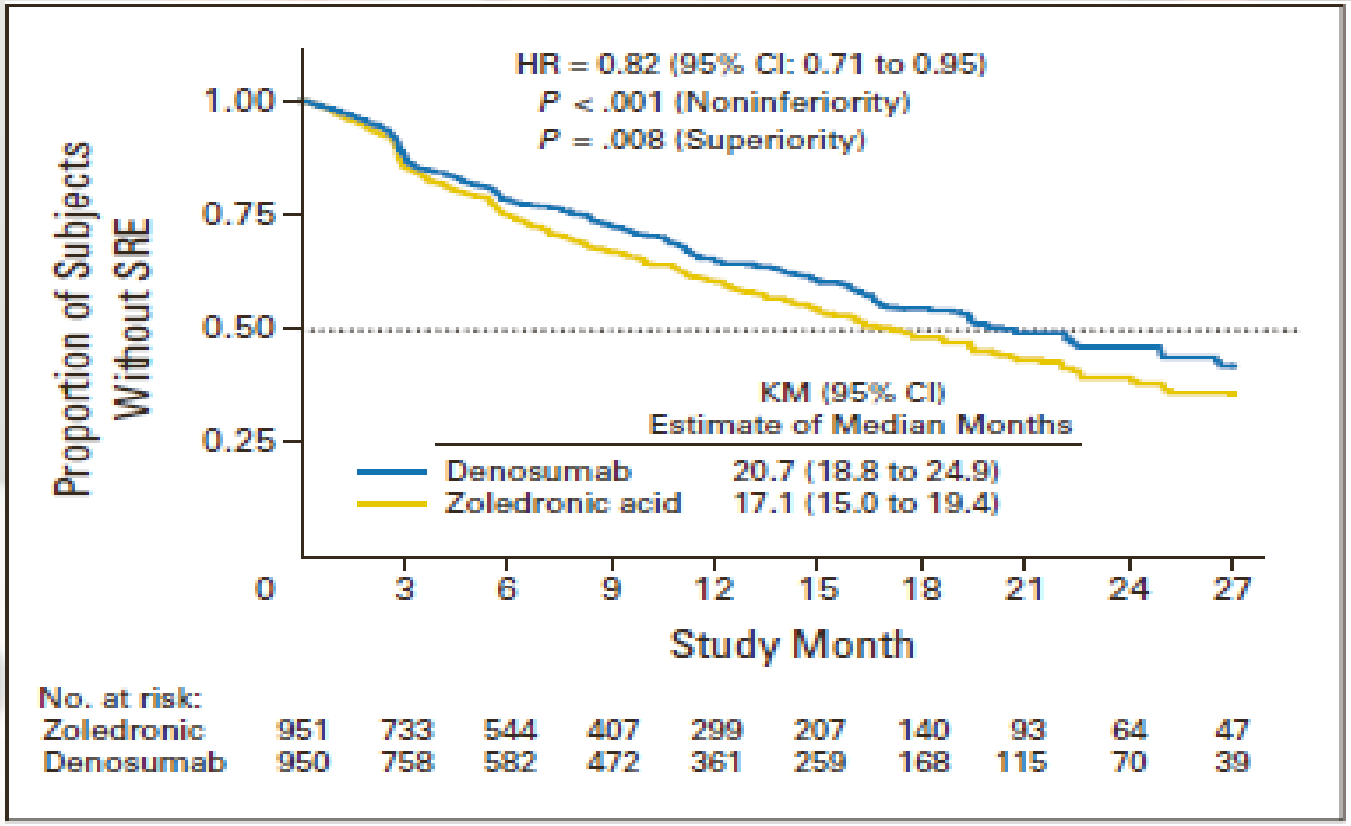


Fig 3. Primary analysis of the Denosumab 103 trial. Denosumab (120 mg subcutaneously every 4 weeks) was compared with zoledronic acid (4 mg intravenously every 4 weeks) in men with castration-resistant prostate cancer metastatic to bone. Median time to first skeletal-related event (SRE) was significantly longer in the denosumab arm (20.7 *v* 17.1 months). Analyses for noninferiority and for superiority were both significant.[33] HR, hazard ratio; KM, Kaplan-Meier.

Saylor, P.J., R.J. Lee, and M.R. Smith, *Emerging Therapies to Prevent Skeletal Morbidity in Men With Prostate Cancer.* J Clin Oncol, 2011. **29**(27): p. 3705-14.

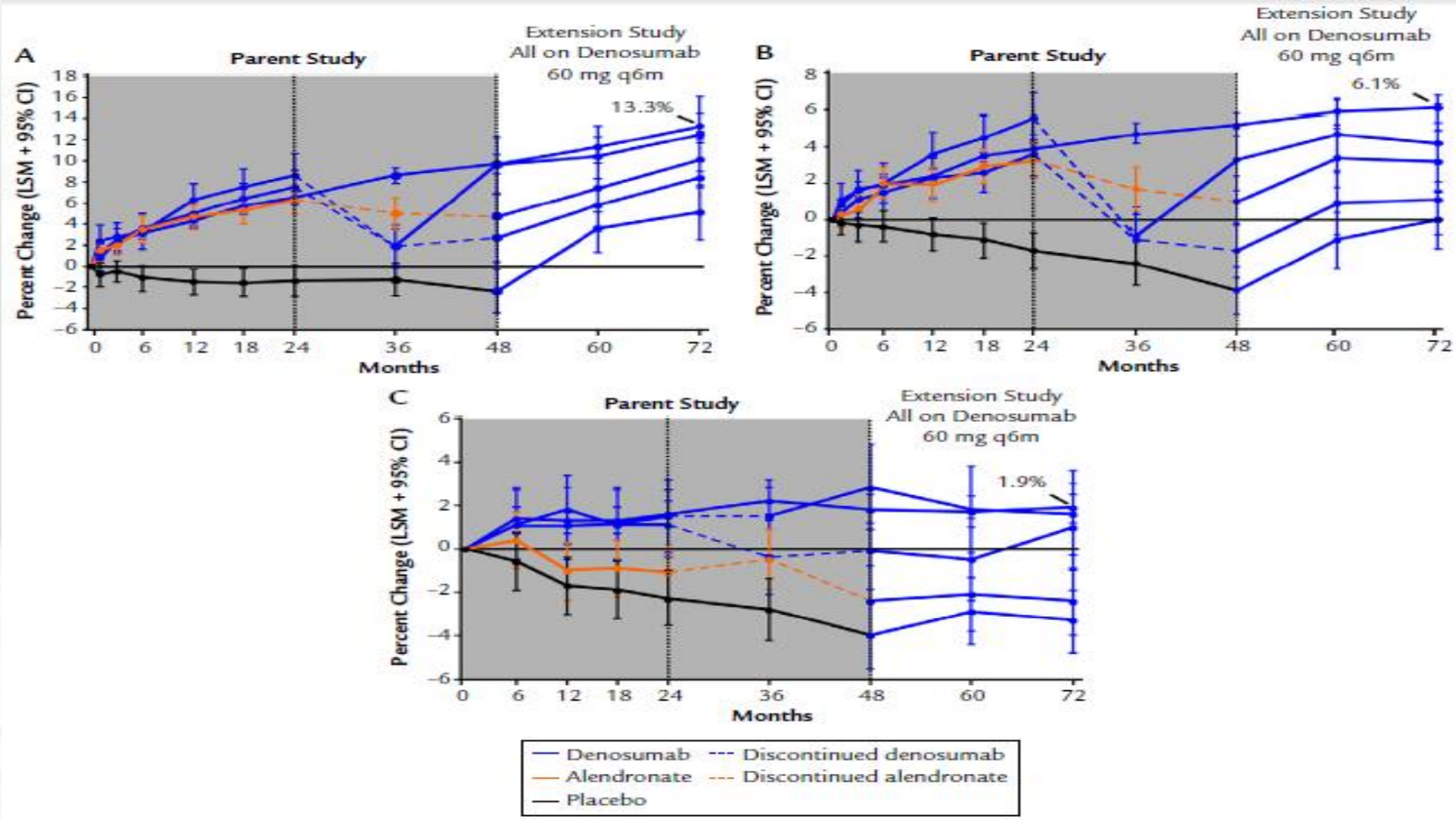


Figure 2. Effect of 6 years of treatment with denosumab on bone mineral density (BMD) at the (A) lumbar spine, (B) total hip, and (C) one-third radius in postmenopausal women with low bone mass. BMD values are shown as percentage change from parent study baseline (least squares mean [LSM] + 95% CI). q6m = every 6 months. Reproduced with permission from Miller PD, Wagman RB, Peacock M, et al. Effect of denosumab on bone mineral density and biochemical markers of bone turnover: six-year results of a phase 2 clinical trial. *J Clin Endocrinol Metab.* 2011;96:394–402. *Copyright 2011, The Endocrine Society.*

Dempster, D.W., et al., *Role of RANK ligand and denosumab, a targeted RANK ligand inhibitor, in bone health and osteoporosis: a review of preclinical and clinical data.* Clin Ther, 2012. **34**(3): p. 521-36.

Adverse effects

Table. Adverse events reported in the FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months) study.

Event	Events (n [%]) Denosumab (n = 3886)	Placebo (n = 3876)	P
All	3605 (92.8)	3607 (93.1)	0.91
Serious	1004 (25.8)	972 (25.1)	0.61
Fatal	70 (1.8)	90 (2.3)	0.08
Leading to study discontinuation	93 (2.4)	81 (2.1)	0.39
Leading to discontinuation of study drug	192 (4.9)	202 (5.2)	0.55
Adverse events			
Infection	2055 (52.9)	2108 (54.4)	0.17
Cancer	187 (4.8)	166 (4.3)	0.31
Hypocalcemia	0 (0)	3 (<0.1)	0.08
Osteonecrosis of the jaw	0 (0)	0 (0)	NA
Serious adverse events			
Cancer	144 (3.7)	125 (3.2)	0.28
Infection	159 (4.1)	133 (3.4)	0.14
Cardiovascular event	186 (4.8)	178 (4.6)	0.74
Stroke	56 (1.4)	54 (1.4)	0.89
Coronary heart disease	47 (1.2)	39 (1.0)	0.41
Peripheral vascular disease	31 (0.8)	30 (0.8)	0.93
Atrial fibrillation	29 (0.7)	29 (0.7)	0.98
Adverse events occurring in ≥2% of subjects*			
Eczema	118 (3.0)	65 (1.7)	<0.001
Falling†	175 (4.5)	219 (5.7)	0.02
Flatulence	84 (2.2)	53 (1.4)	0.008
Serious adverse events occurring in ≥0.1% of subjects‡			
Cellulitis (including erysipelas)	12 (0.3)	1 (<0.1)	0.002
Concussion	1 (<0.1)	11 (0.3)	0.004

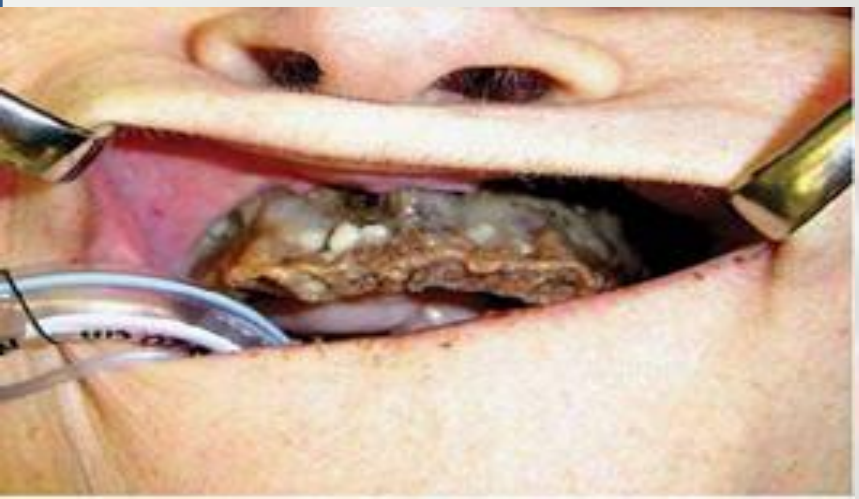
Reproduced with permission from Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med.* 2009;361:756–765. *Copyright 2009, Massachusetts Medical Society.*

*$P \leq 0.05$ for the between-group comparison.

†Excludes falls that occurred on the same day as fracture.

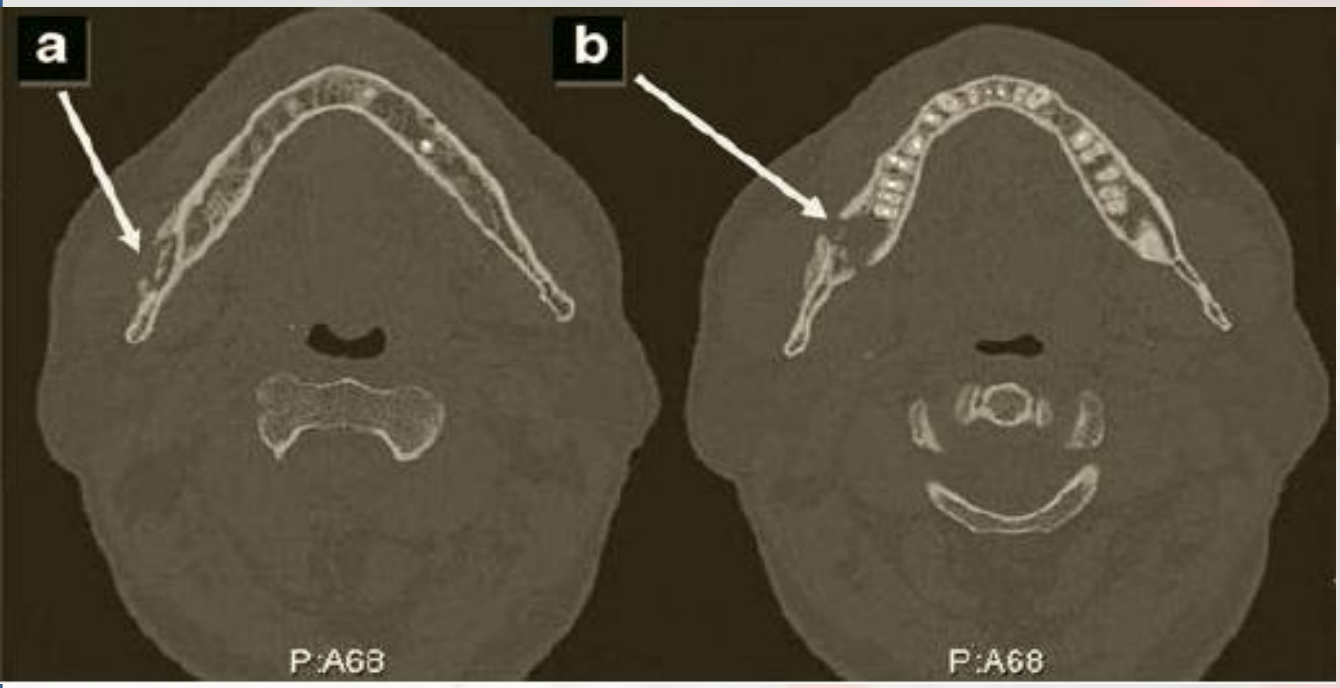
‡$P \leq 0.01$ for the between-group comparison.

Dempster, D.W., et al., *Role of RANK ligand and denosumab, a targeted RANK ligand inhibitor, in bone health and osteoporosis: a review of preclinical and clinical data.* Clin Ther, 2012. **34**(3): p. 521-36.



Osteonecrosis of the jaw

http://www.med.cmu.ac.th/dept/obgyn/2011/index.php?option=com_content&view=article&id=536:osteonecrosis-of-the-jaw&catid=45:topic-review&Itemid=561

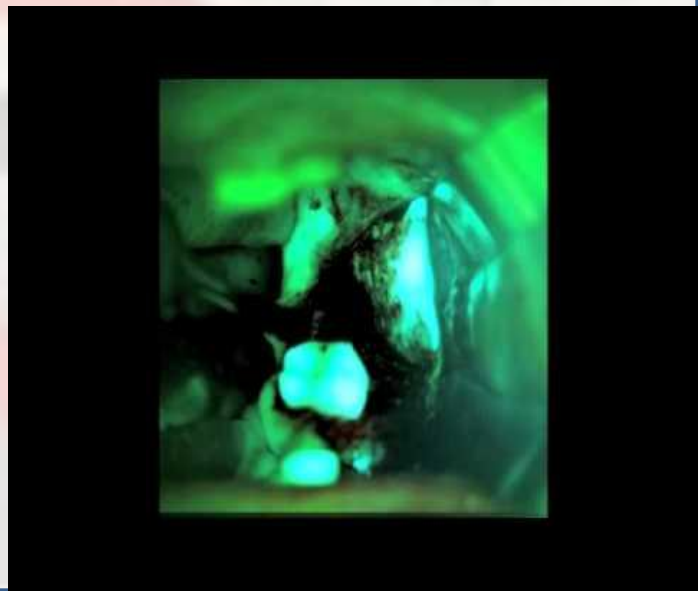


Neuprez, A., et al., *Osteonecrosis of the jaw in a male osteoporotic patient treated with denosumab.* Osteoporos Int, 2013.

Managment of osteonecrosis of the jaw

- Conservative method

- Fluorescence guided surgery



Conclusion

- Denosumab did not solve the problem of ONJ

- Denosumab is more superior than bisphosphonates

Thank you for your kind attention

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Background source