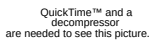
Para ver esta película, debe disponer de QuickTime™ y de un descompresor .

Nuevos fármacos:

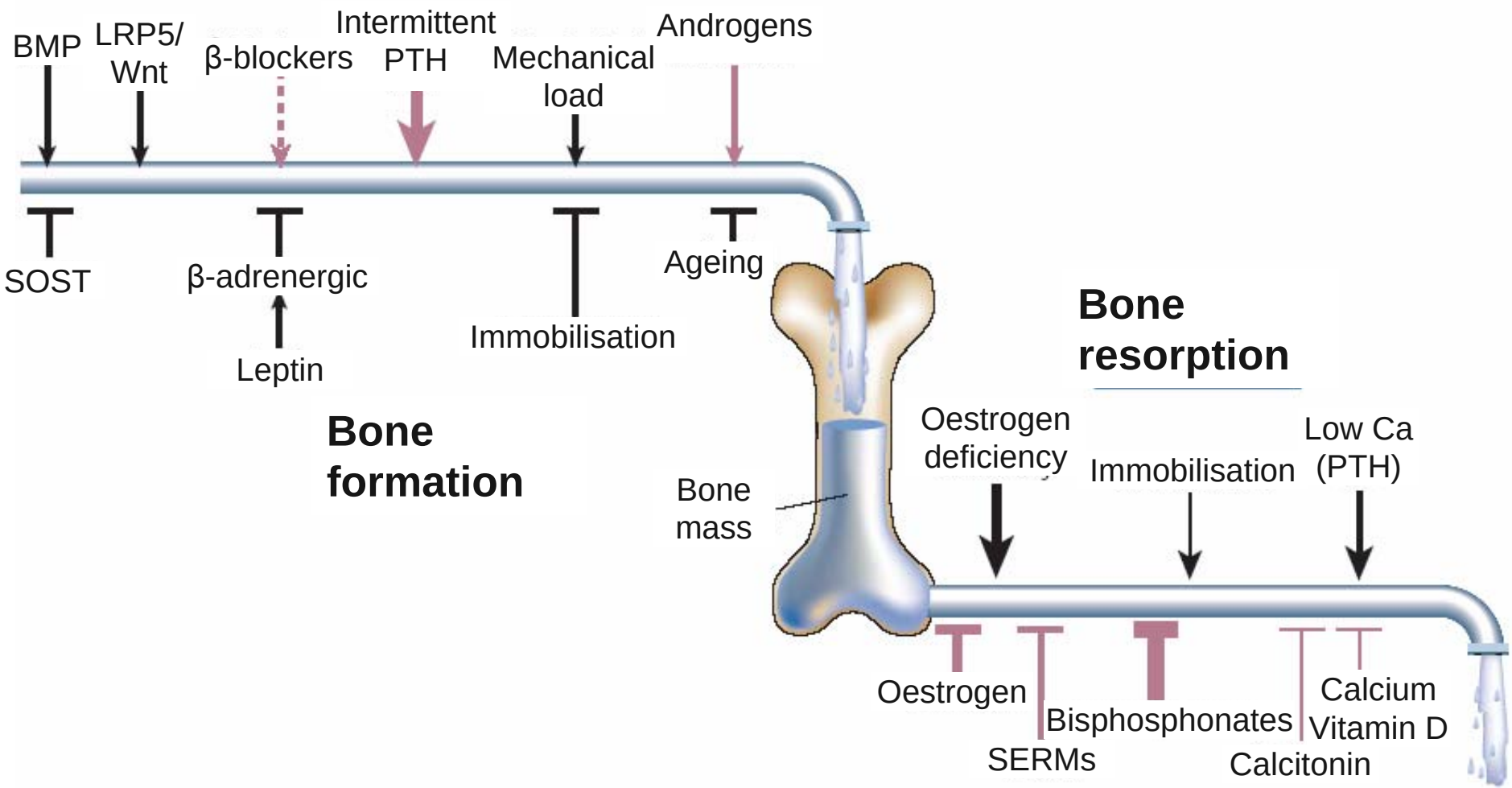
Denosumab



Adolfo Díez Pérez
Hospital del Mar -
Institut Municipal
d'Investigacions Mèdiques

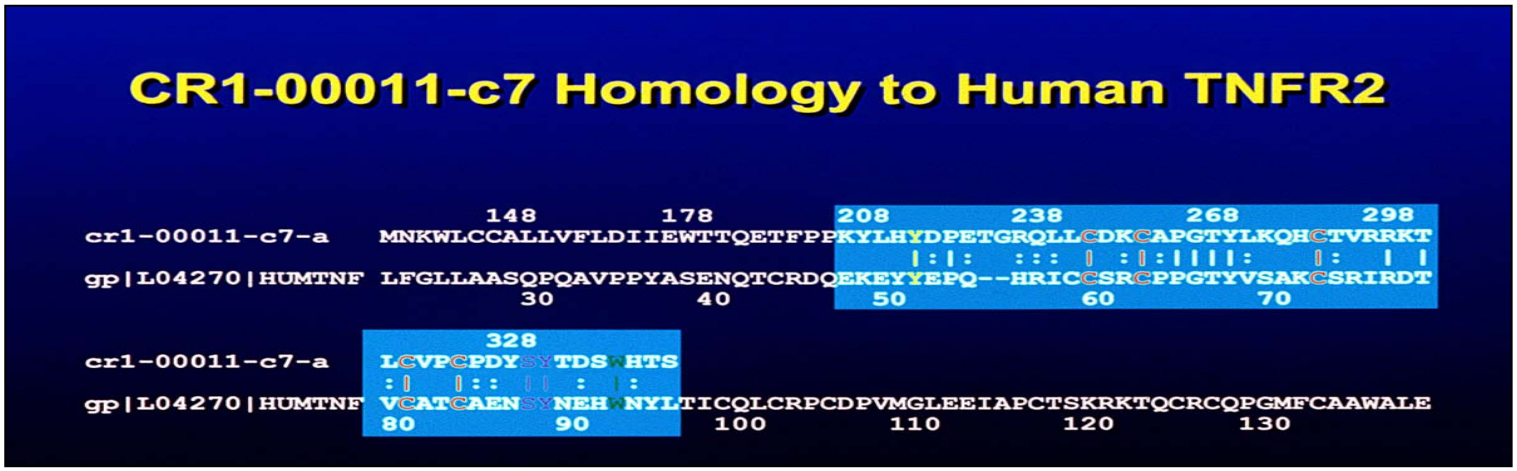
Universitat Autònoma
de Barcelona

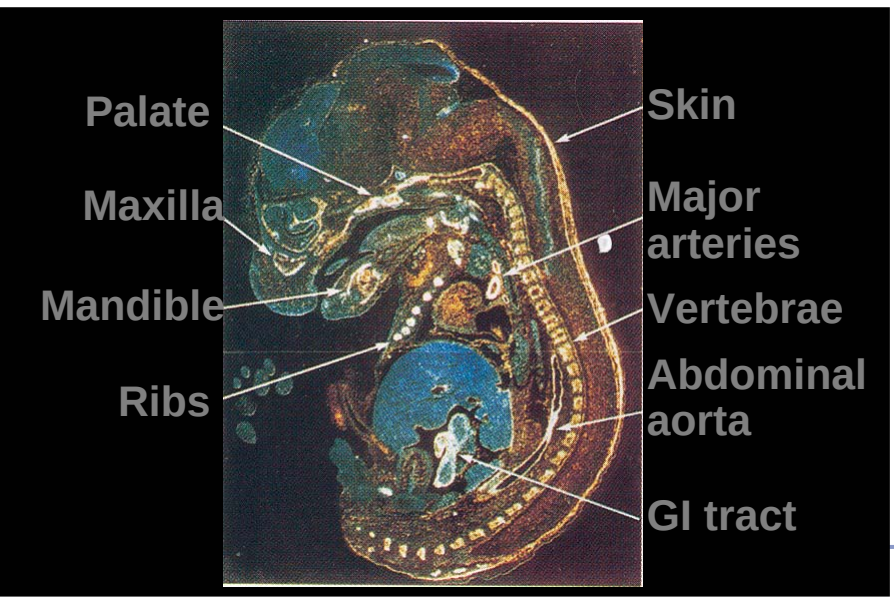
Regulación del remodelamiento



Harada S and Rodan GA. *Nature*. 2003;423:349-55.

Novel EST Sequence Identified in a Rat Foetal Intestinal cDNA Library





Tissue Distribution of OPG

- **Human:**
  - **lung, heart, placenta, kidney, osteoblasts**
- **Mouse:**
  - **Embryo: placenta, skin, major arteries, gastrointestinal tract, bone, cartilage**
  - **Adult: lung, liver, kidney, brain, testis, articular cartilage**

La ausencia de actividad OPG causa fracturas por fragilidad

Ratón
OPG
Knockout

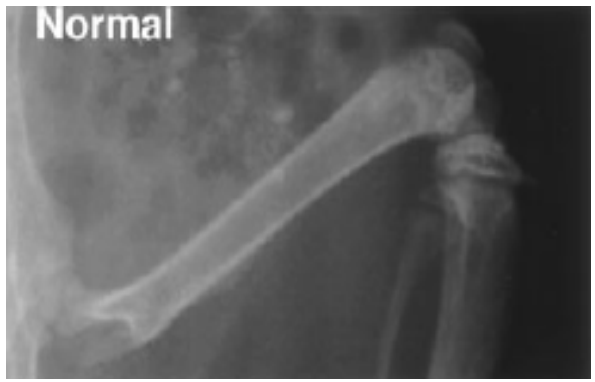
Radiografía de un ratón de 1 mes de edad OPG knockout con fracturas espontáneas por fragilidad

Bucay N, et al. *Genes Dev*. 1998;12:1260-1268.

Efecto de los niveles de OPG en la regulación de la densidad ósea

Radiografías de fémur de ratón

Ratón knockout
OPG: no producción natural de OPG



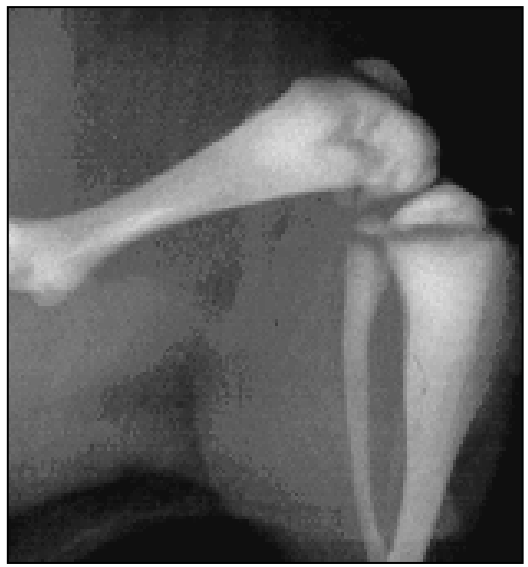
Ratón transgénico
OPG: producción aumentada de OPG

Bolon B, et al. *Arthritis Rheum.* 2002;46:3121-3135.

Efecto de RANK y Ligando RANK en la regulación de la densidad mineral

Normal

Ausencia de Ligando RANK[1]

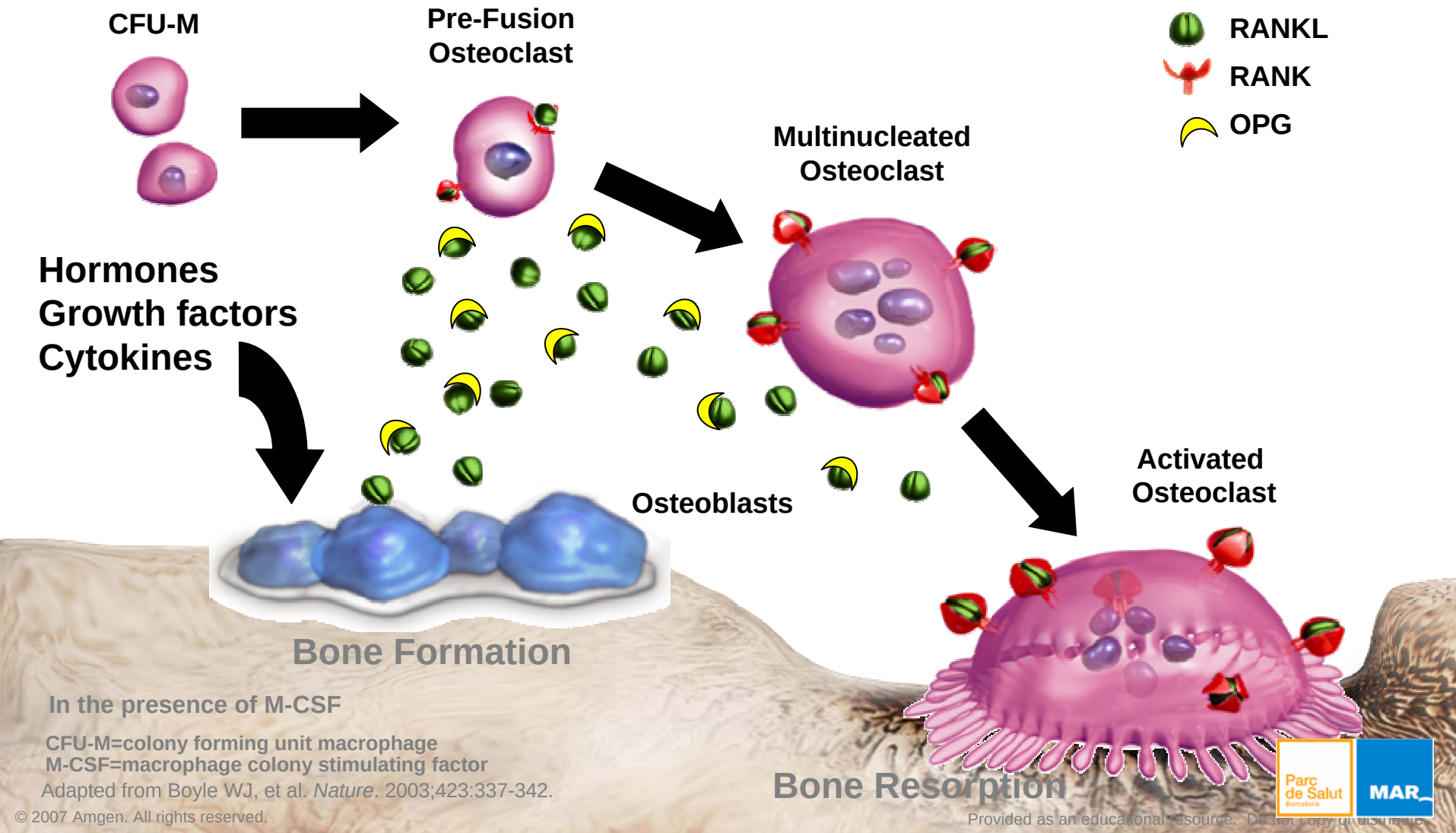


Ausencia de RANK[2]

Aumento de BMD

1 Kong YY *et al.* Nature 1999; 397: 315–323;
2 Li J *et al.* Proc Natl Acad Sci USA 2000; 97: 1566–1571

RANKL como mediador esencial de la formación, función y supervivencia del osteoclasto

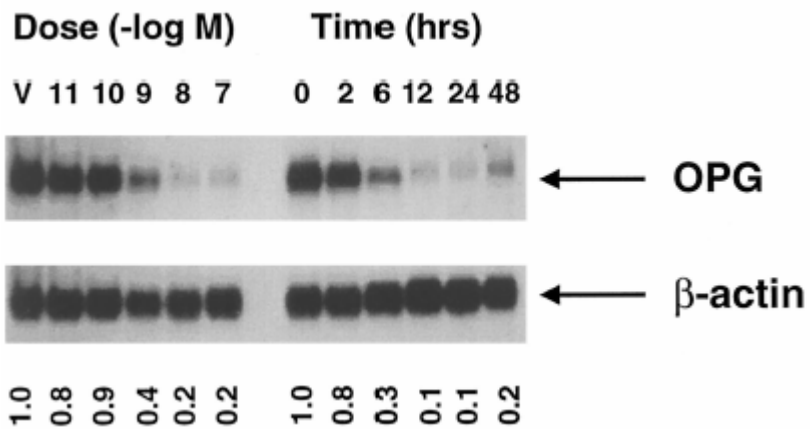


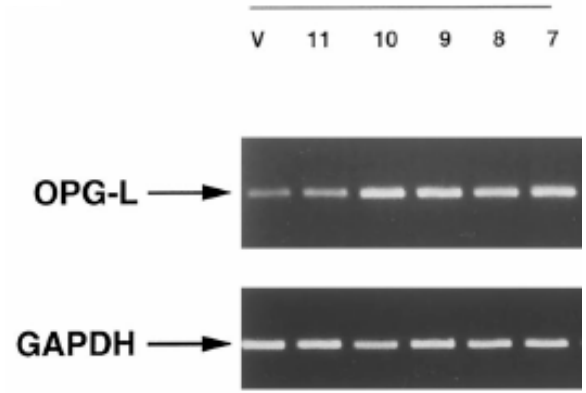
In the presence of M-CSF

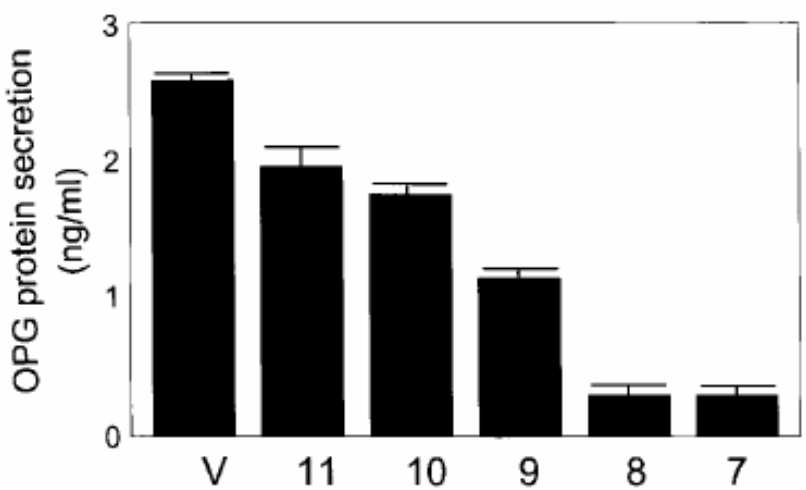
CFU-M=colony forming unit macrophage
M-CSF=macrophage colony stimulating factor

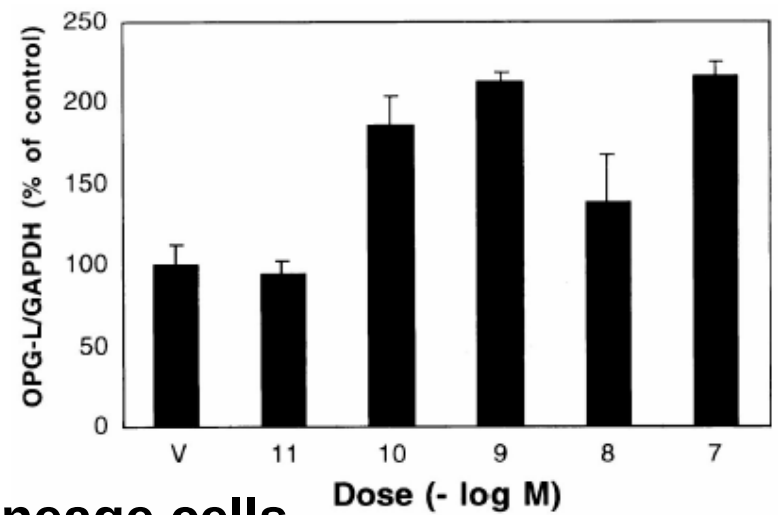
Adapted from Boyle WJ, et al. *Nature*. 2003;423:337-342.

Inhibición de OPG y estimulación de RANKL por glucocorticoides





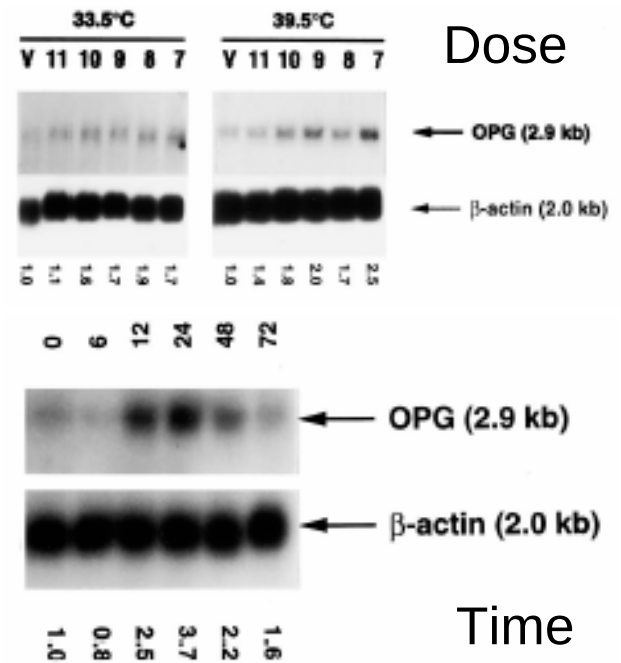




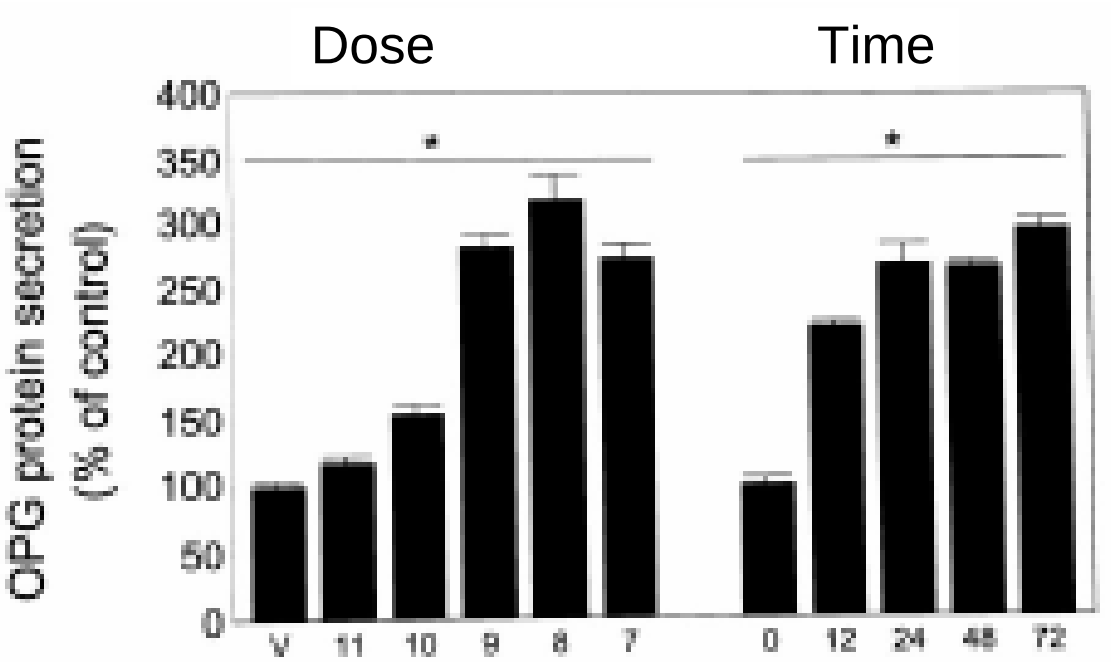
hOB lineage cells

Hofbauer LC et al. Endocrinology 1999; 140: 4382–4389

Los estrógenos estimulan la expresión génica y producción protéica de OPG por hOB



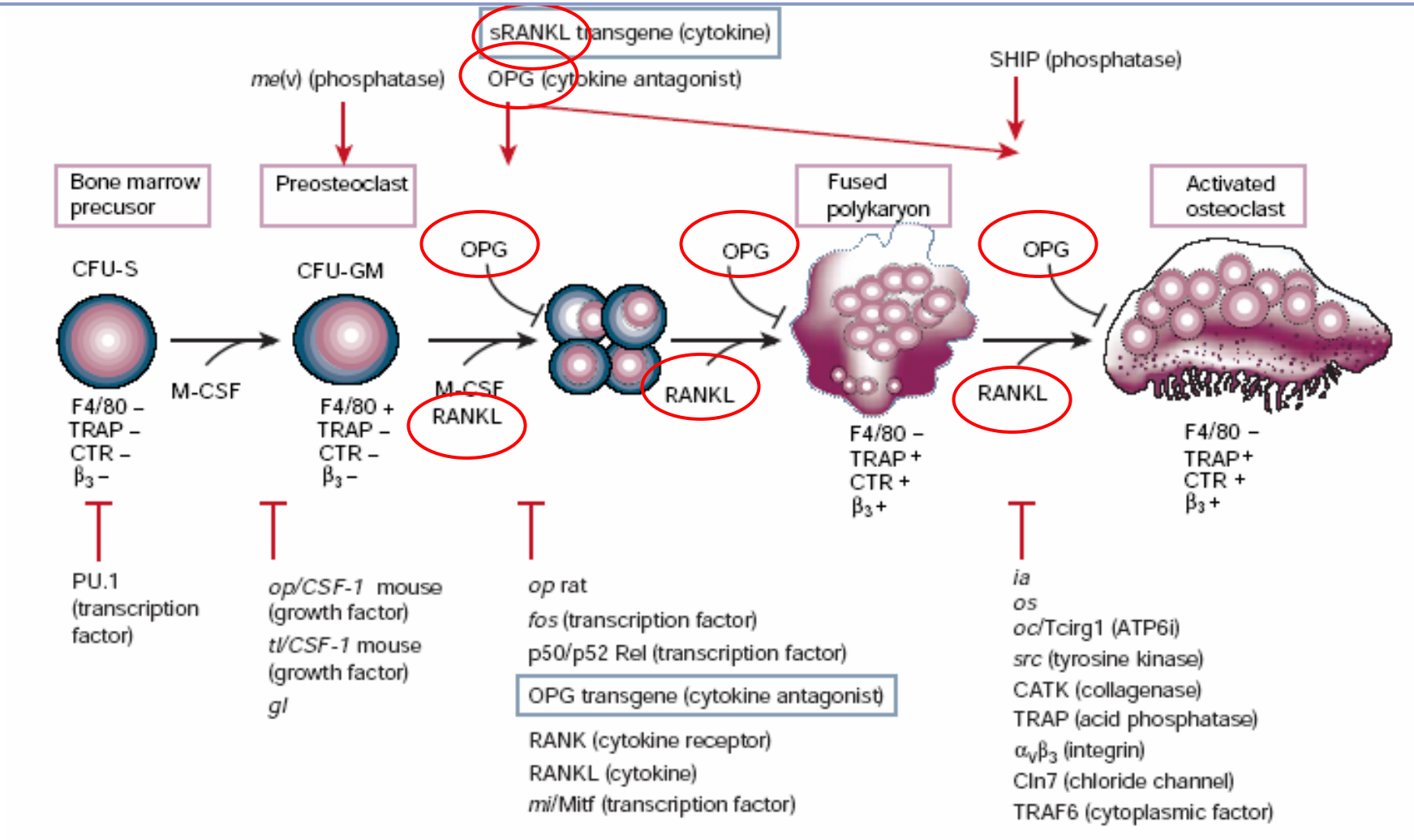
OPG nRNA levels by 17β-E2 in FOB/ER-9 cells



OPG protein secretion by 17β-E2 in FOB/ER-9 cells

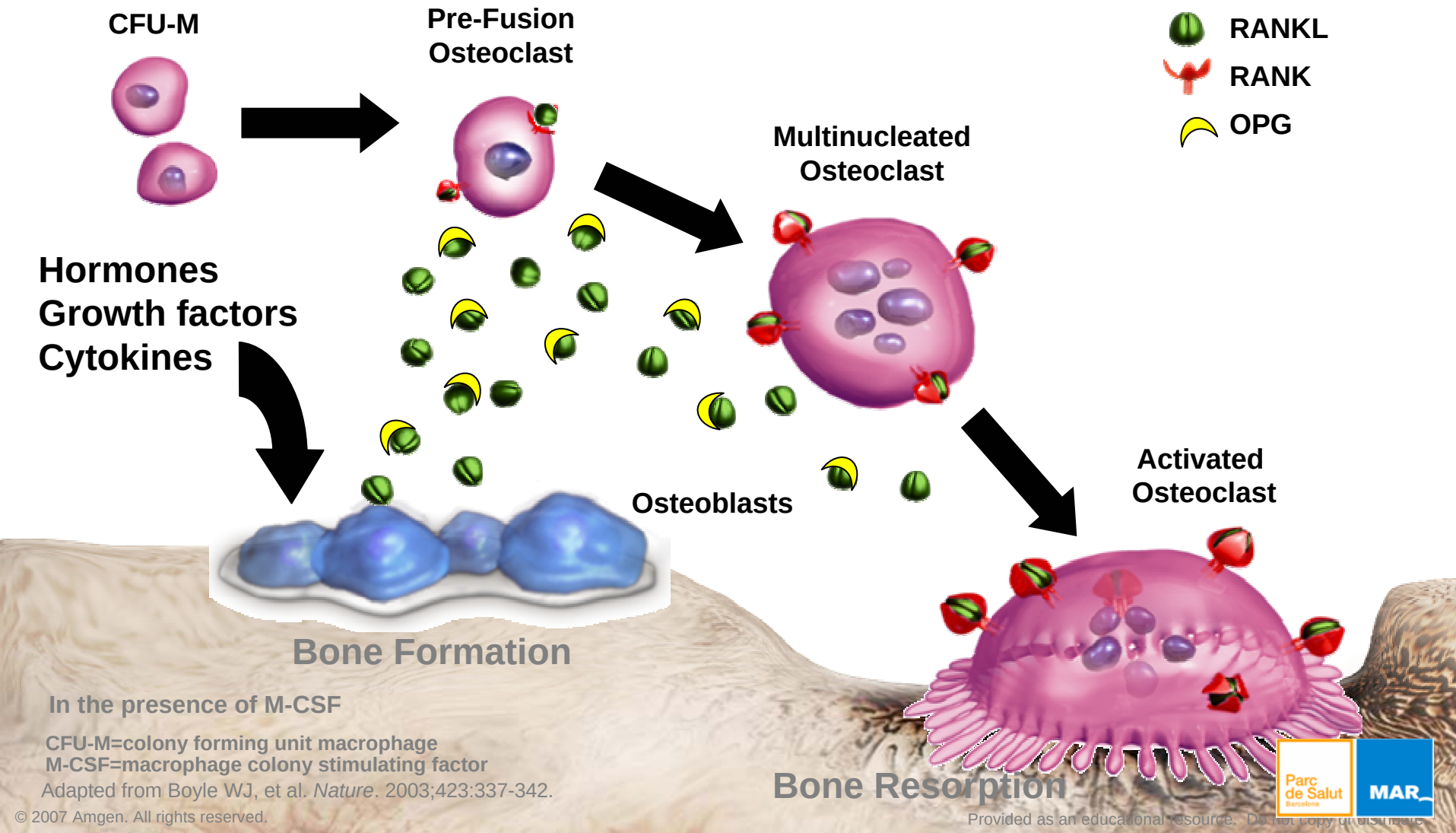
Hofbauer LC et al. Endocrinology 1999; 140: 4367-70

Diferenciación de células precursoras hematopoyéticas a osteoclasto



Boyle WJ et al. Nature 2003; 423: 337-42

RANKL como mediador esencial de la formación, función y supervivencia del osteoclasto



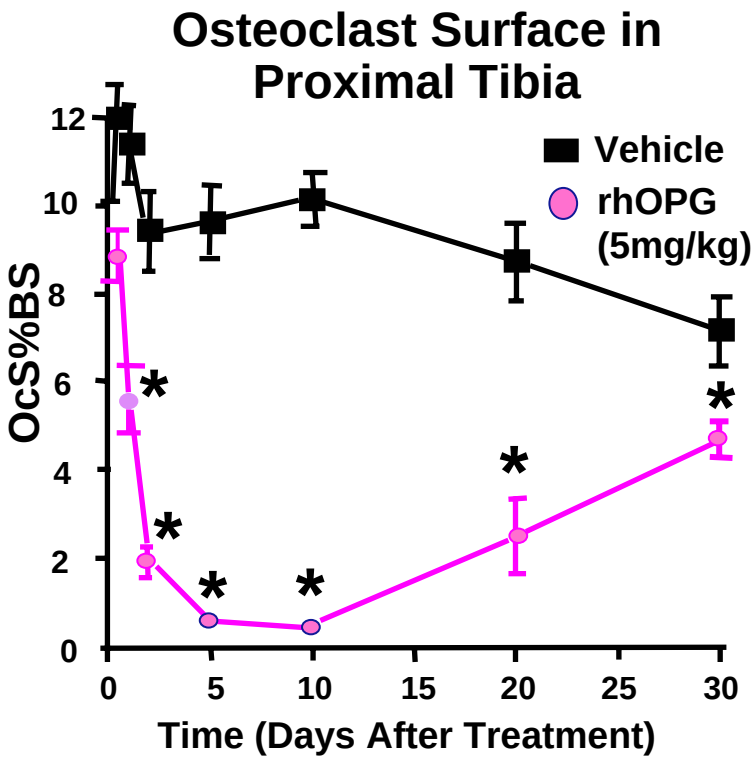
In the presence of M-CSF

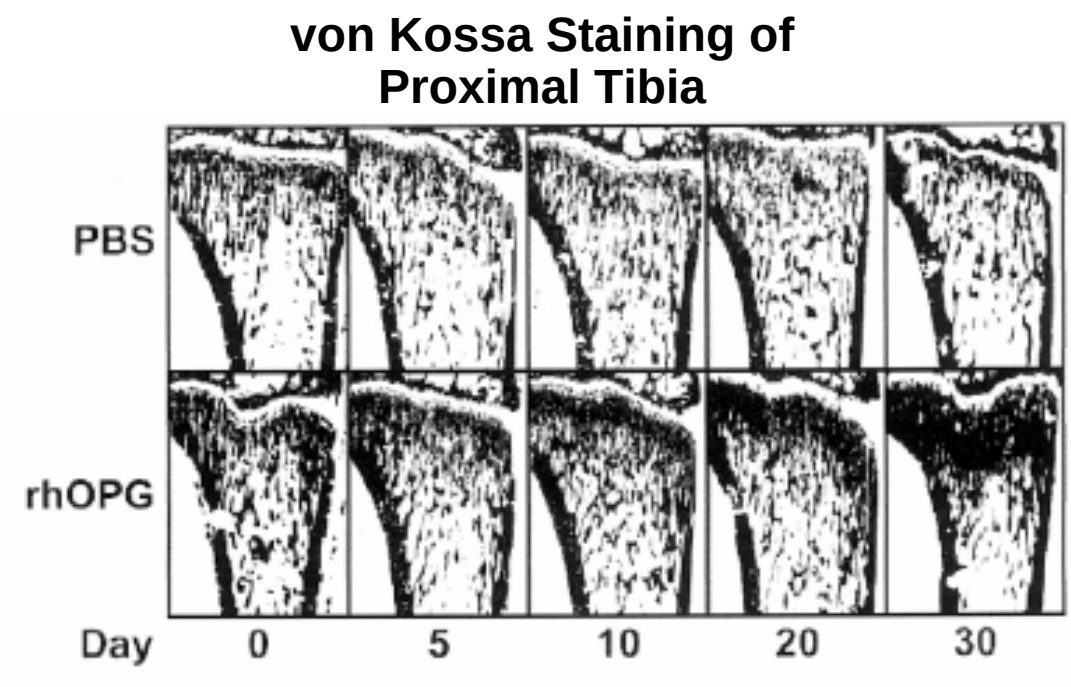
CFU-M=colony forming unit macrophage
M-CSF=macrophage colony stimulating factor

Adapted from Boyle WJ, et al. *Nature*. 2003;423:337-342.

Efecto de la OPG recombinante sobre Osteoclastos y Mineralización

Rapid but reversible reductions in OC.N. and increases in Bone Mineralization in Intact Rats

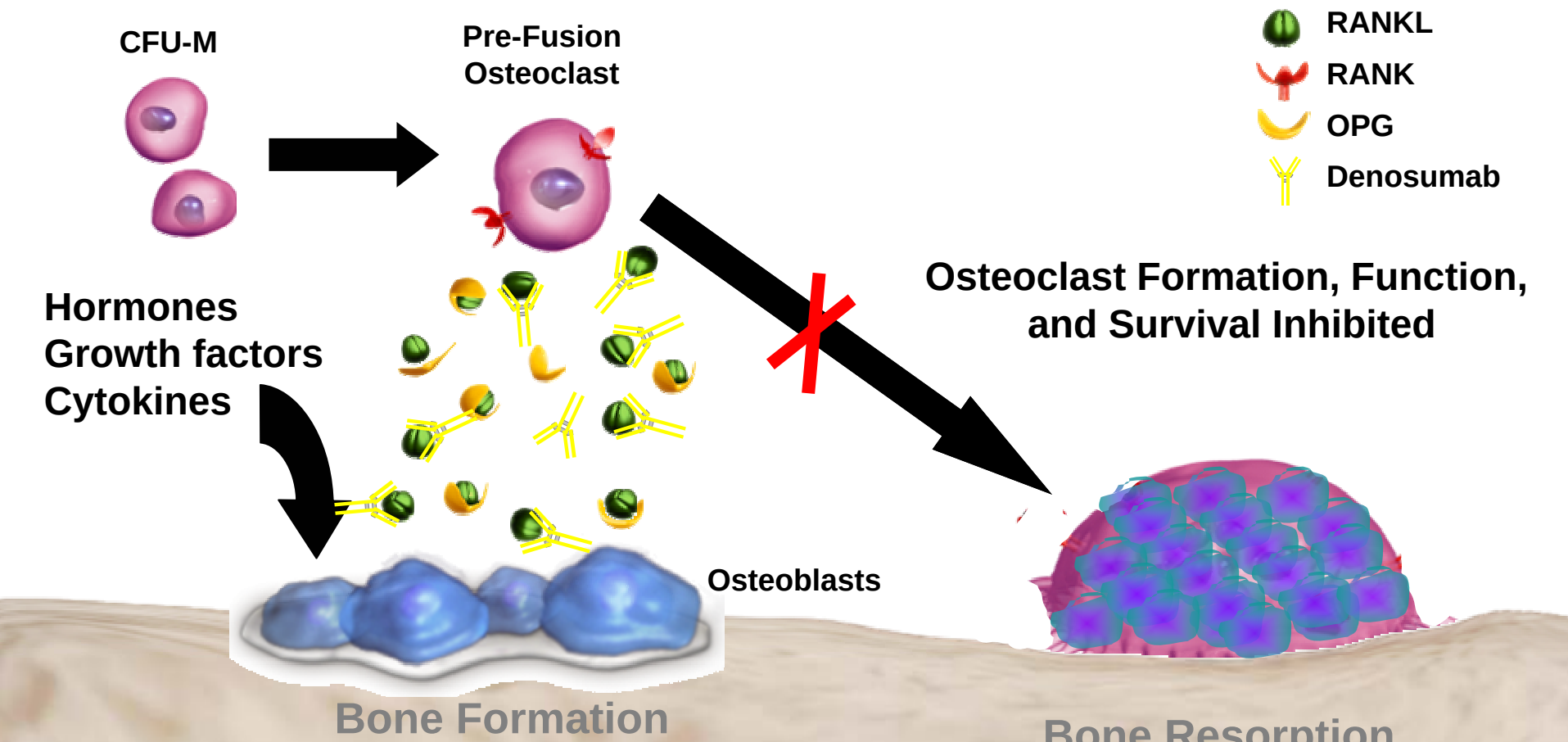




*Significantly different from vehicle, $P < 0.05$
OcS%BS = osteoclast surface

Capparelli C, *et al*. J Bone Miner Res. 2003;18:852–858

Denosumab se une al Ligando RANK e Inhibe la Formación, Función y Supervivencia del Osteoclasto



In the presence of M-CSF

CFU-M=colony forming unit macrophage
M-CSF=macrophage colony stimulating factor

Propiedades Farmacológicas de Denosumab

- Isotipo de inmunolobulina IgG_2
- Alta afinidad por el Ligando RANK humano
- Alta especificidad por el Ligando RANK
  - No unión detectable a TNFα, TNFβ, TRAIL, or CD40L
- No se han detectados anticuerpos neutralizantes

Denosumab

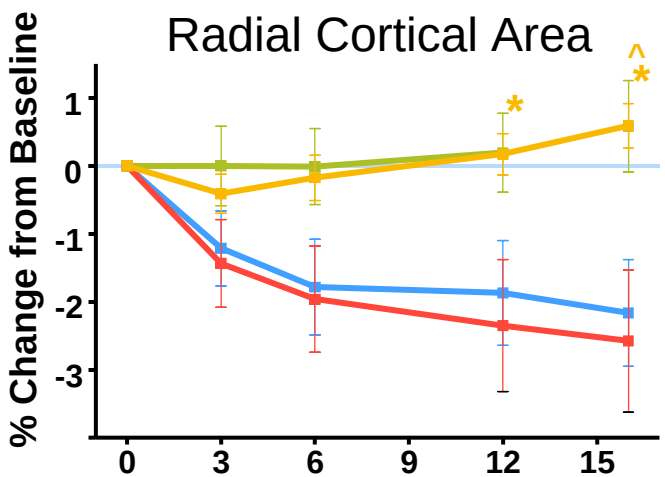
TNF = tumor necrosis factor; TRAIL = TNFα-related apoptosis-inducing Ligand.

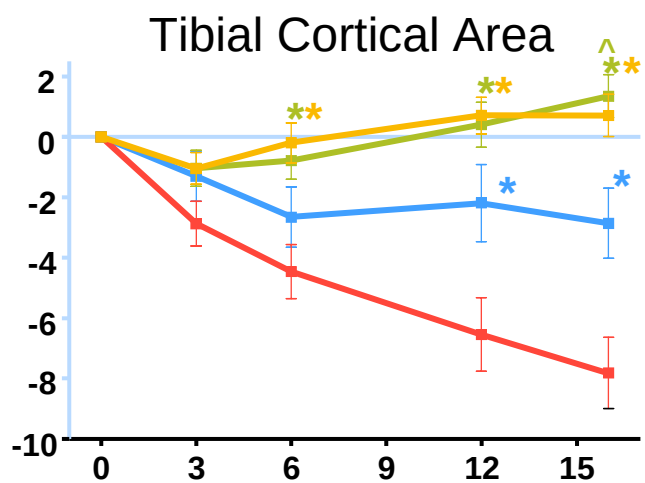
Bekker PJ, et al. *J Bone Miner Res.* 2004;19:1059-1066. Elliott R, et al. *Osteoporos Int.* 2007;18:S54. Abstract P149. McClung MR, et al. *New Engl J Med*. 2006;354:821-31.

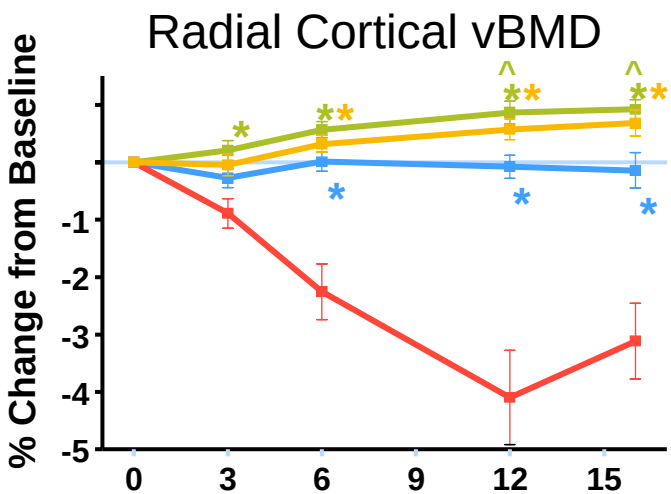
Cambios en Hueso Cortical (Masa, Area y vBMD) en Monos OVX

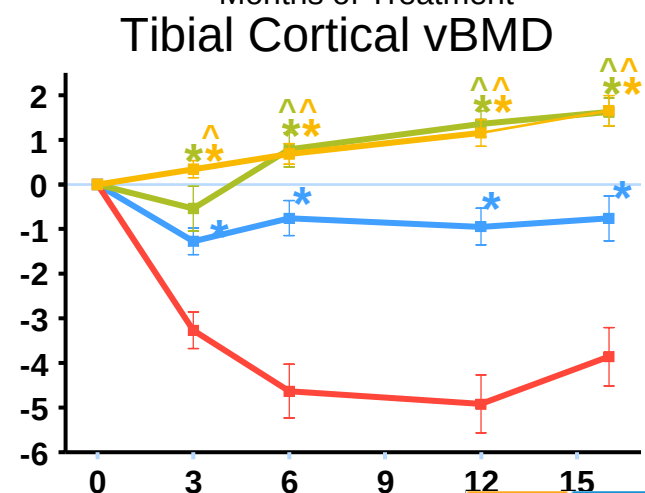
SHAM Control
OVX Control
OVX + 25 mg/kg DMAB
OVX + 50 mg/kg DMAB

pQCT Tibial Diaphysis





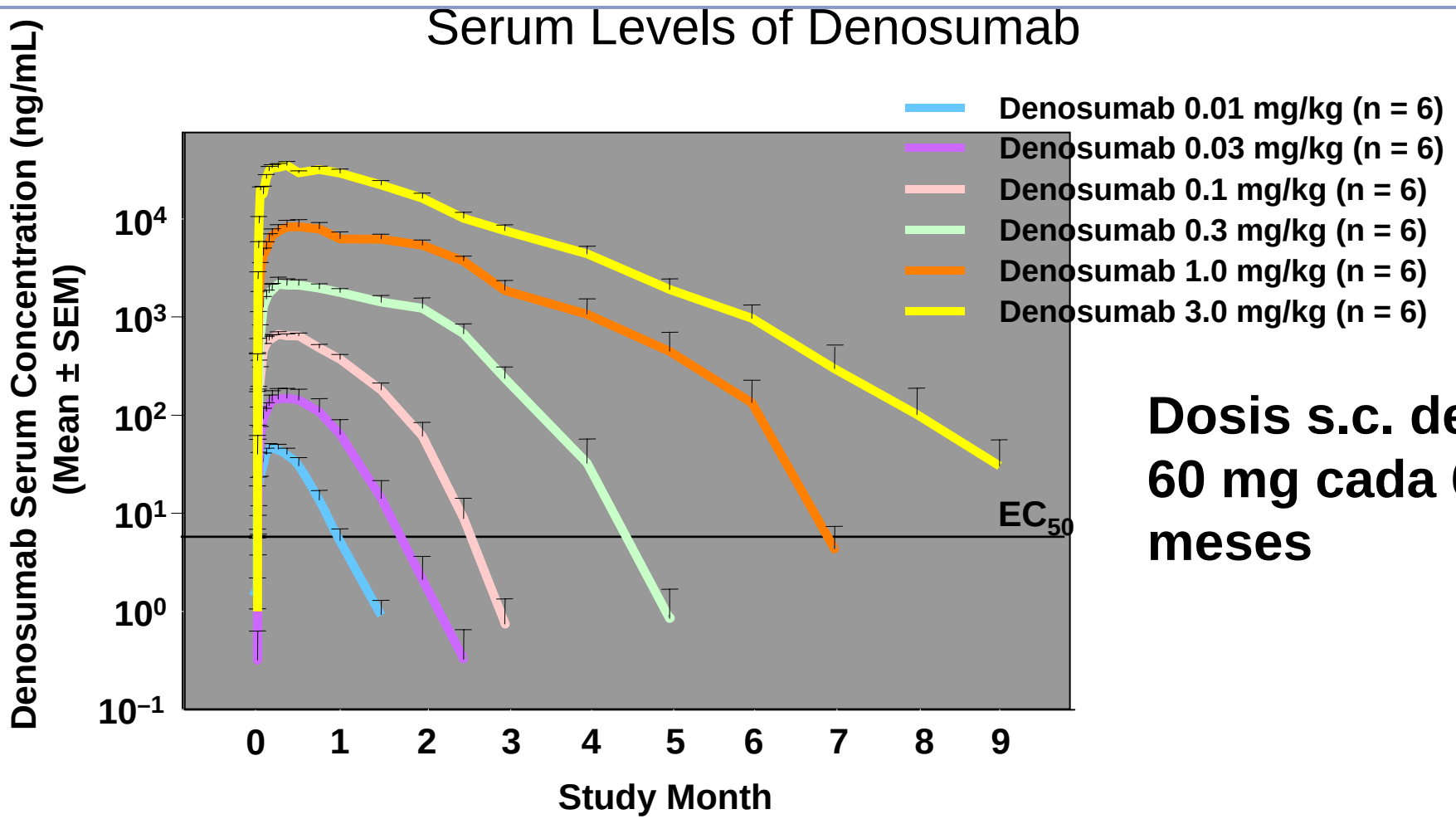




Data: Mean ± SE
**P*< 0.05 vs. OVX-Veh
^*P*< 0.05 vs. Sham-Veh

Ominsky *et al*. JBMR 2007 (Suppl 1) abstract 1082

Denosumab Fase 1 en Mujeres Sanas Postmenopáusicas

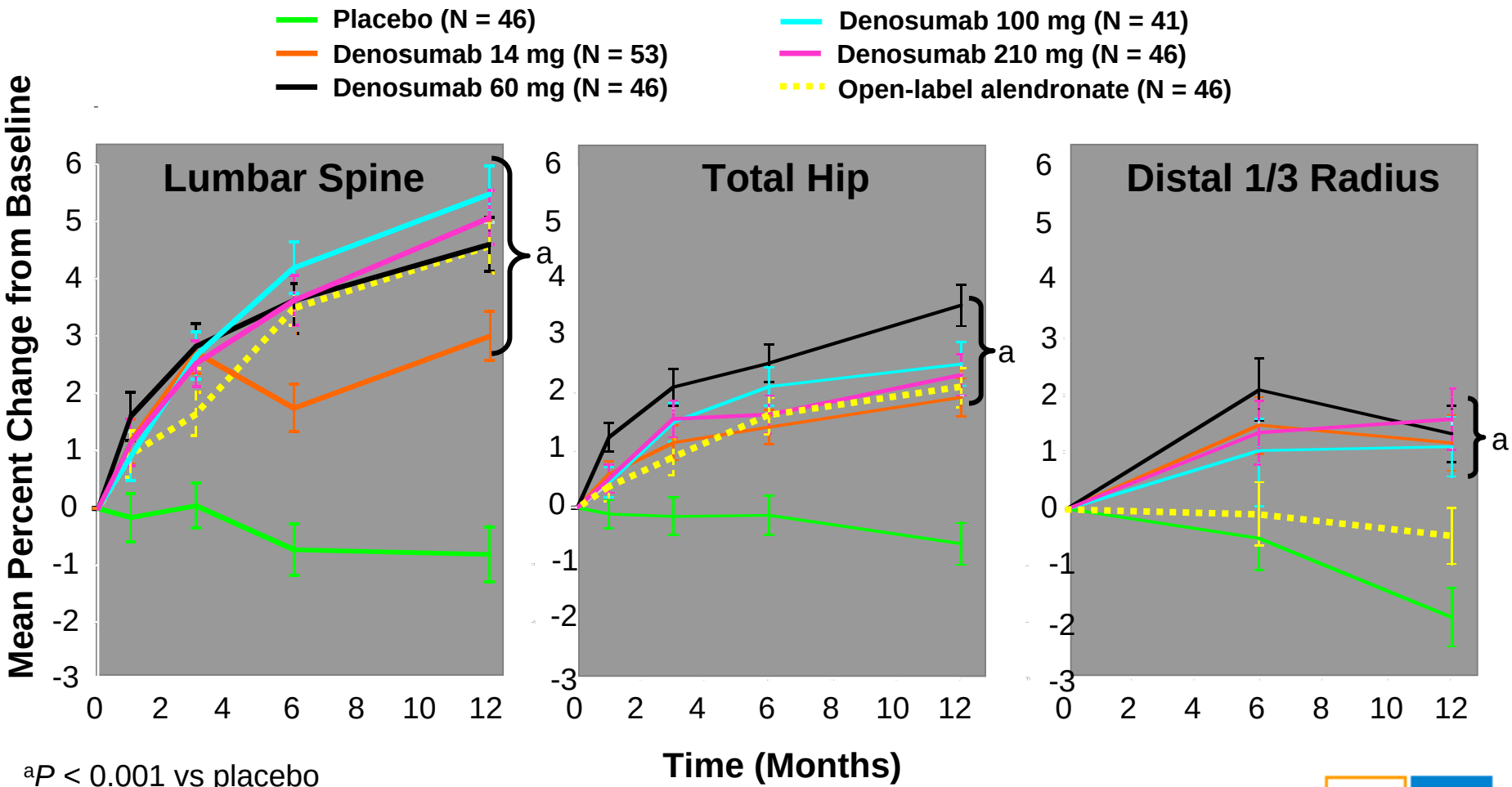


Dosis s.c. de 60 mg cada 6 meses

Bekker PJ, et al. *J Bone Miner Res.* 2004;19:1059-1066.

Fase II Mujeres Postmenopáusicas con Baja DMO

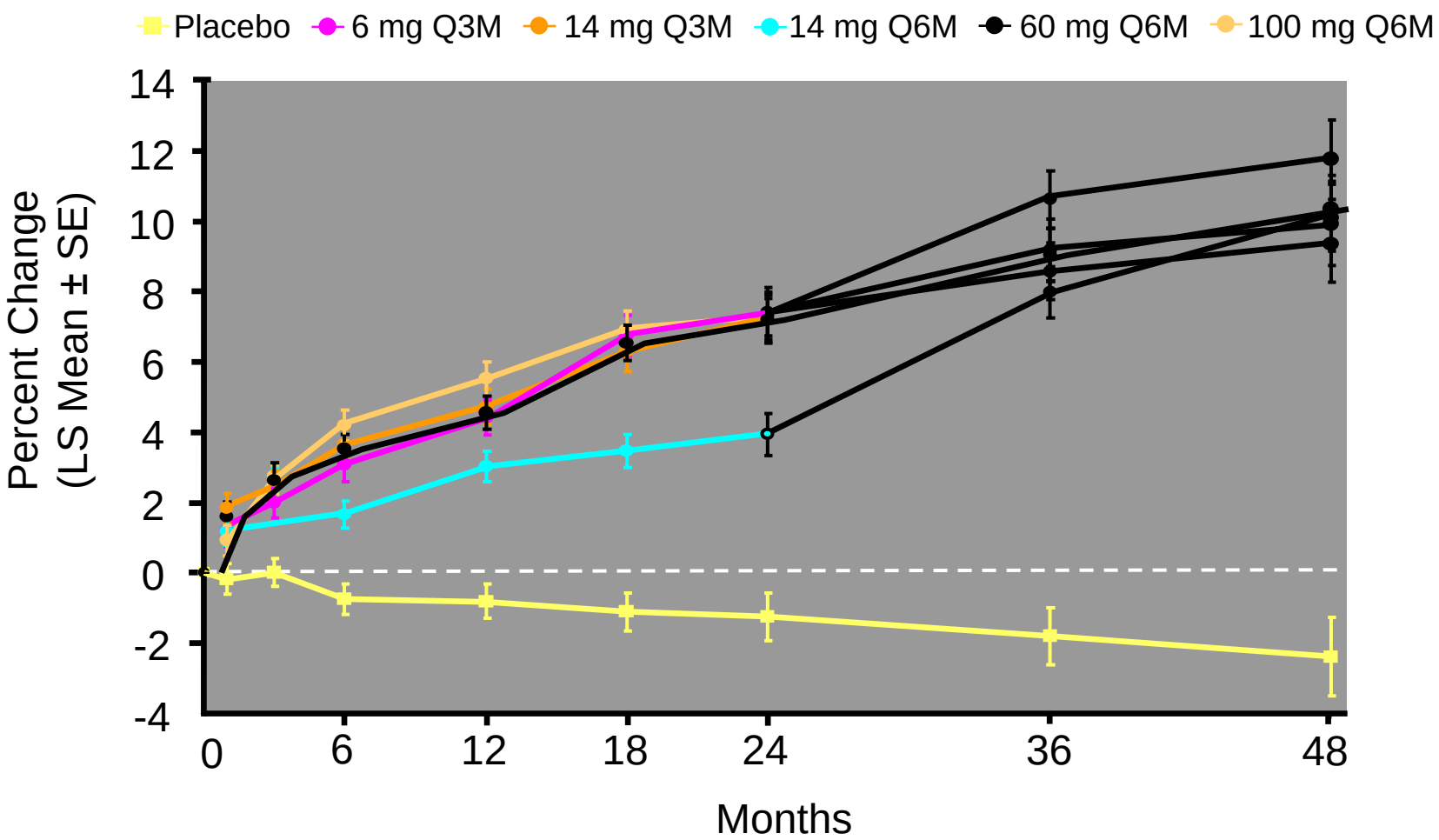
Lumbar Spine Hip, and Distal 1/3 Radius BMD at 12 months



[a]*P* < 0.001 vs placebo

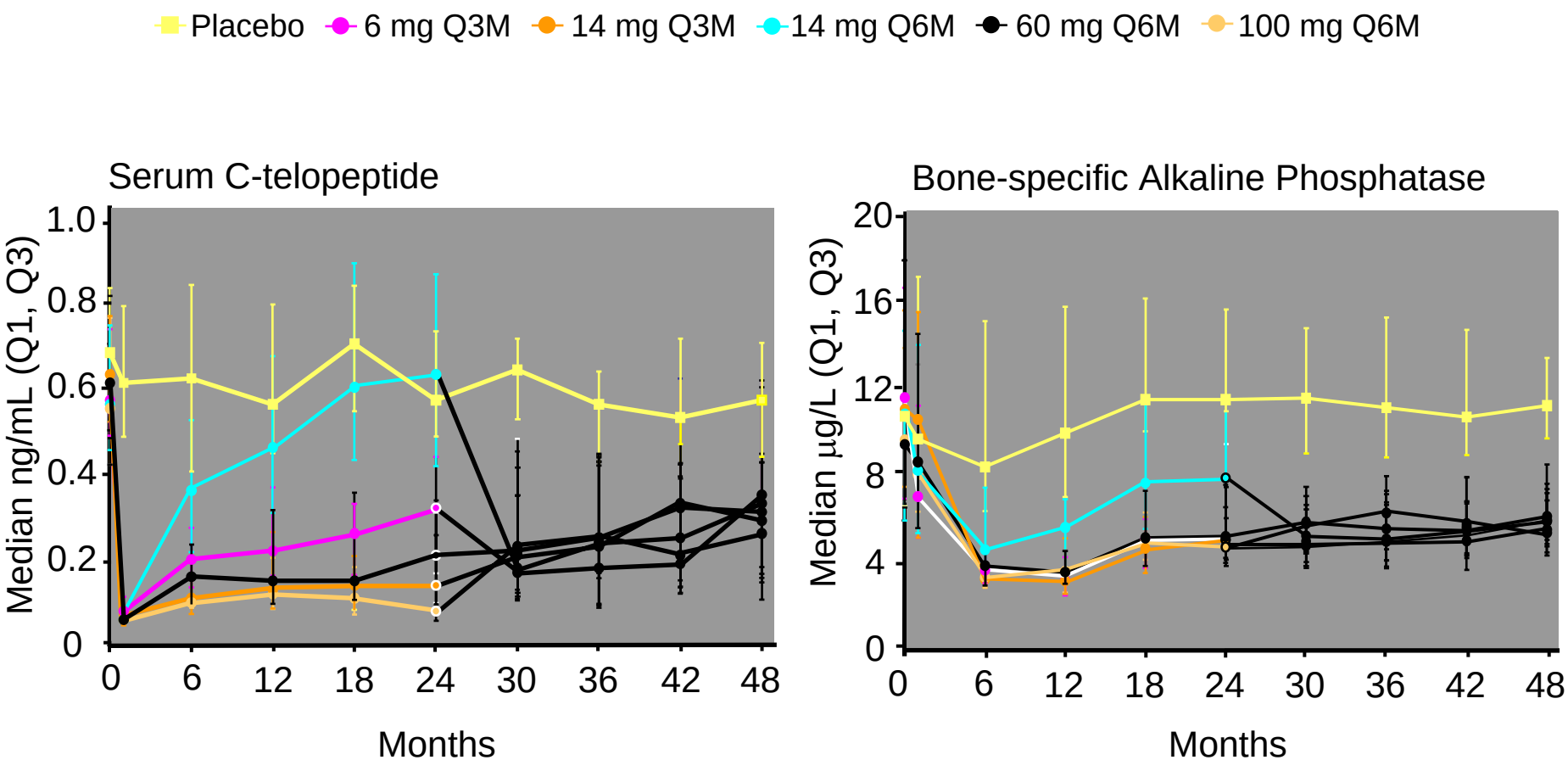
McClung MR, et al. *N Engl J Med.* 2006;354:821-831.

Efecto de 4 Años de Tratamiento con Denosumab en DMO Lumbar



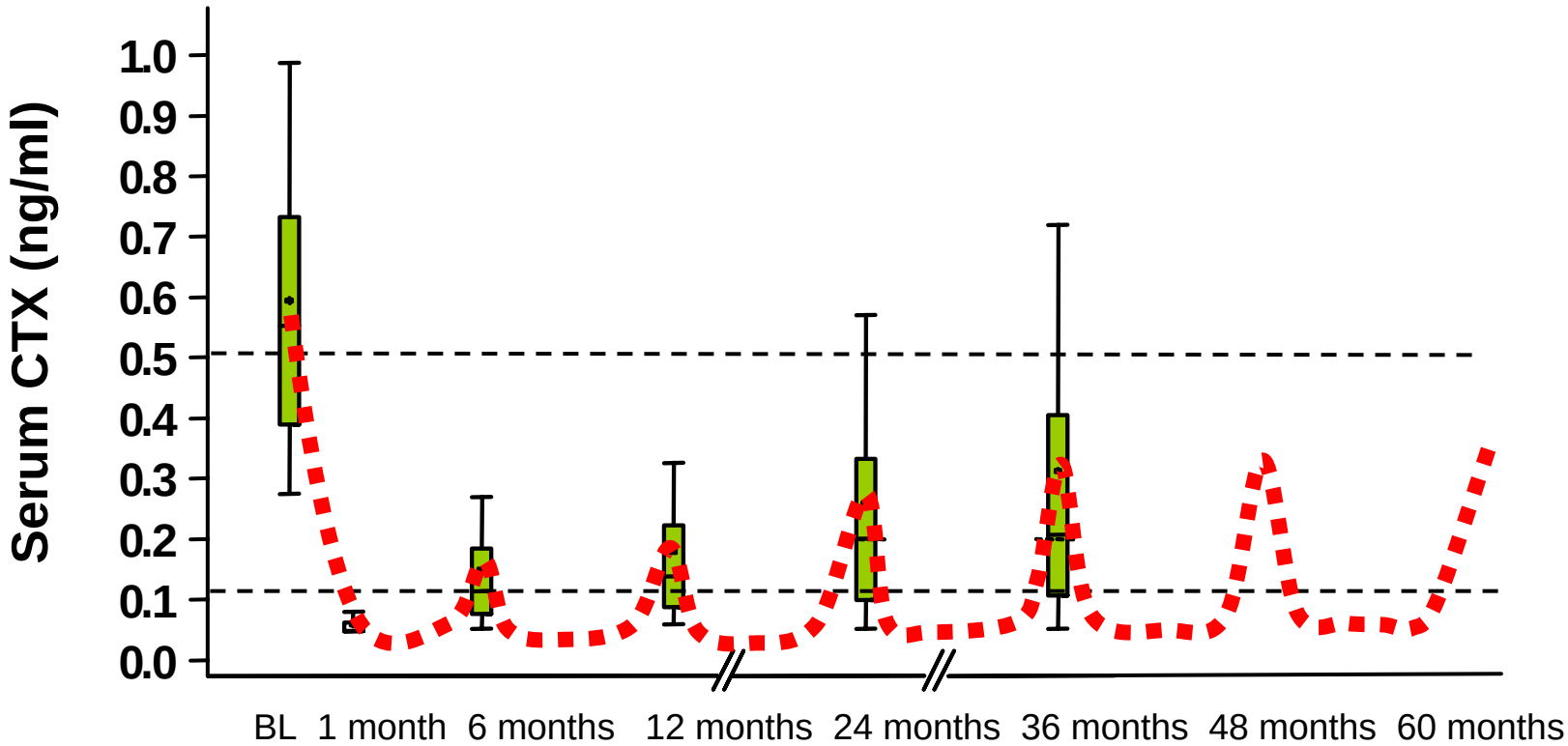
Miller PD et al *Bone* 2008;doi:10.1016/j.bone.2008.04.007

Efecto de 4 Años de Tratamiento con Denosumab Sobre CTX y BSAP



Miller PD et al *Bone* 2008;doi:10.1016/j.bone.2008.04.007

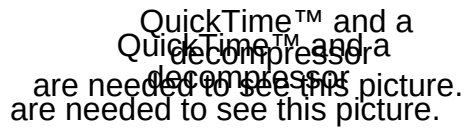
CTX Sérico a los 5 Años con Denosumab



Each box-and-whisker plot shows the middle 80% of the observations (deleting the top and bottom 10% of the data). Horizontal lines represent the premenopausal range from the BONTURNO study Reference Range Study: 0.11 to 0.51 ng/mL for CTX)

Adami et al Calcif Tissue Int. 2008 May;82(5):341-7

Estudio fase III: FREEDOM



Cummings SR et al. N Engl J Med 2009; 361: 756-65

Efecto de Denosumab sobre el Riesgo de Fractura Vertebral

QuickTime™ and a
decompressor
are needed to see this picture.

Risk Ratio
0,32
(0,26-0,41)
P<0,001

Cummings SR et al. N Engl J Med 2009; 361: 756-65

Efecto de Denosumab sobre el Riesgo de Fractura No-vertebral

QuickTime™ and a
decompressor
are needed to see this picture.

Hazard Ratio
0,80
(0,67-0,95)
P=0,01

Cummings SR et al. N Engl J Med 2009; 361: 756-65

Efecto de Denosumab sobre el Riesgo de Fractura de Fémur

QuickTime™ and a
decompressor
are needed to see this picture.

Hazard Ratio
0,60
(0,37-0,97)
P=0,04

Cummings SR et al. N Engl J Med 2009; 361: 756-65

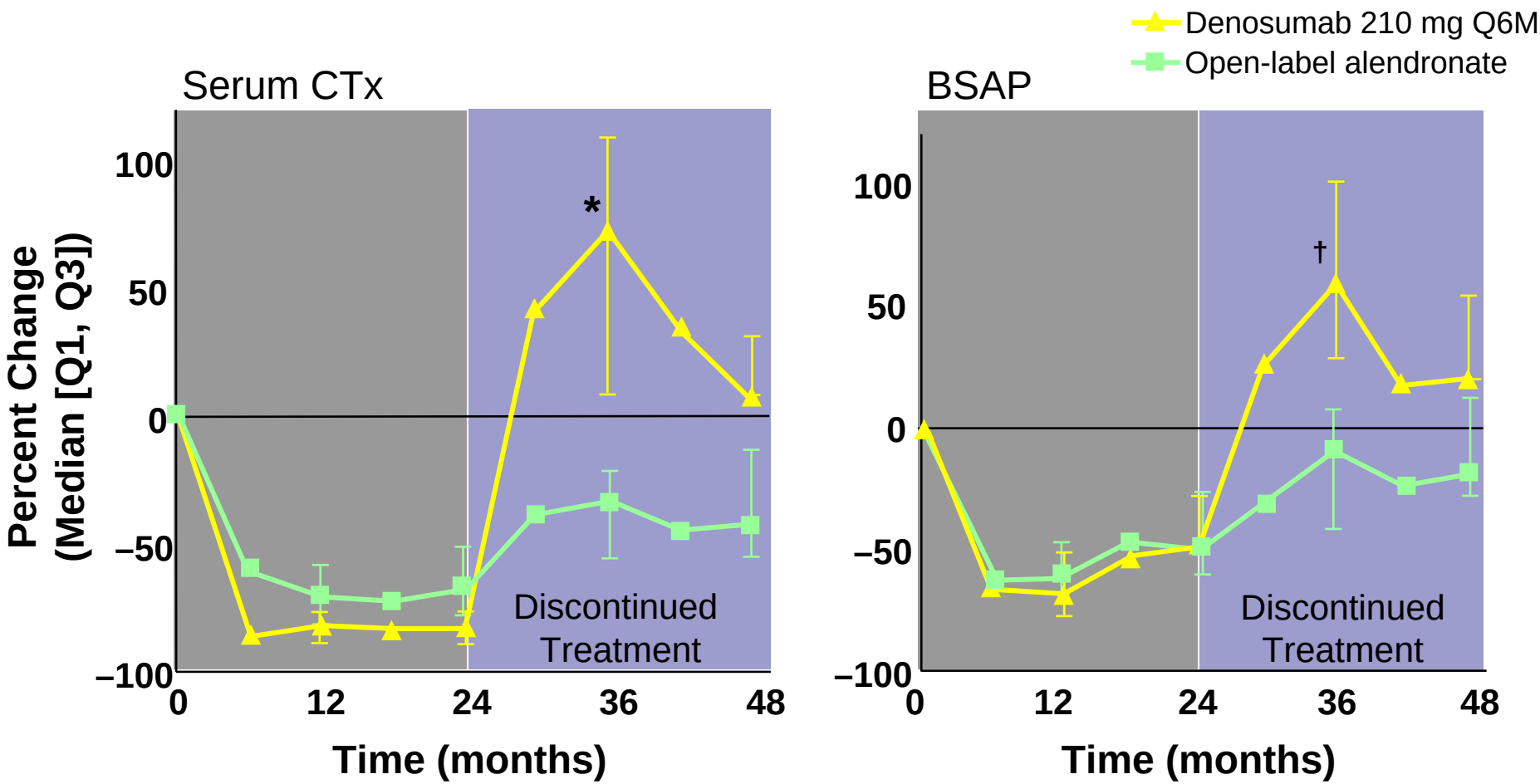
Efecto sobre los Marcadores Bioquímicos de Remodelamiento

QuickTime™ and a
decompressor
are needed to see this picture.

QuickTime™ and a
decompressor
are needed to see this picture.

Cummings SR et al. N Engl J Med 2009; 361: 756-65

CTx y BSAP tras Interrupción de Denosumab o Alendronato

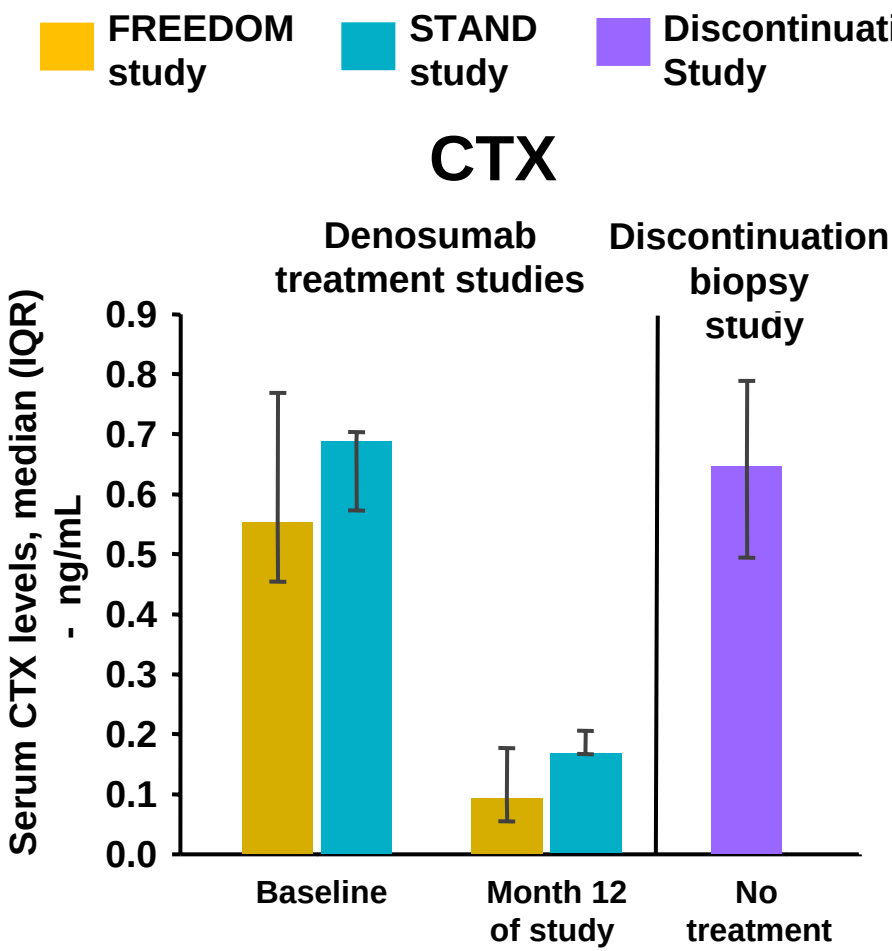


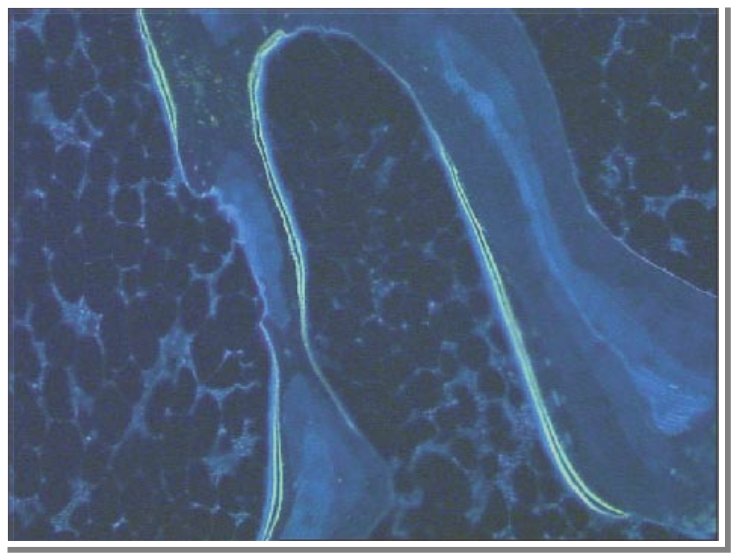
*P < 0.001 at month 36 and = 0.05 at month 48 vs placebo

†P = 0.008 at month 36 vs placebo

Miller P, *et al. Bone* 2008;43:222-9.

Reversibilidad del Efecto de Denosumab sobre el Remodelamiento





Denosumab discontinued for 24 months

Brown J. et al. ASBMR 2010

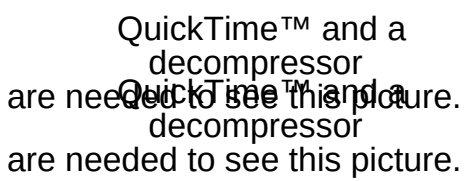
Acontecimientos Adversos de Denosumab vs. Placebo

QuickTime™ and a
decompressor
are needed to see this picture.

* NA denotes not applicable.
🖬 P values are based on the log-rank test, except for between-group comparisons of deaths and cardiovascular events, which were based on the Cox proportionalhazards model with adjustment for the baseline cardiovascular risk score.

Cummings SR et al. N Engl J Med 2009; 361: 756-65

Acontecimientos Adversos Graves de Denosumab vs. Placebo



* NA denotes not applicable.

🖬 P values are based on the log-rank test, except for between-group comparisons of deaths and cardiovascular events, which were based on the Cox proportionalhazards model with adjustment for the baseline cardiovascular risk score.

Cummings SR et al. N Engl J Med 2009; 361: 756-65

Acontecimientos Adversos Poco frecuentes (< 1-2%)

QuickTime™ and a
decompressor
are needed to see this picture.

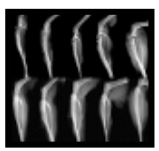
* NA denotes not applicable.
🖬P values log-rank test, except for between-group comparisons of deaths and cardiovascular events, which were based on the Cox proportionalhazards model with adjustment for the baseline cardiovascular risk score. ‡P≤0.05 for the between-group comparison (MedDRA). ¶ Excludes falls that occurred on the same day as a fracture.§ P≤0.01 for the between-group comparison.

Cummings SR et al. N Engl J Med 2009; 361: 756-65

Descubrimiento y desarrollo de la Vía RANK/RANKL/OPG y Denosumab

1995

OPG is disclosed in patent filings as an important regulator of bone density

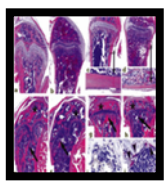


1997

Identification and cloning of RANK/ RANKL and OPG published in *Nature* and *Cell* [1,2]

1998

A molecule that binds to OPG was identified and referred to as OPGL; found to be identical to RANKL; OPG recognized as a decoy receptor[3,4]



1999

OPG protein enters human testing

Publications of scientific findings in journals including *Nature* and *Journal of Cell Biology* [5-7]

2000

OPG-Fc and Fc-OPG enter human testing

2001

First dose of denosumab administered in human on June 30th

Additional approaches to inhibiting RANKL are explored in humans

2004

First single-dose study of denosumab in post-menopausal women published in *JBMR*[8]

Phase 3 trials with denosumab in post-menopausal women initiated[9]

2006

Phase 2 trial in post-menopausal women with low BMD published in *NEJM*[10]

2008

Key denosumab clinical data published:

Ph 2 PMO 4-year data in *Bone*[11]

Ph 3 DEFEND trial in *JCEM*[12]

DECIDE Ph 3 trial in *JBMR*[13]

2009

Key denosumab clinical data published:

Ph 3 STAND in *JBMR*[14]

Ph 3 FREEDOM in *NEJM*[15]

1. Anderson DM, et al. *Nature*. 1997;39 0:175-179.
2. Simonet WS, et al. *Cell*. 1997;89:309 -319.
3. Lacey DL, et al. *Cell*. 1998;93:165-1 6.
4. Yasuda H, et al. *Proc Natl Acad Sci U S A*. 1998;95:3597-3602.
5. Kong Y, et al. *Nature*. 1999;397:315-323.
6. Kong Y, et al. *Nature*. 1999;402:304-309.
7. Burgess TL, et al. *J Cell Biol*. 1999;145:527-538.
8. Bek er PJ, et al. *J Bone Miner Res*. 2004;19:1059-1066.
9. Ava lable at: www.clinic altrials.gov. Access d June 16, 2008.
10. Mc Clung MR, et al. *N Engl J Med*. 2006;3 4:821-831.
11. Miller PD, et al. *Bone*. 2008;43:222-229.
12. Bone HG, et al. *J Clin Endocrinol Metab*. 2008;93(6):2149-2157.
13. Brown JP, et al. *J Bone Miner Res*. 2009;24:153-161.
14. Kendler DL, et al. [Published online ahead of print July 13, 2009]. *J Bone Miner Res*. doi:10.1359/JBMR.090716.
15. Cummings SR, et al. N Engl J Med. 2009 Aug 20;361(8):756-65.

RANKL = RANK ligand
OPG = osteoprotegerin
OPGL = OPG Ligand (OPG-binding molecule)

Conclusiones

- El tratamiento con Ac monoclonales anti-RANKL (Denosumab) en inyección subcutánea cada 6 meses, es un supresor de la resorción:
  - Potente
  - Altamente selectivo
  - Reversible

Conclusiones

- Denosumab es eficaz en reducir las fracturas:
  - Vertebrales
  - No vertebrales
  - De fémur
- La posología es muy adecuada
- El tratamiento es seguro