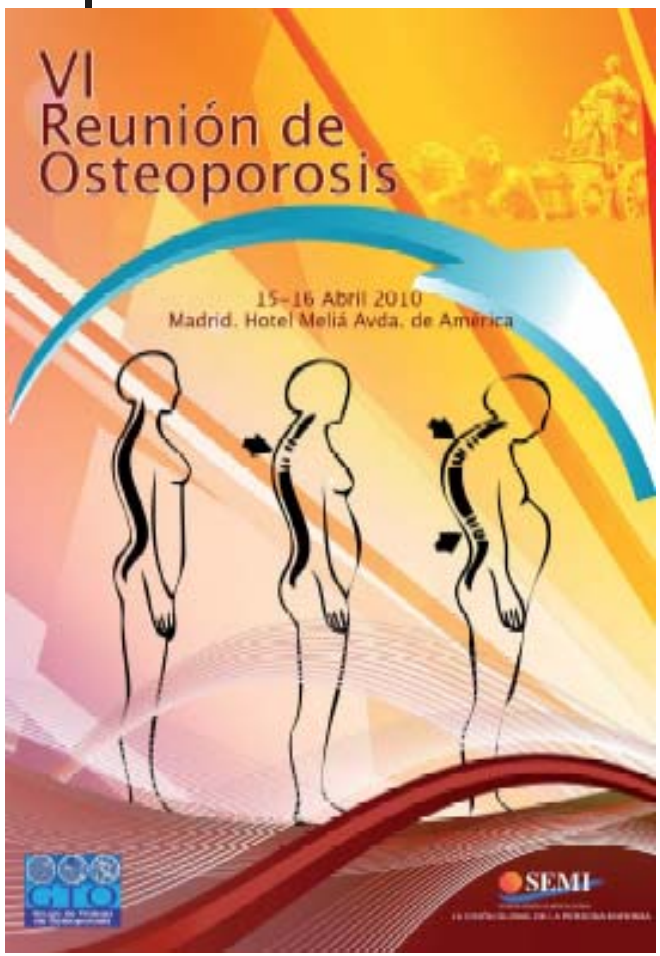
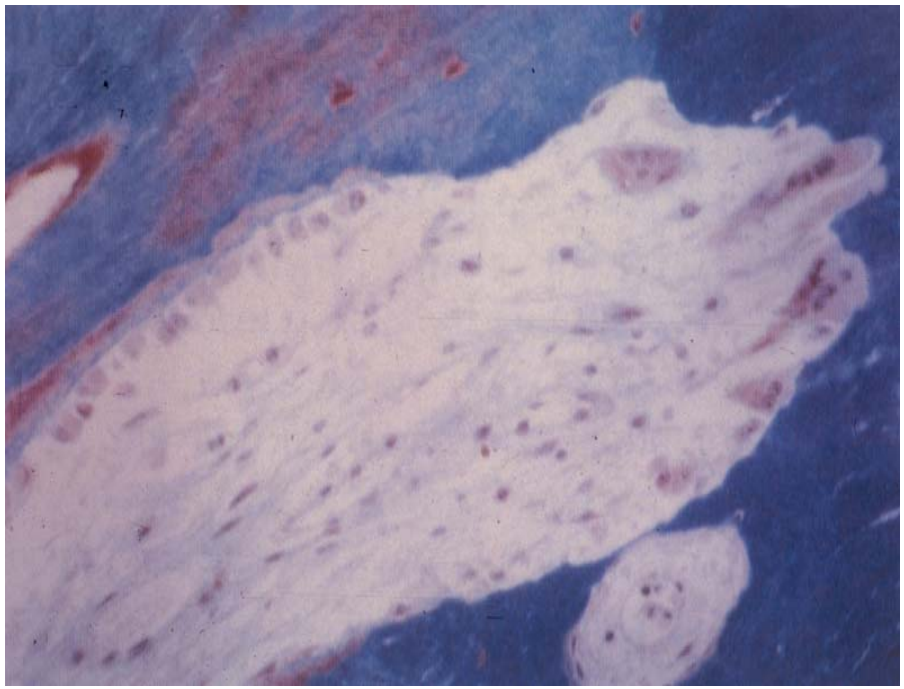


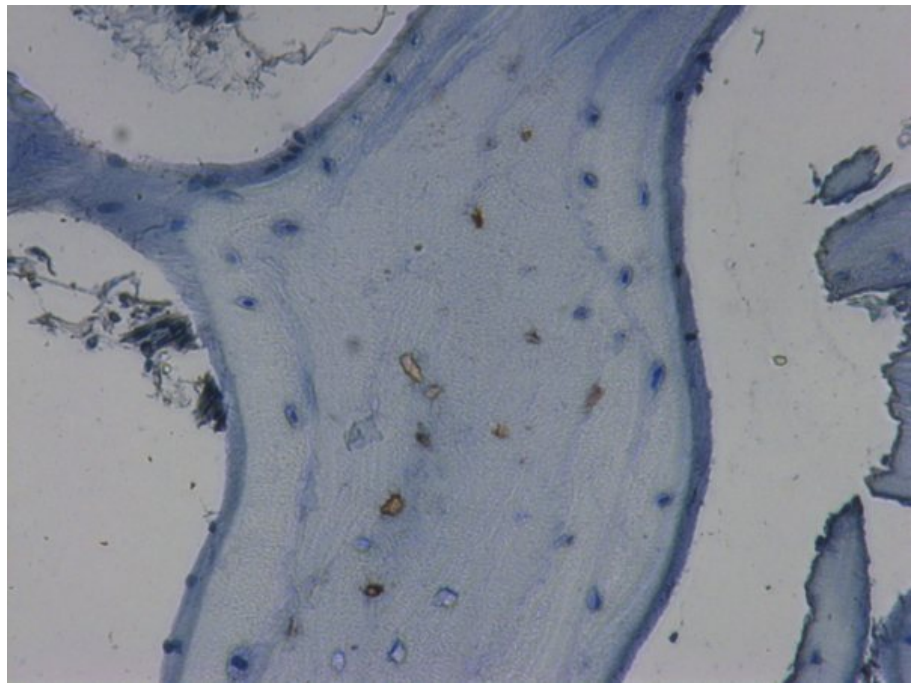
Desarrollo de terapias biológicas en el tratamiento de la osteoporosis: inhibición del sistema RANKL y otras dianas terapéuticas

José A. Riancho
Serv. Medicina Interna
Hospital U.M.Valdecilla
Universidad de Cantabria
Santander

Remodelado óseo



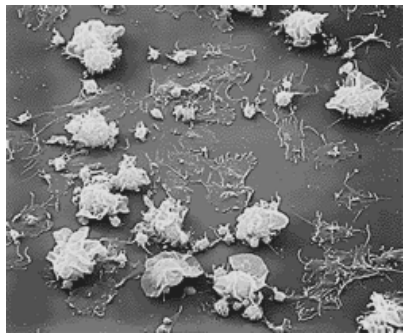
Acoplamiento espacio-temporal de OBs y OCs*

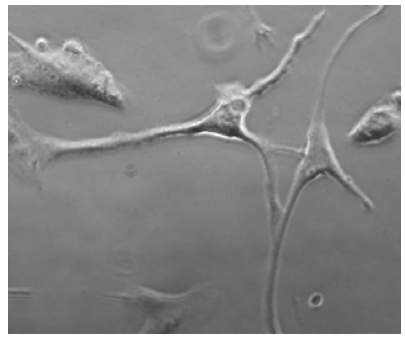


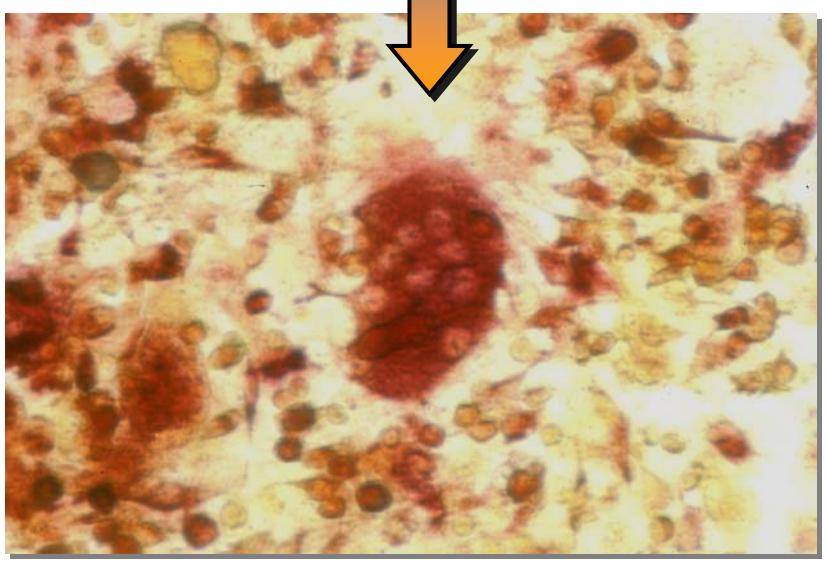
OBs y OCs son visitantes, no residentes en la zona

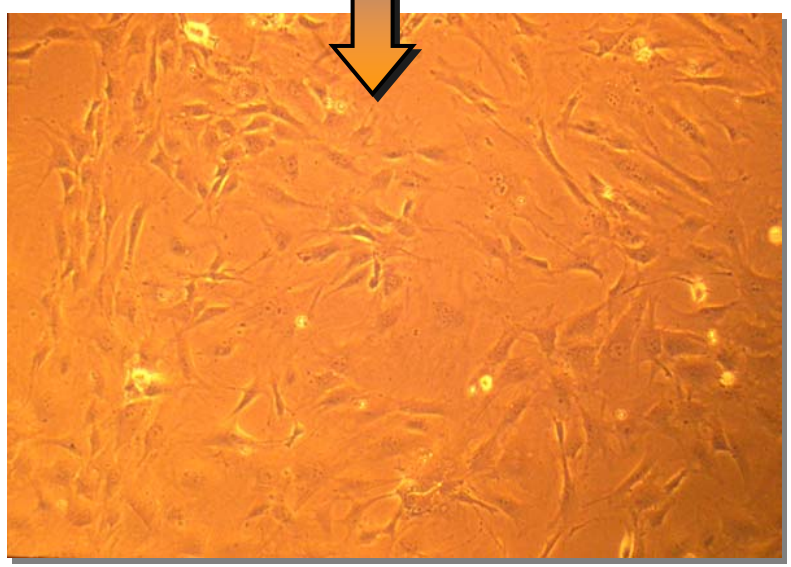
(*figura tomada de Malluche)

Remodelado: papel crítico de proliferación y diferenciación de precursores de OC y OB

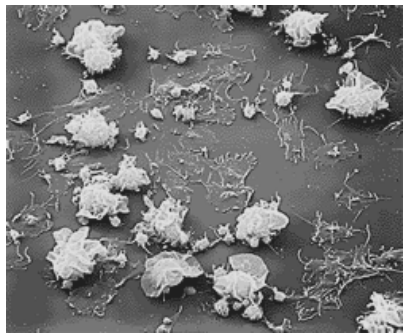


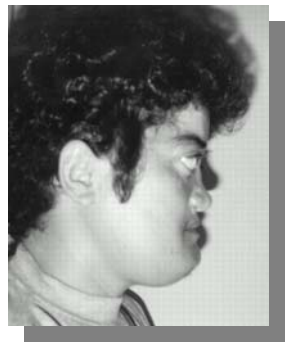


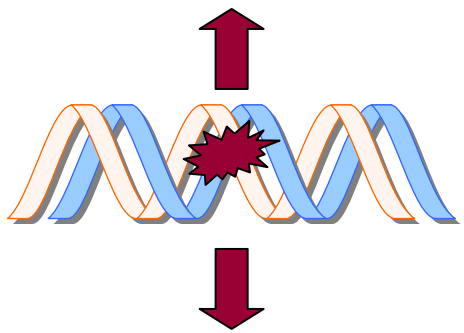


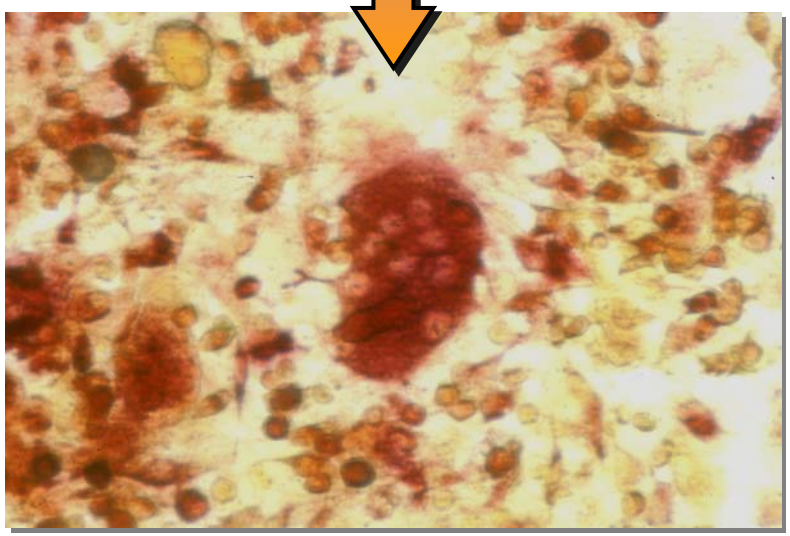


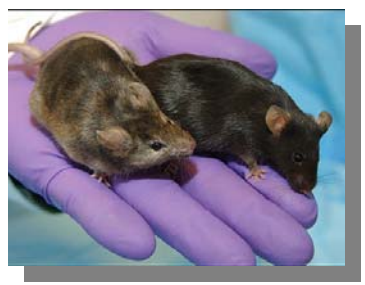
Identificación de factores clave de la osteoclastogénesis





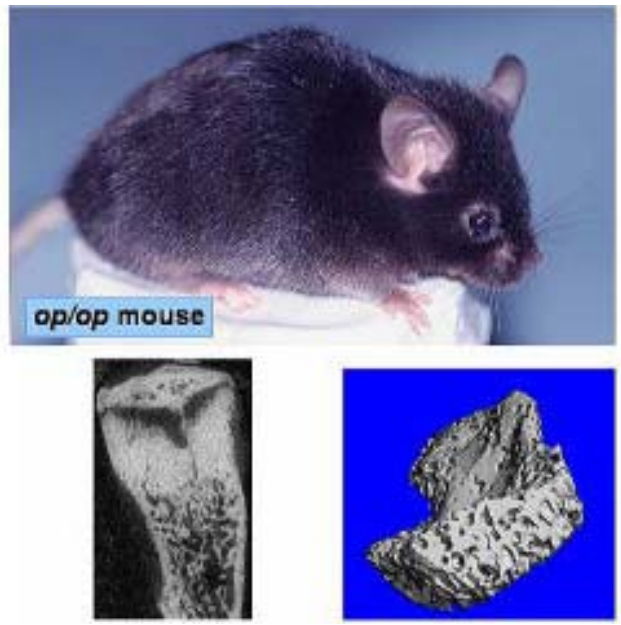




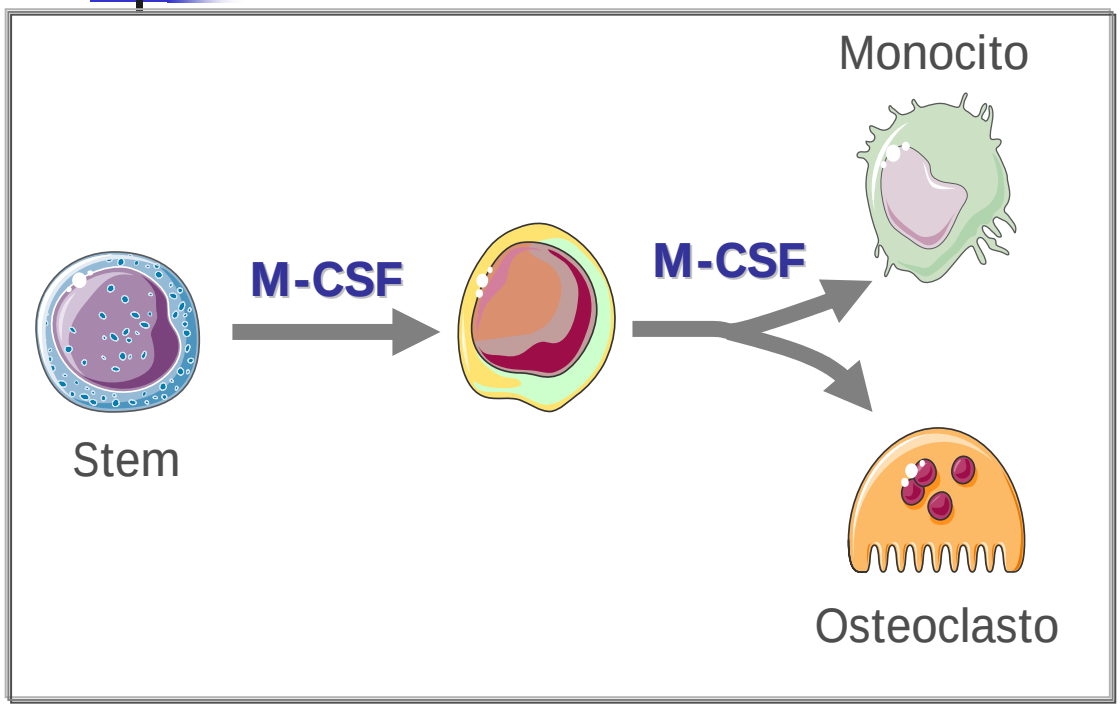


Factores clave de la osteoclastogénesis

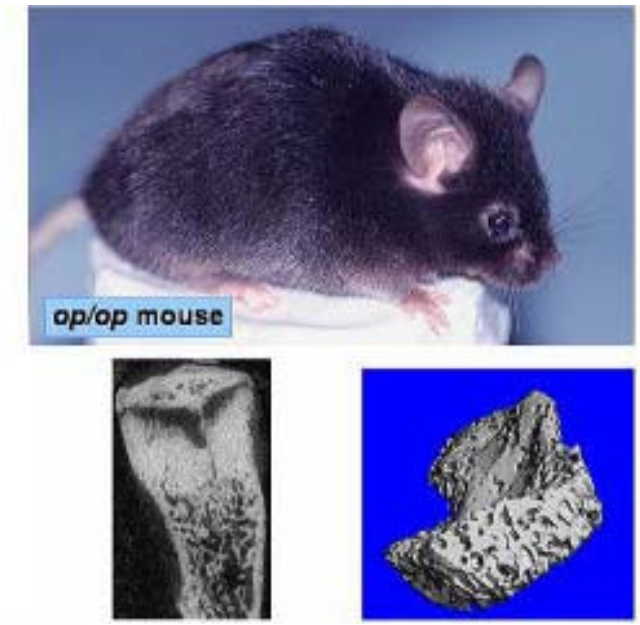
Osteopetrosis



Factores clave de la osteoclastogénesis



Osteopetrosis



Proc. Natl. Acad. Sci. USA
Vol. 87, pp. 4828–4832, June 1990
Medical Sciences

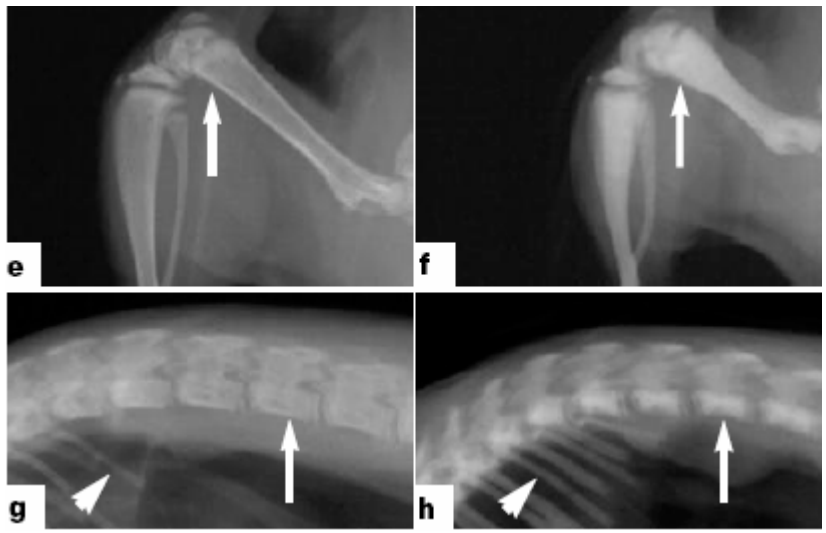
Total absence of colony-stimulating factor 1 in the macrophage-deficient osteopetrotic (*op/op*) mouse

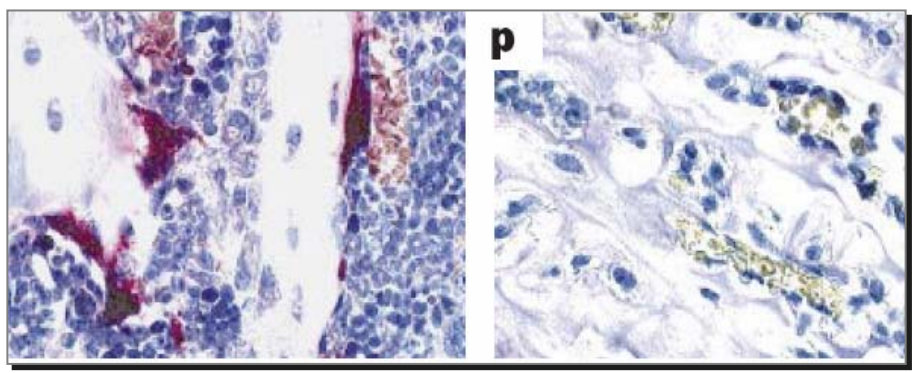
(macrophage growth factor/mouse mutant/osteopetrosis/macrophage deficiency)

WIESLAW WIKTOR-JEDRZEJCZAK*†, ANNA BARTOCCI‡, ANTHONY W. FERRANTE, JR.‡, AFTAB AHMED-ANSARI*, KENNETH W. SELL*, JEFFREY W. POLLARD‡, AND E. RICHARD STANLEY‡

*Department of Pathology, Emory University School of Medicine, Atlanta, GA 30322; and ‡Department of Developmental Biology and Cancer, Albert Einstein College of Medicine, Bronx, NY 10461

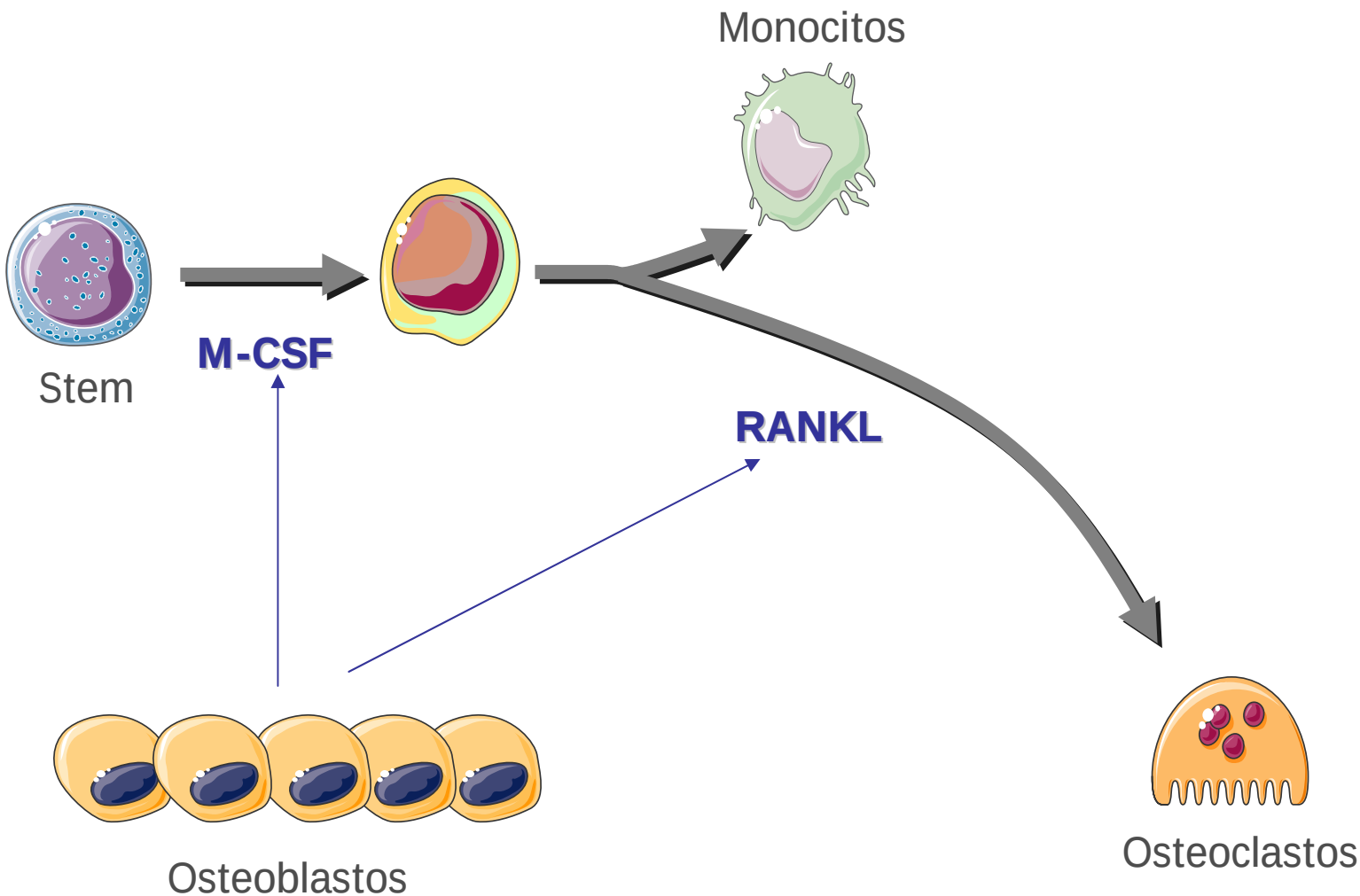
RANKL: promotor clave de la osteoclastogénesis





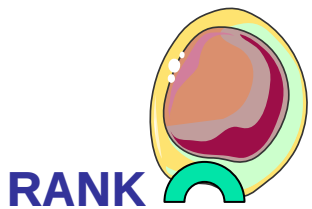
Kong et al. Nature 1999

OBs modulan la formación de OCs



RANK-RANKL

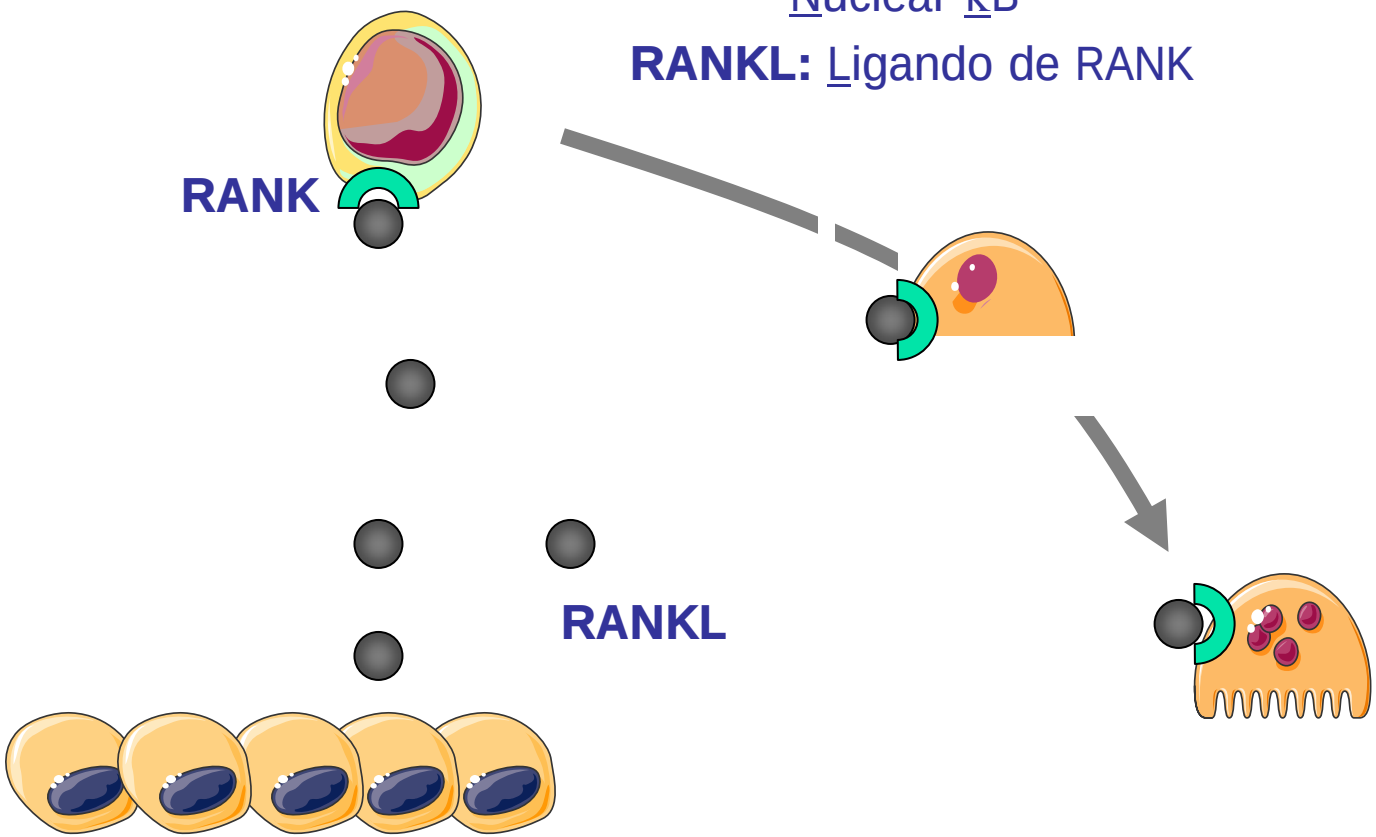
RANK: Receptor Activador del factor Nuclear κB



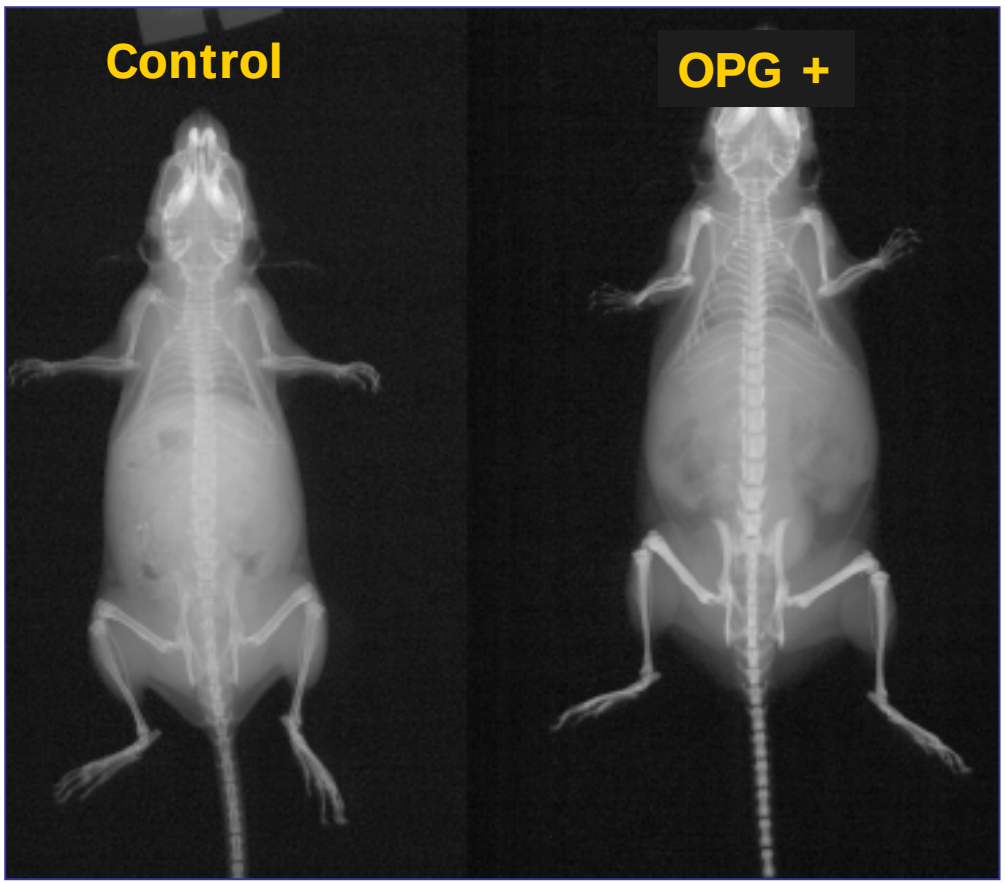
RANK-RANKL

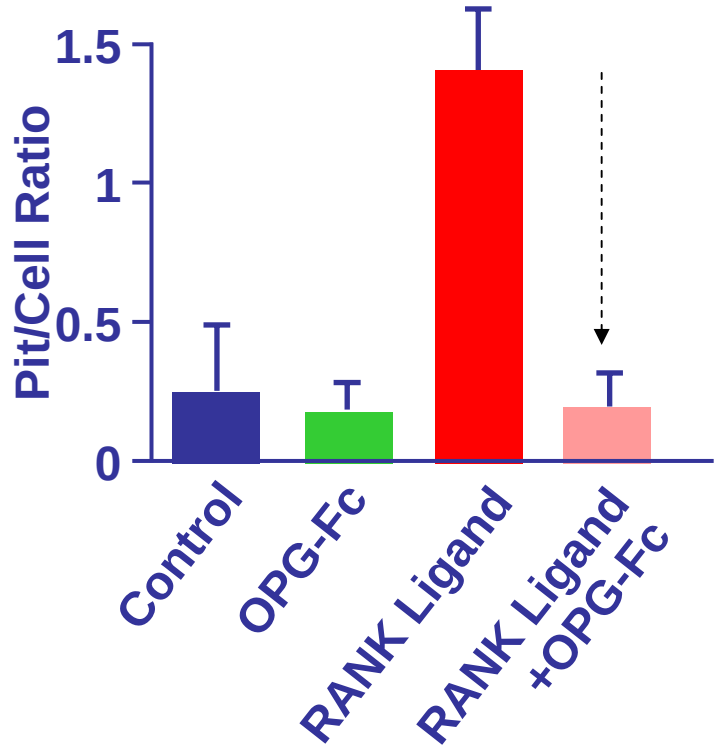
RANK: Receptor Activador del factor Nuclear κB

RANKL: Ligando de RANK



La Osteoprotegerina bloquea la formación de osteoclastos



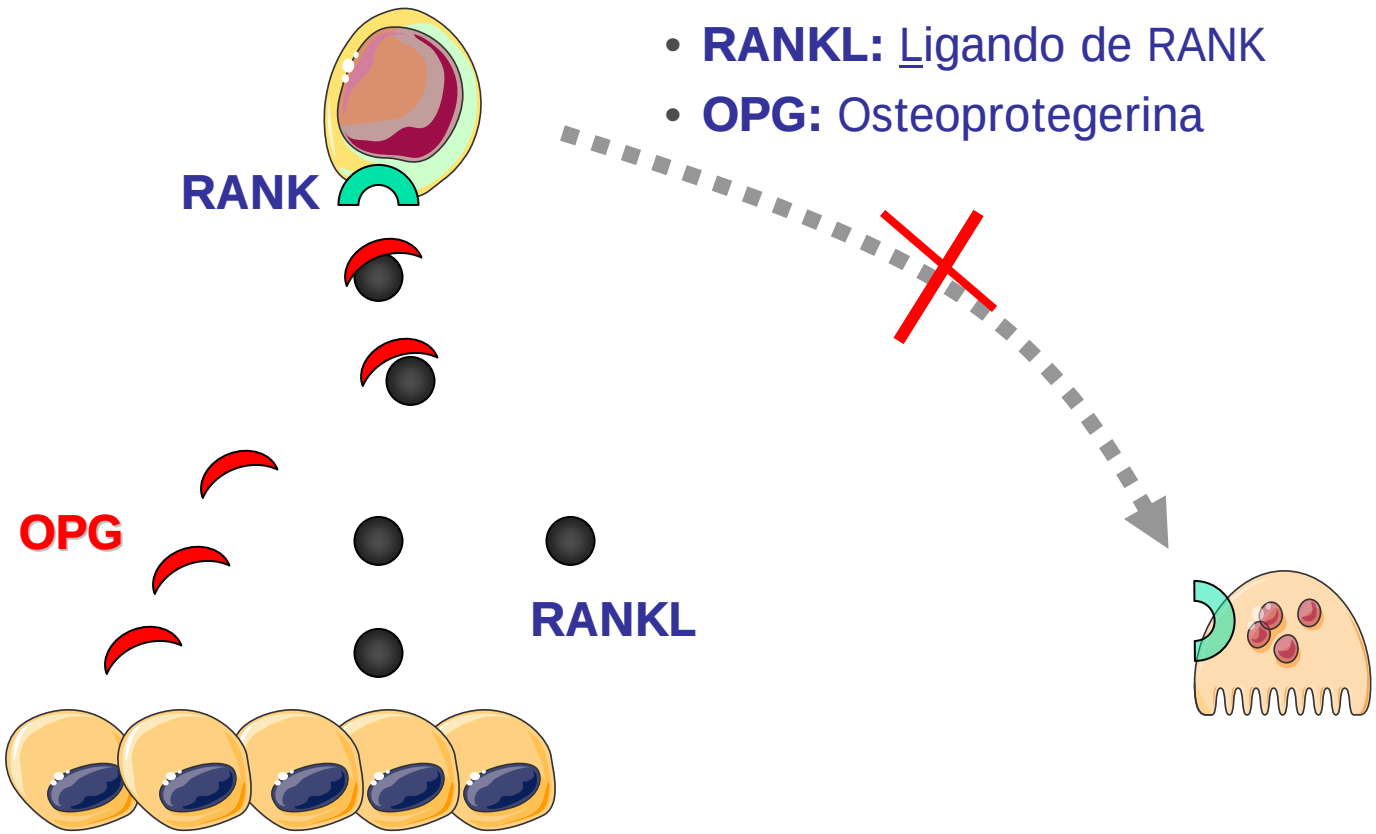


Simonet WS *et al.* Cell 1997; 89: 309–319

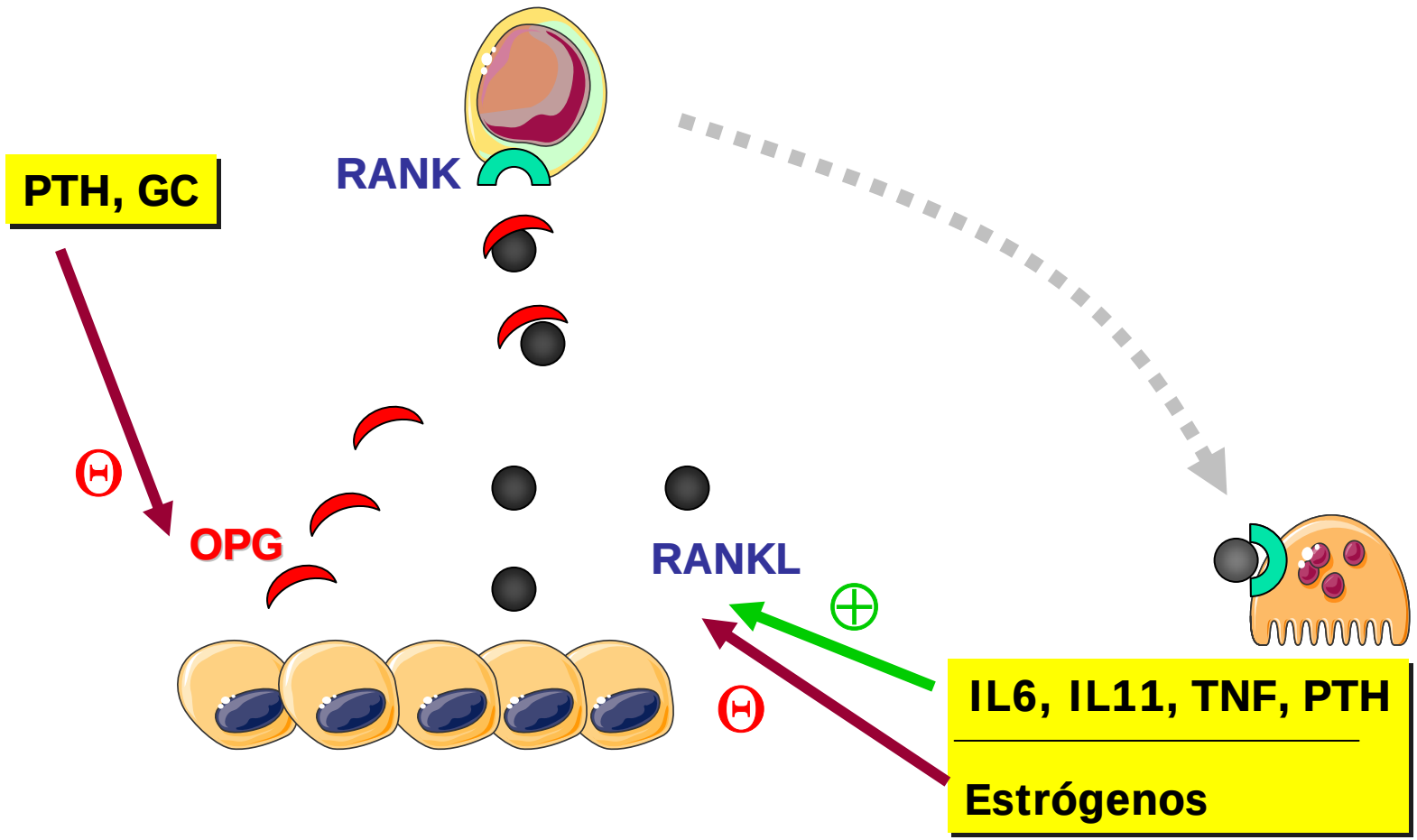
Lacey DL *et al.* Cell 1998; 93: 165–176

RANK-RANKL-OPG

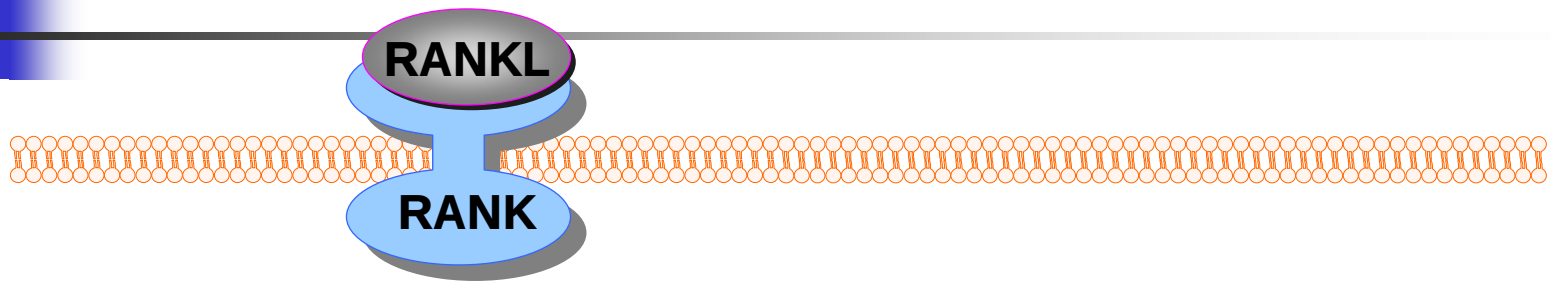
- **RANK:** Receptor Activador del factor Nuclear κB
- **RANKL:** Ligando de RANK
- **OPG:** Osteoprotegerina



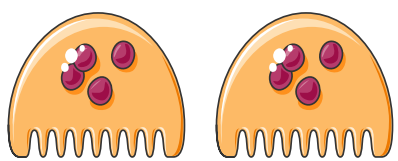
RANK-RANKL-OPG: Modulación



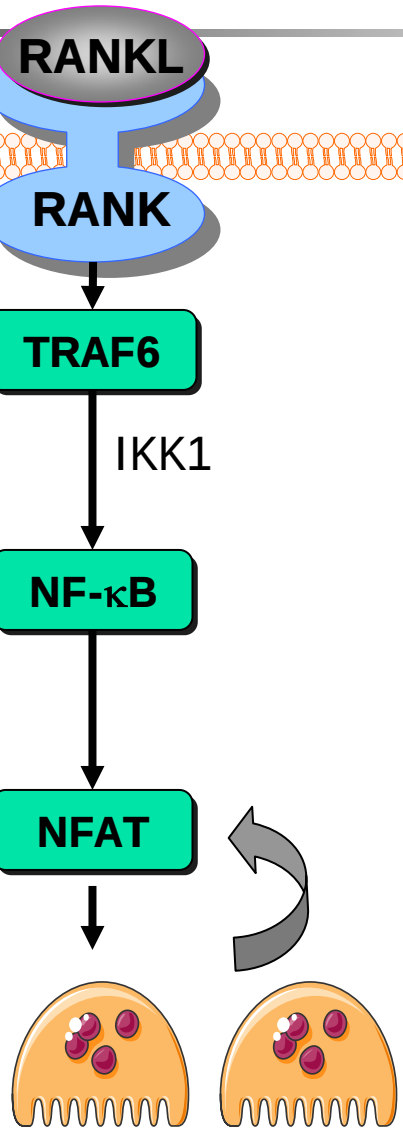
Mediadores intracelulares de RANK-RANKL



↑ Formación OC
Activación
↓ Apoptosis



Mediadores intracelulares de RANK-RANKL



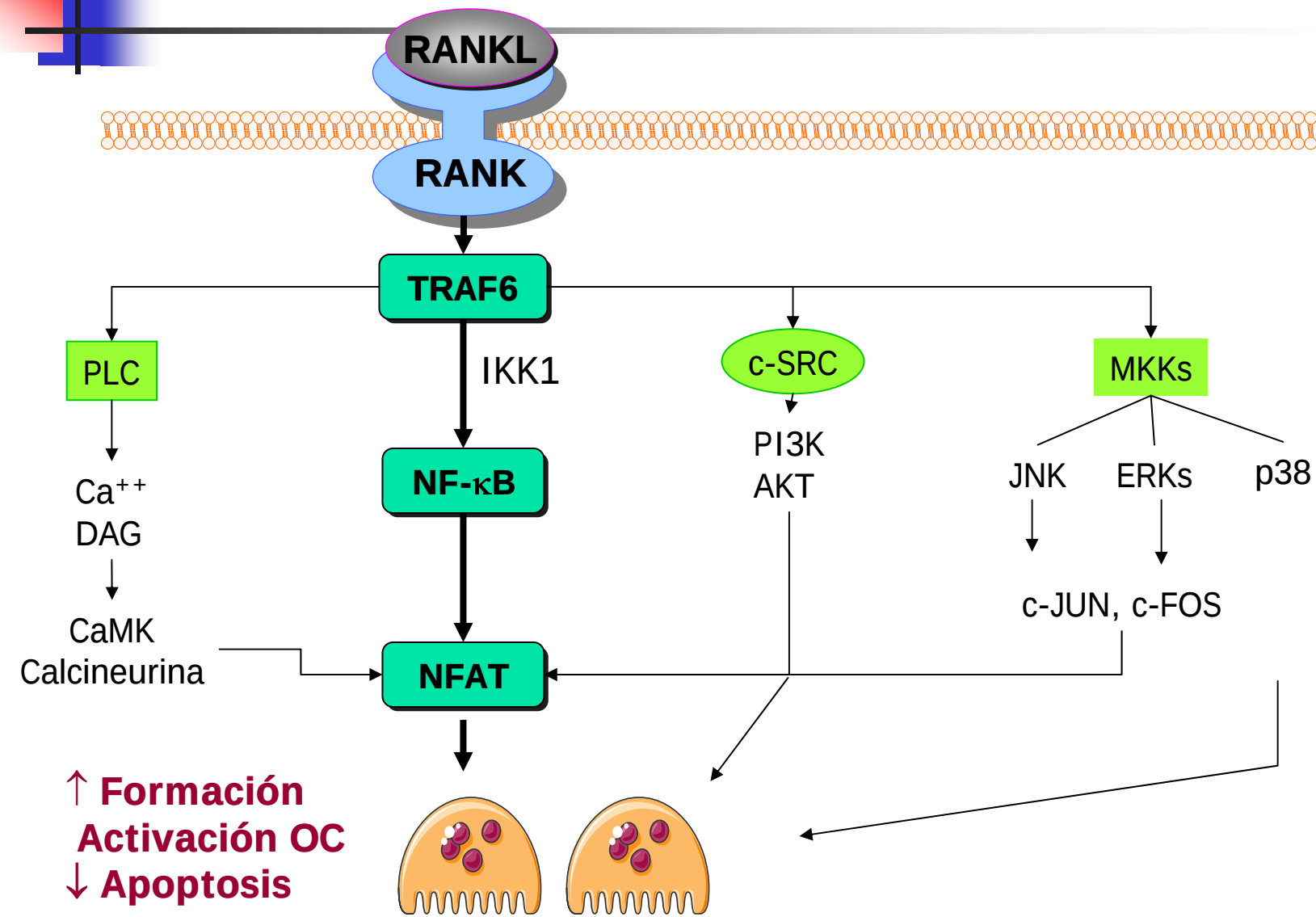
TRAF: TNF receptor associated factor

NF-κB: Nuclear factor κB

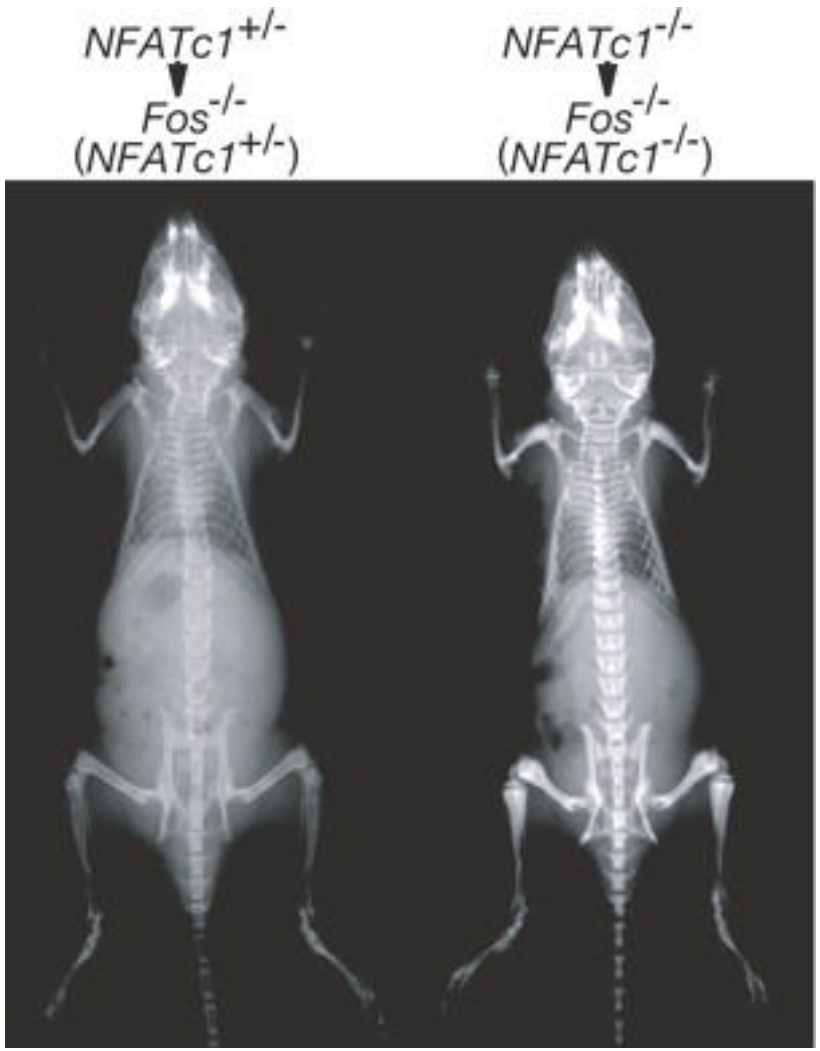
NFAT: Nuclear factor of activated T cells

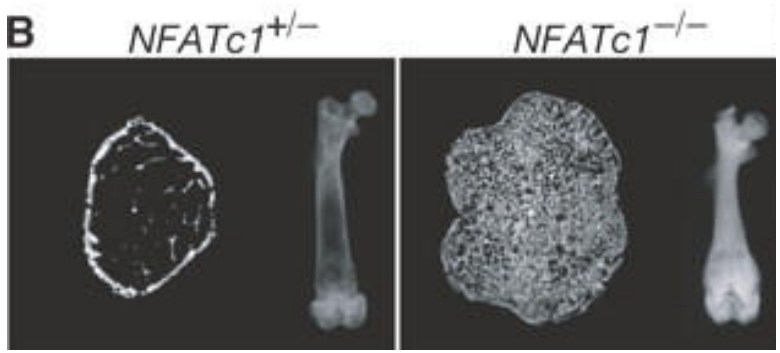
↑ Formación OC
Activación
↓ Apoptosis

Mediadores intracelulares de RANK-RANKL



El bloqueo de NFAT produce osteopetrosis con ausencia de OC





Asagiri et al. J Exp Med 2005

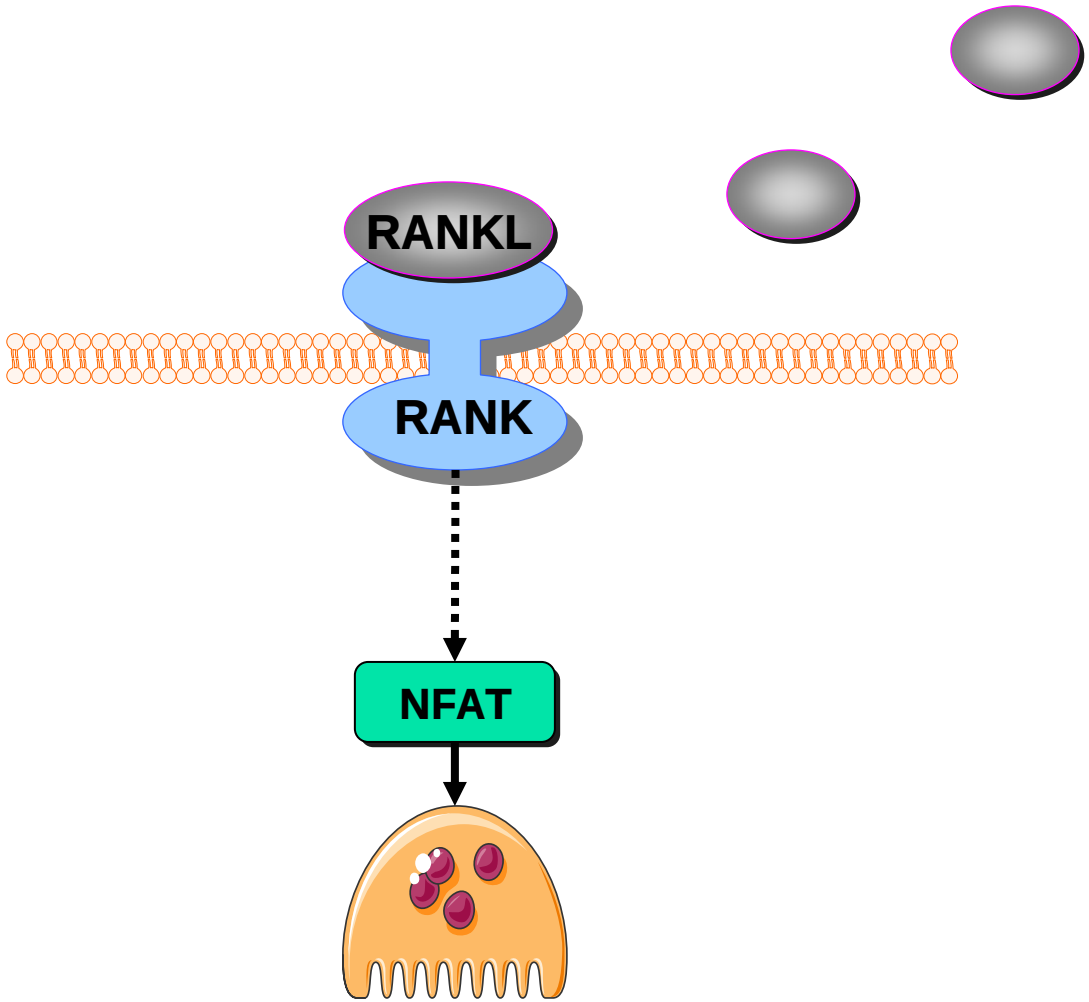
Mutaciones de la vía RANKL-RANK-OPG en humanos

Table 1 A summary of human diseases caused by mutations in the RANK, RANKL and OPG genes

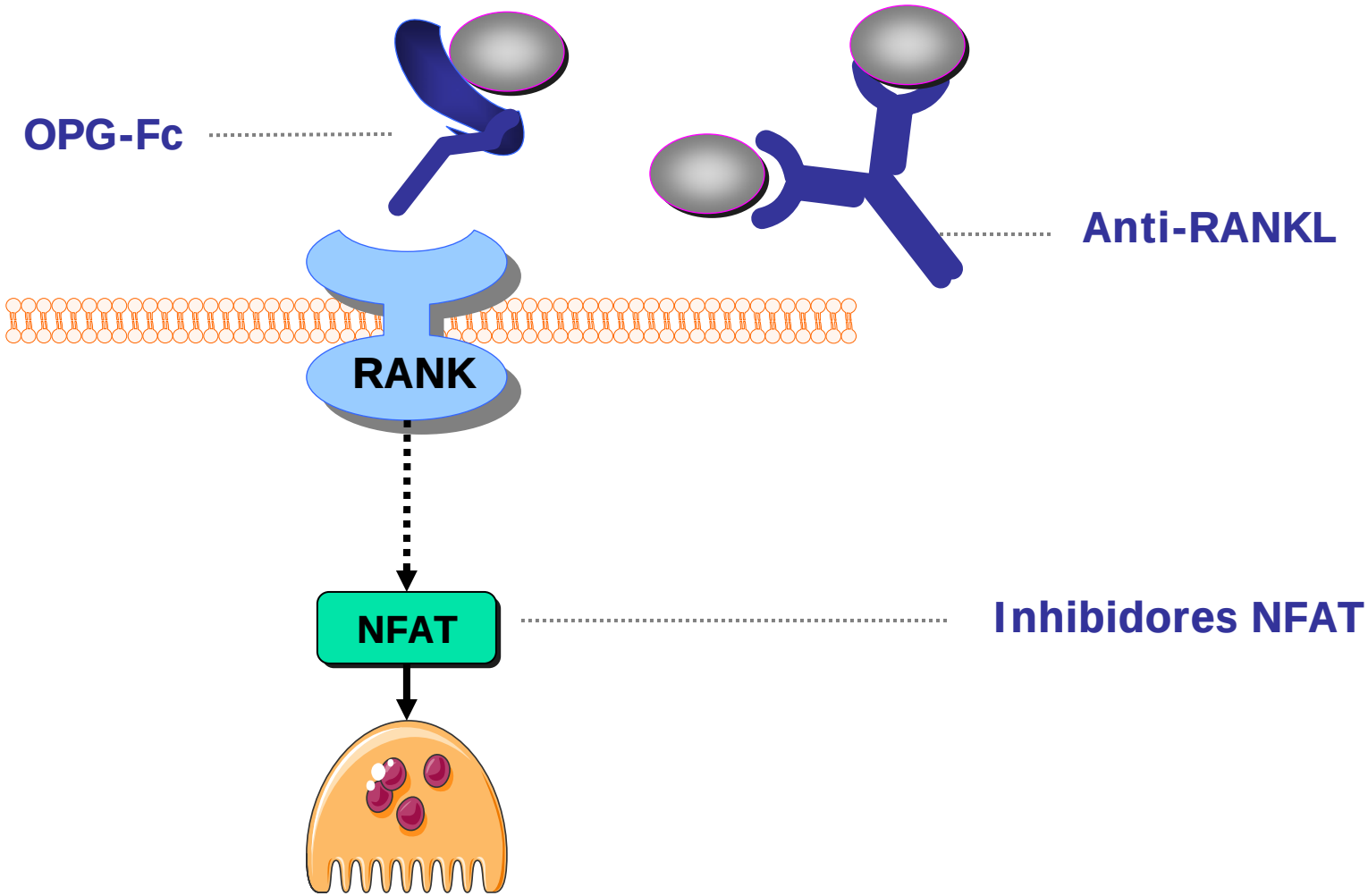
Gene	Mutation	Disease
RANK	18 bp duplication	Familial expansile osteolysis
	27 bp duplication	Early onset Paget's disease
	15 bp duplication	Expansile skeletal hyperphosphatasia
RANKL	Deletion of amino acids 145-177	Autosomal recessive osteopetrosis
	A single nucleotide change (596T-A) in exon 8 of both alleles	Autosomal recessive osteopetrosis
	Deletion of two nucleotides (828_829delCG)	Autosomal recessive osteopetrosis
OPG	Deletion making OPG inactive	Juvenile Paget's disease
	20 bp deletion resulting in premature termination of OPG translation	Juvenile Paget's disease

Wright et al Curr Rev Musculoskelet Med 2009

Dianas inhibición vía RANK

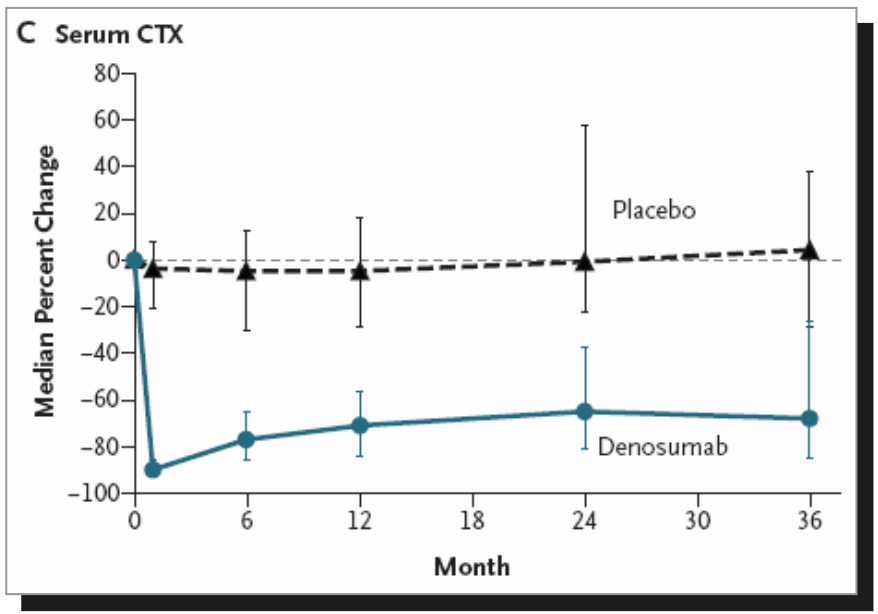


Dianas inhibición vía RANK

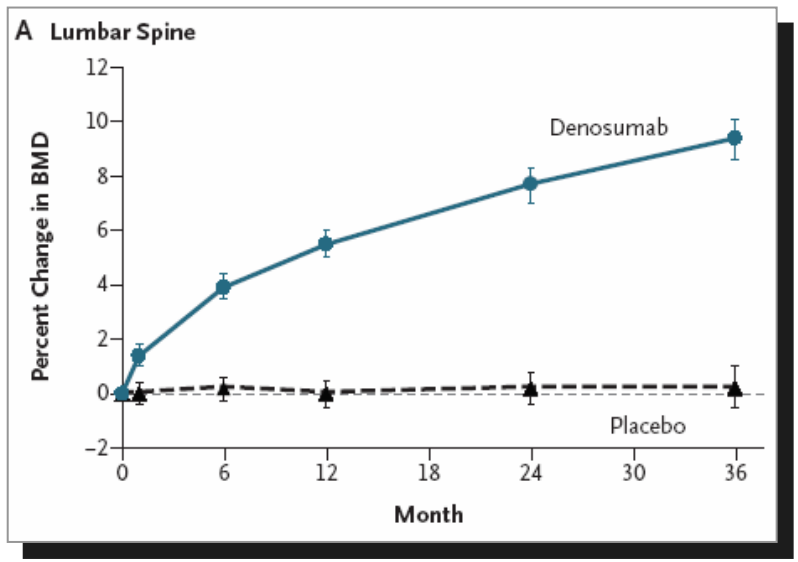


Denosumab (anti-RANKL) en mujeres postmenopáusicas

Marcadores resorción (CTX)

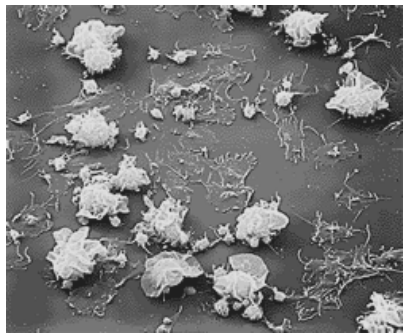


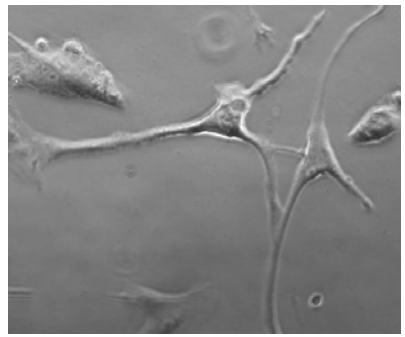
DMO (columna)

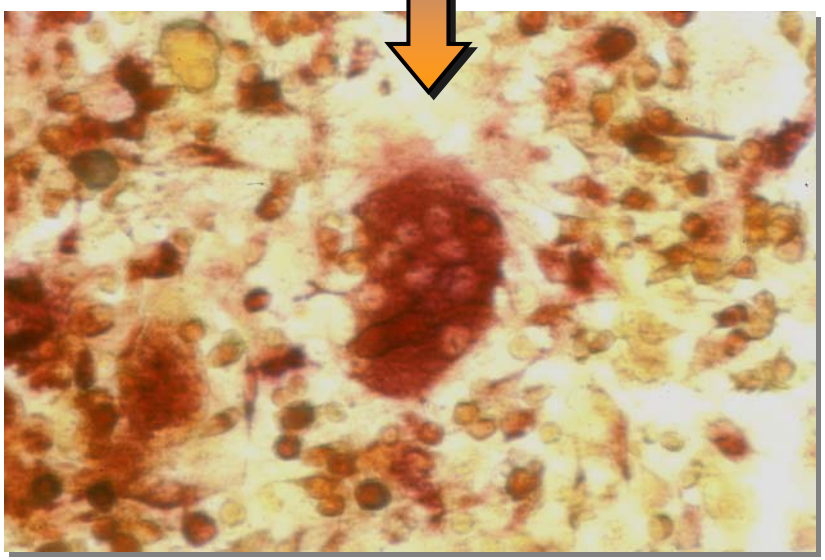


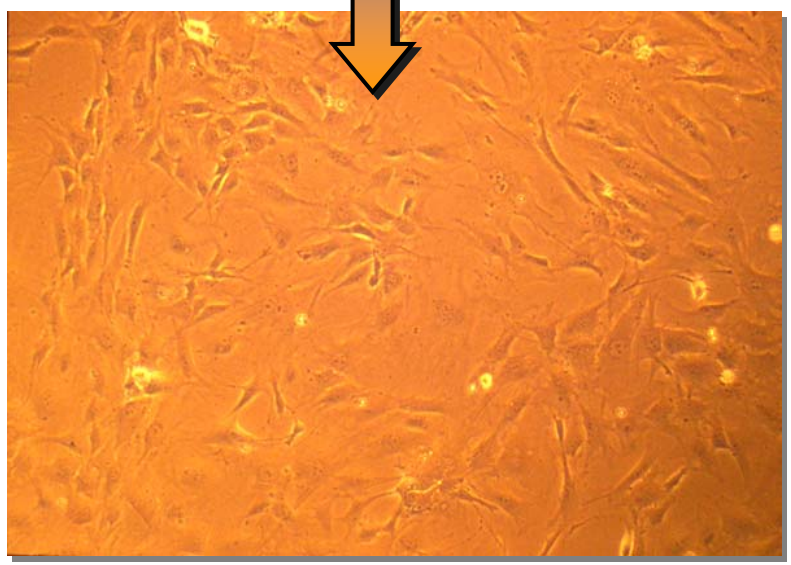
Cummings et al NEJM 2009

Papel crítico de proliferación y diferenciación de precursores de OC y OB

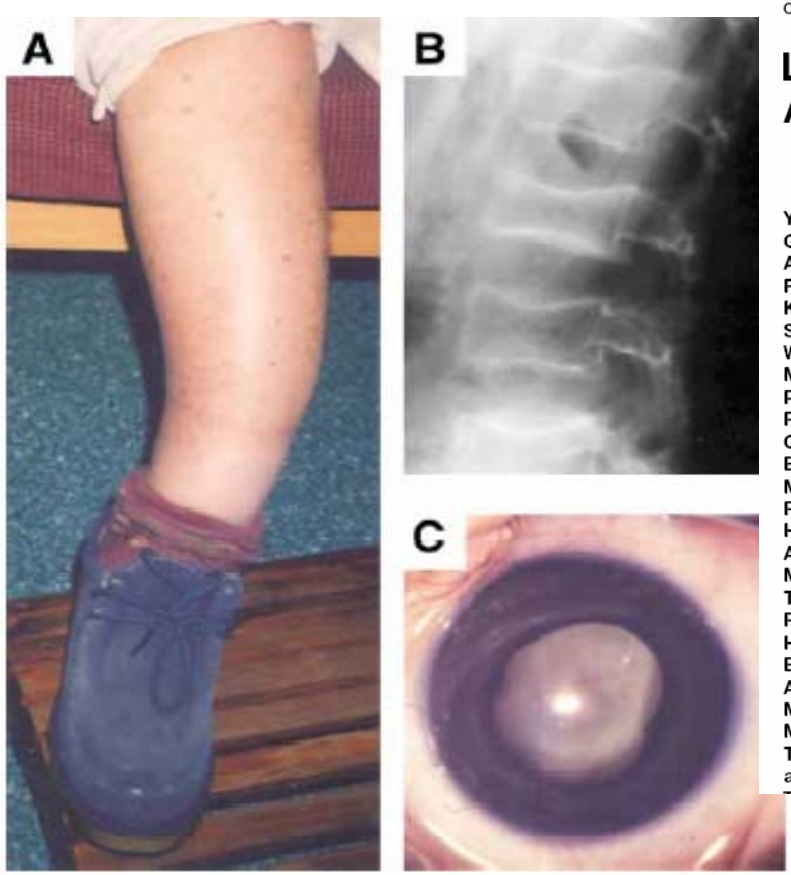








Osteoporosis-pseudoglioma y LRP5



Cell, Vol. 107, 513–523, November 16, 2001, Copyright ©2001 by Cell Press

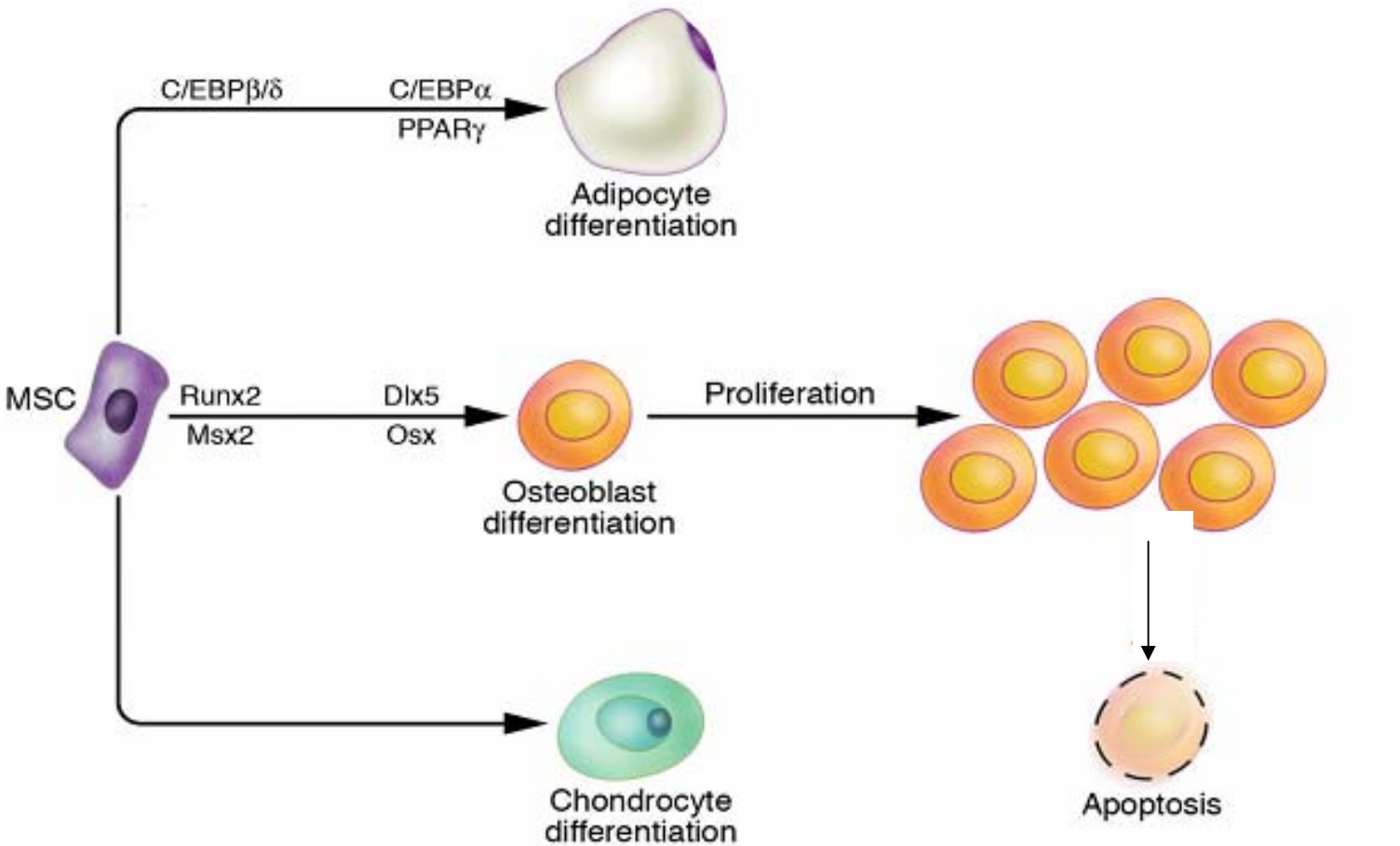
LDL Receptor-Related Protein 5 (LRP5) Affects Bone Accrual and Eye Development

Yaoqin Gong,[2] Roger B. Slee,[2] Naomi Fukai,
Georges Rawadi, Sergio Roman-Roman,
Anthony M. Reginato, Hongwei Wang, Tim Cundy,
Francis H. Glorieux, Dorit Lev, Margaret Zacharin,
Konrad Oexle, Jose Marcelino, Wafaa Suwairi,
Shauna Heeger, George Sabatakos, Suneel Apte,
William N. Adkins, Jeremy Allgrove,
Mine Arslan-Kirchner, Jennifer A. Batch,
Peter Beighton, Graeme C. M. Black,
Richard G. Boles, Laurence M. Boon,
Carla Borrone, Han G. Brunner, Georges F. Carle,
Bruno Dallapiccola, Anne De Paepe, Barbara Floege,
Melissa Lees Halfhide, Bryan Hall,
Raoul C. Hennekam, Tatsuo Hirose, Ab Jans,
Harald Jüppner, Chong Ae Kim, Kim Keppler-Noreuil,
Alfried Kohlschuetter, Didier LaCombe,
Marie Lambert, Emmanuelle Lemyre,
Tom Letteboer, Leena Peltonen,
Rajkumar S. Ramesar, Marta Romanengo,
Hannu Somer, Elisabeth Steichen-Gersdorf,
Beat Steinmann, Beth Sullivan,
Andrea Superti-Furga, Walter Swoboda,
Marie-José van den Boogaard, Wim Van Hul,
Miikka Vikkula, Marcela Votruba, Bernhard Zabel,
Teresa Garcia, Roland Baron, Bjorn R. Olsen,
and Matthew L. Warman[1]

in life when bone catabolism supe
significant loss of bone mass (os
a common medical problem (Rig
In the United States, it is estimate
are spent annually for the treatmen
tures (NIH Consensus Developme
rosis Prevention, 2001). The world
of osteoporotic hip fracture exce
(http://www.who.int/inf-pr-1 99
Numerous factors have been impl
ment of osteoporosis. Family and
ies indicate that the peak bone
growth is an important risk factor (I
opment Panel on Osteoporosis P
man et al., 1994).

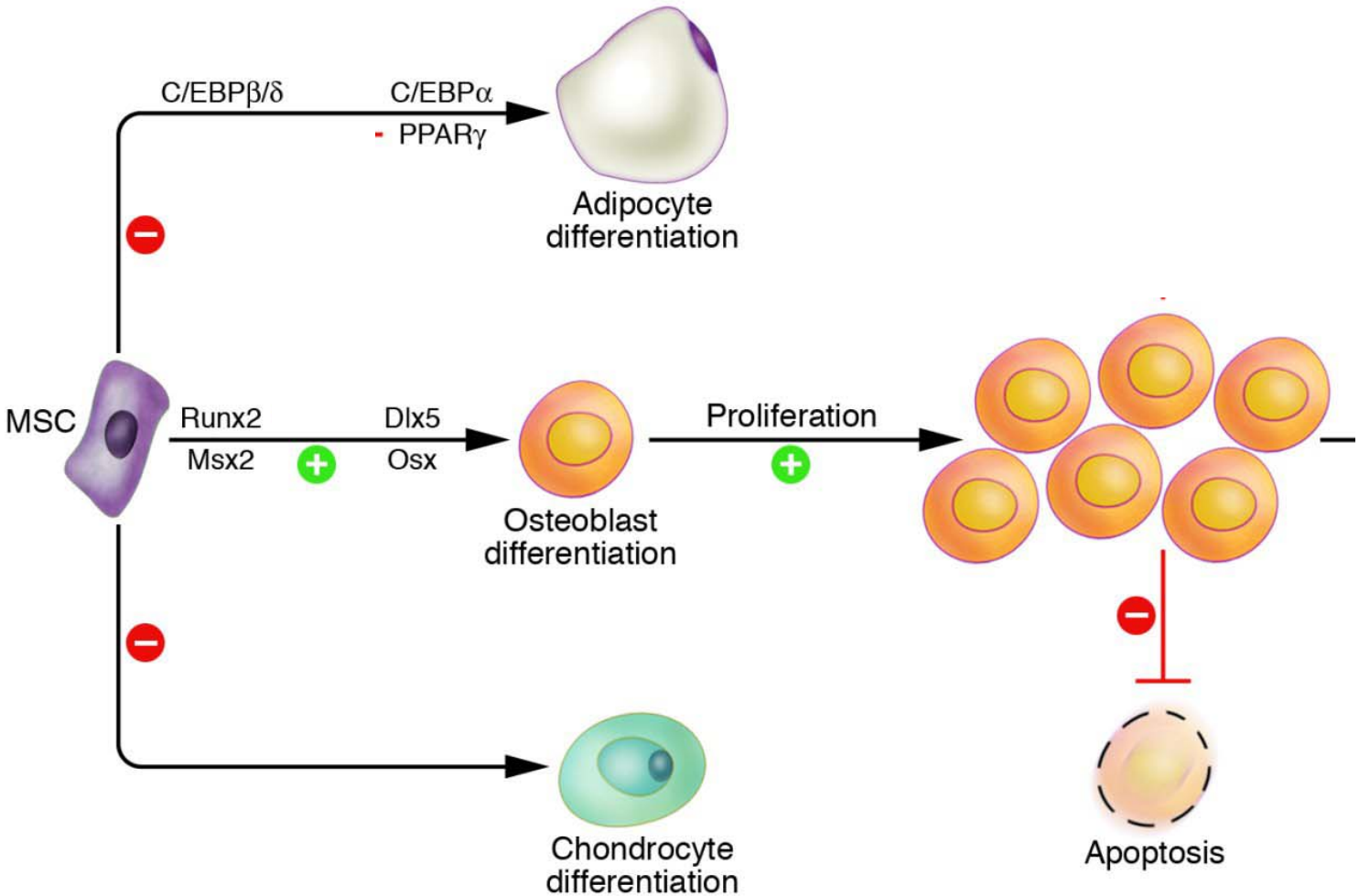
Two principal cell types are resp
sition and degradation of bone ma
cells, osteoblasts, differentiate fro
cells at sites of membranous bon
teum of endochondral bones, a
stroma (Aubin, 1998). The bone-d
clasts, differentiate from hemato
cells present in peripheral bloo
(Roodman, 1996). In order for bon
ing the growth and maturation
formation by osteoblasts must e
tion by osteoclasts

Diferenciación de OB



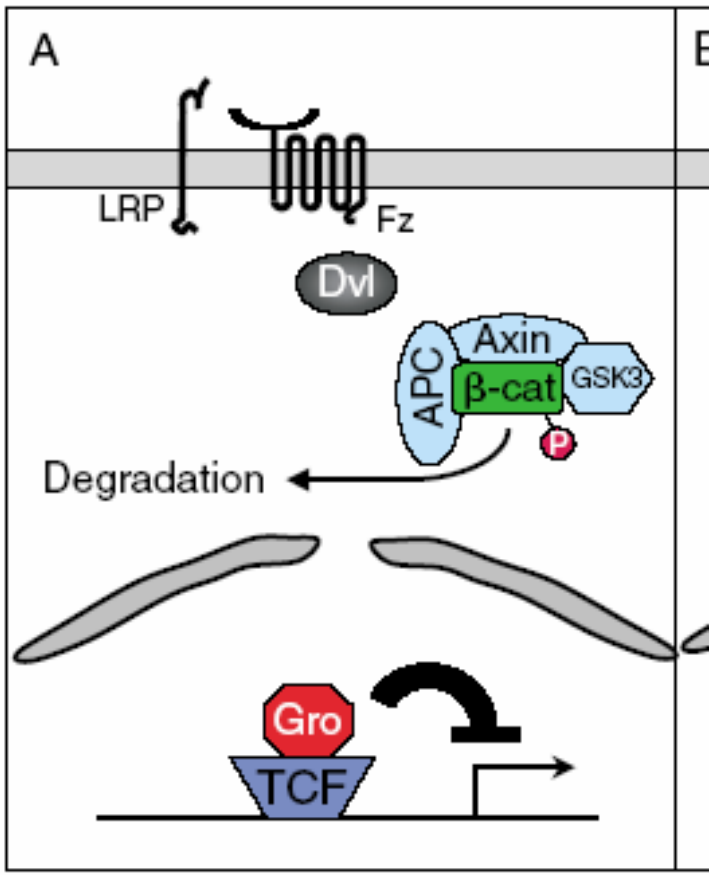
Krishnan et al JCI 2006

Wnt y Diferenciación de OB



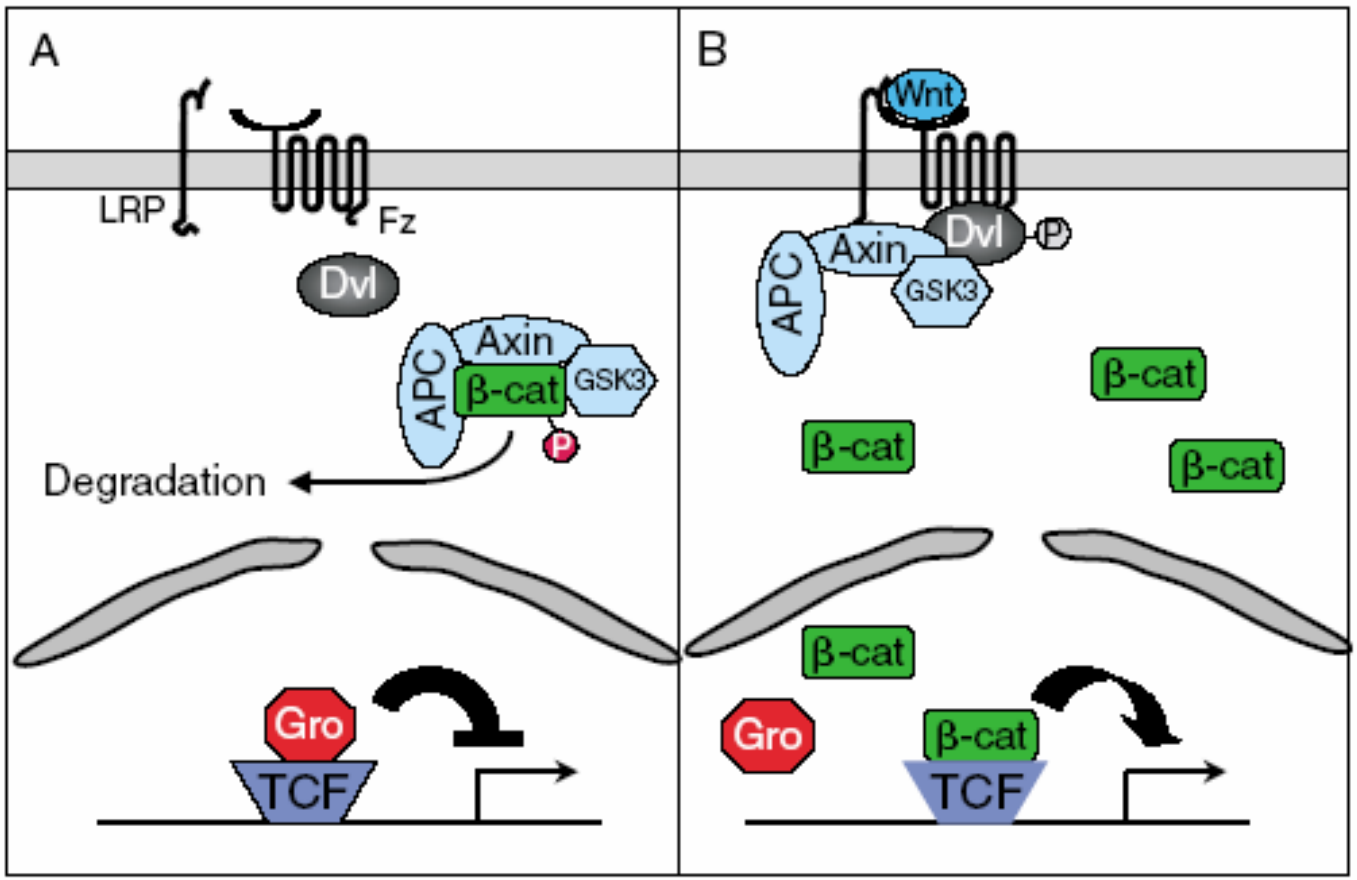
Krishnan et al JCI 2006

Vía Wnt canónica



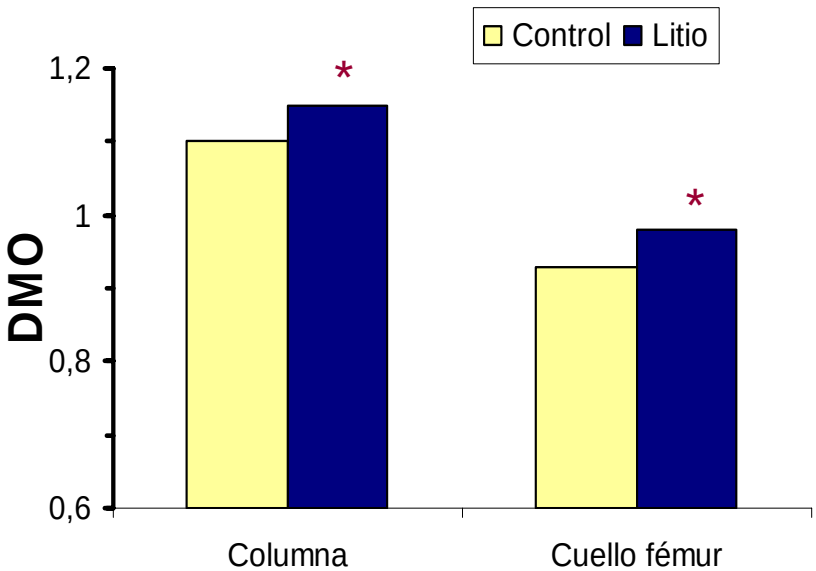
Cadigan y Liu. J Cell Sci 2006

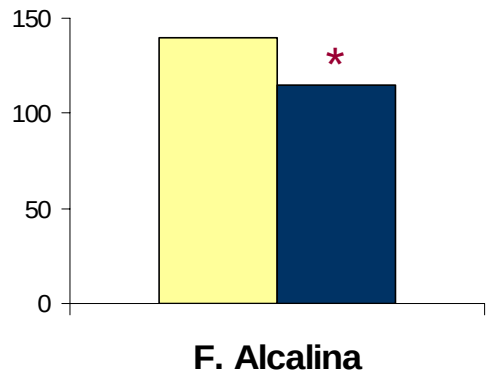
Vía Wnt canónica

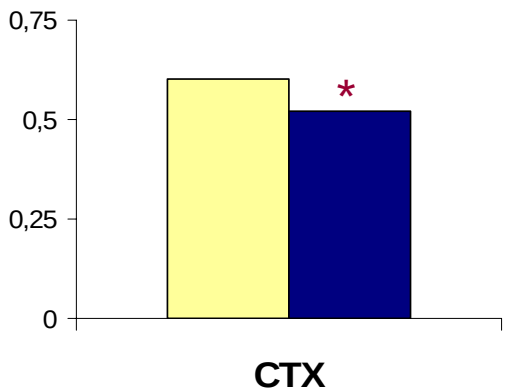


Cadigan y Liu. J Cell Sci 2006

Litio y hueso

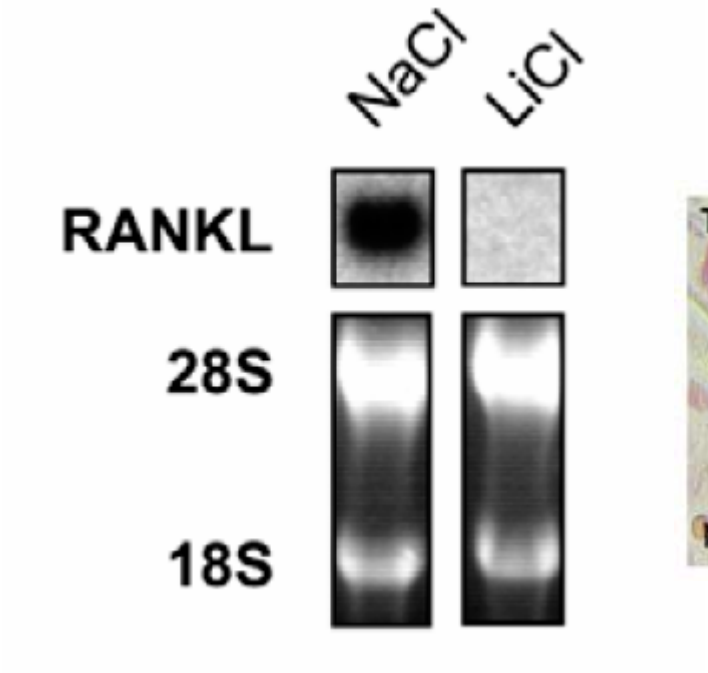


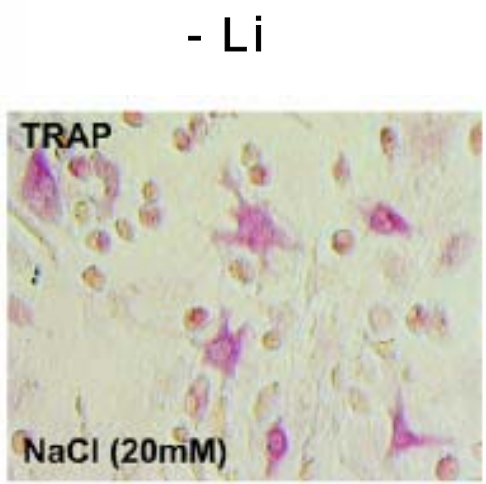


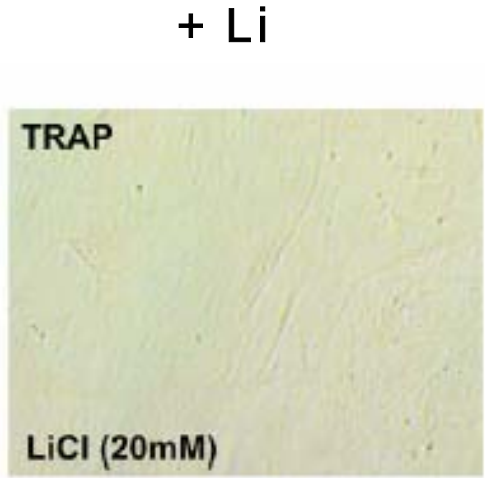


Zamani et al. Bone 2009

Vía Wnt - RANKL

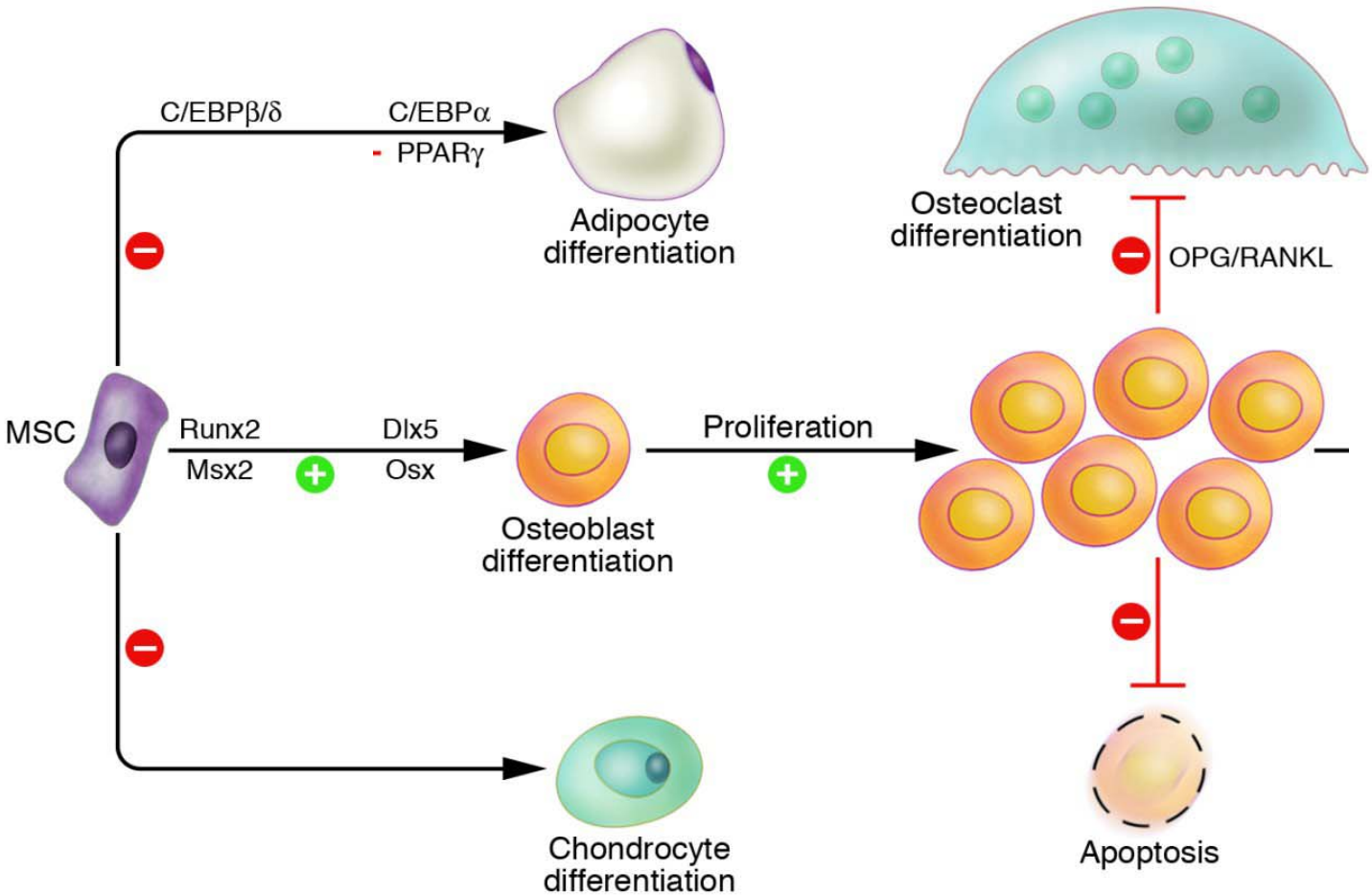






Spencer at al J Cell Sci 2006

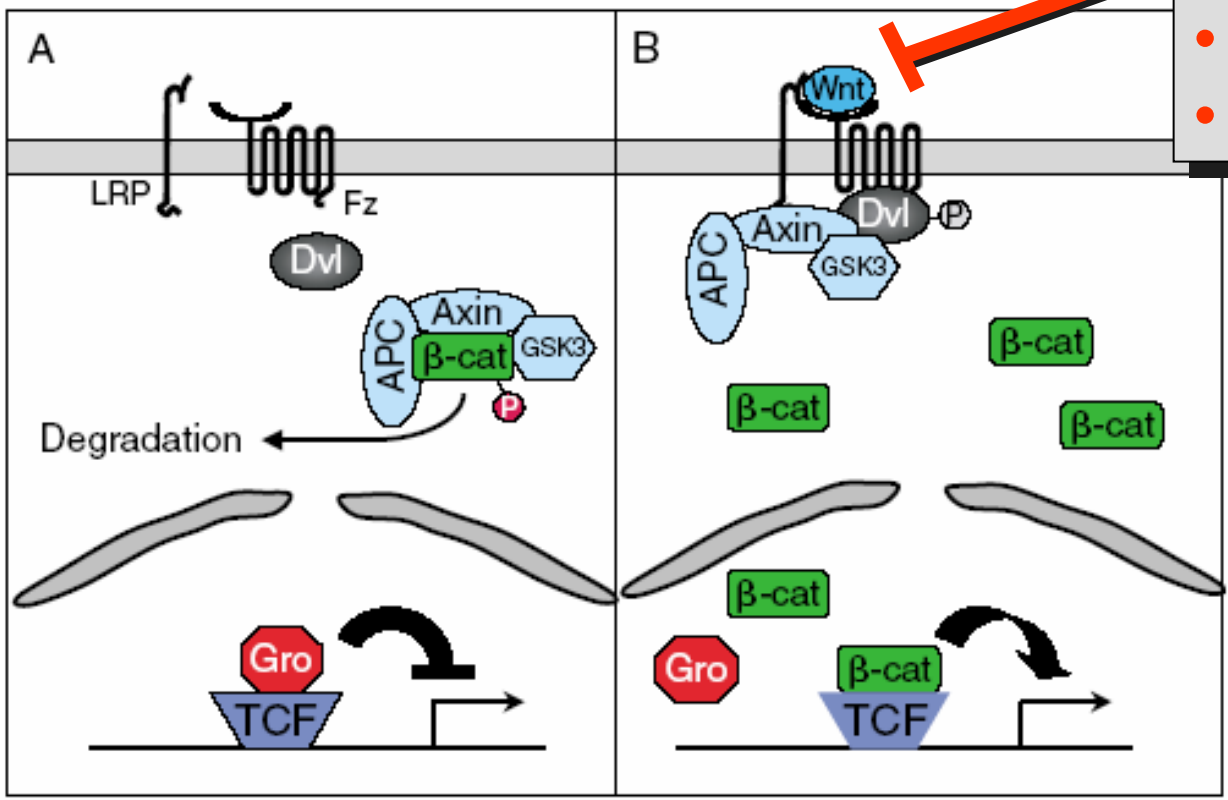
Vía Wnt - RANKL



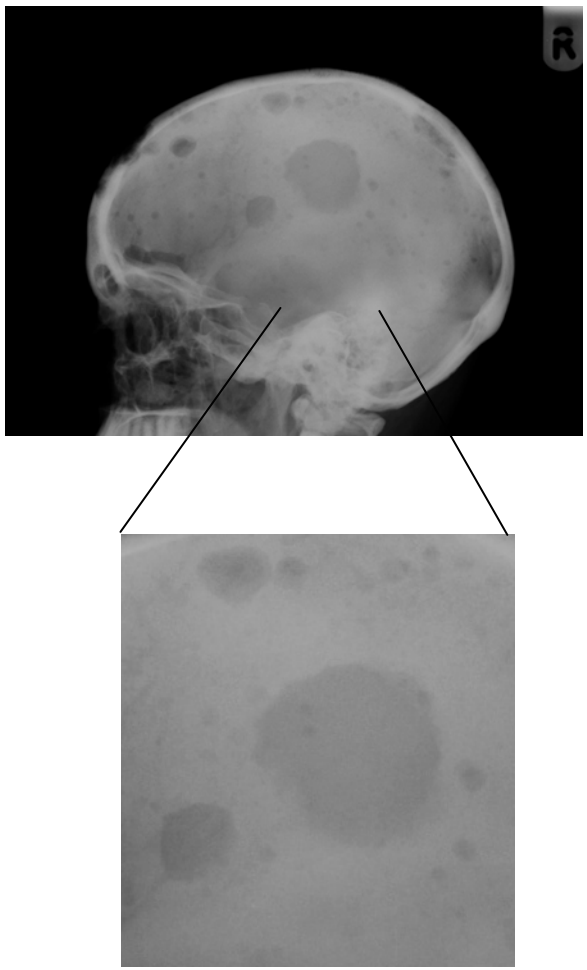
Krishnan et al JCI 2006

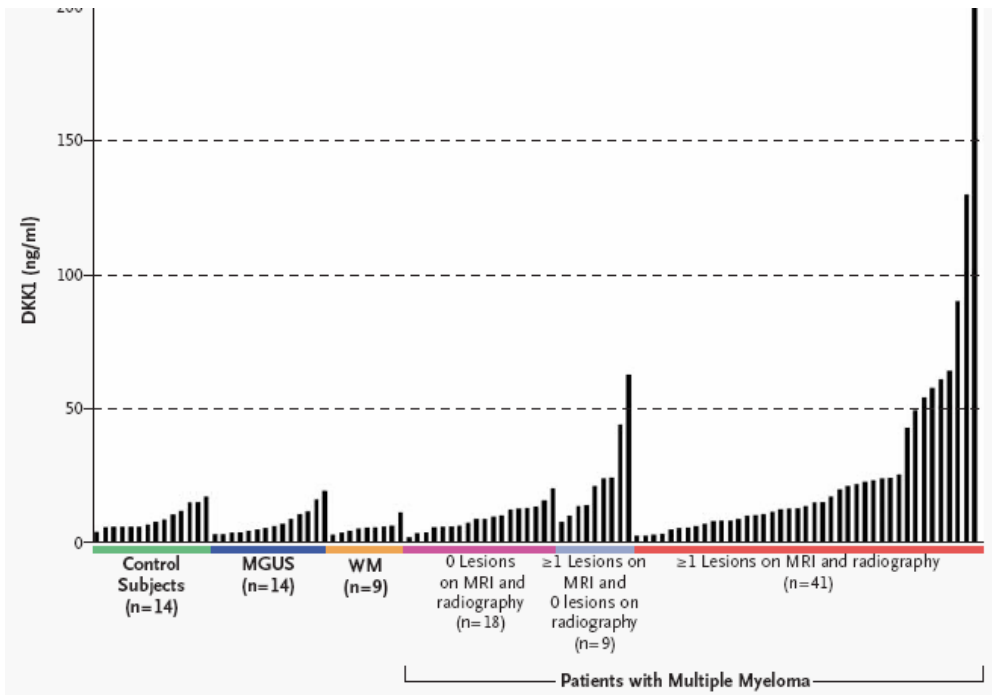
Inhibidores de Wnt

- sFRP
- WIF
- DKK
- SOST



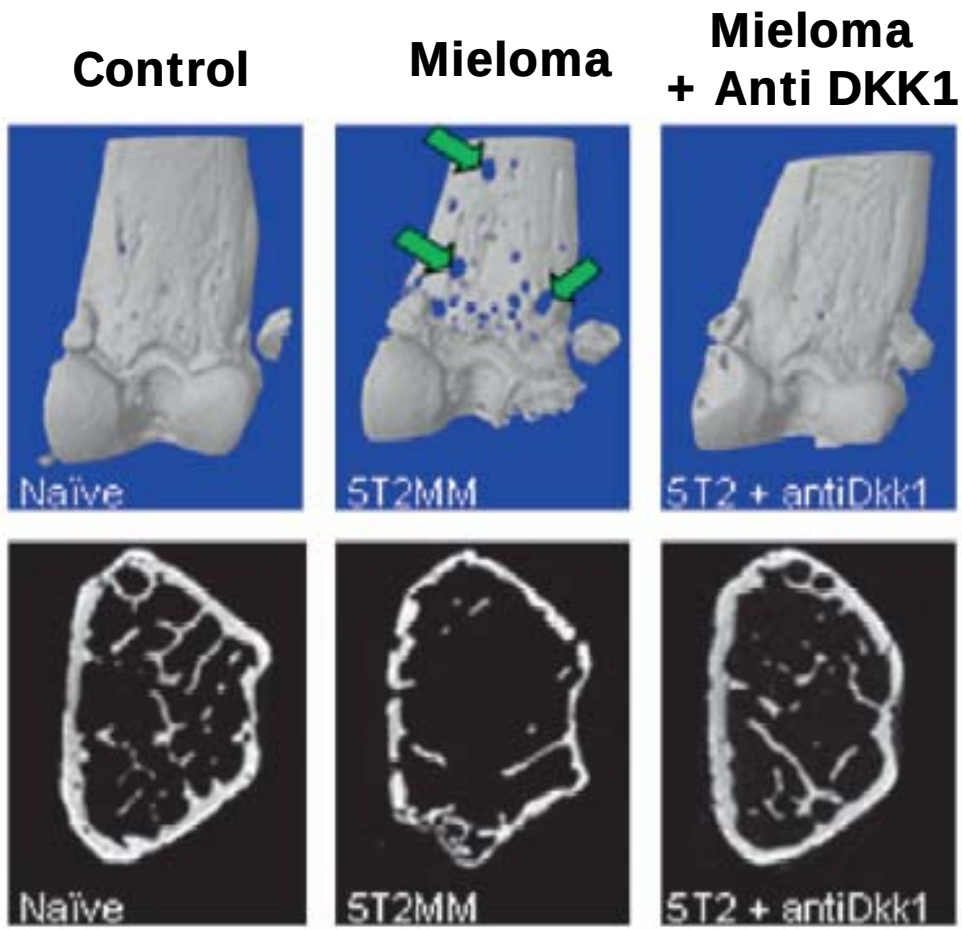
Dickkopf-1 (DKK1) y mieloma





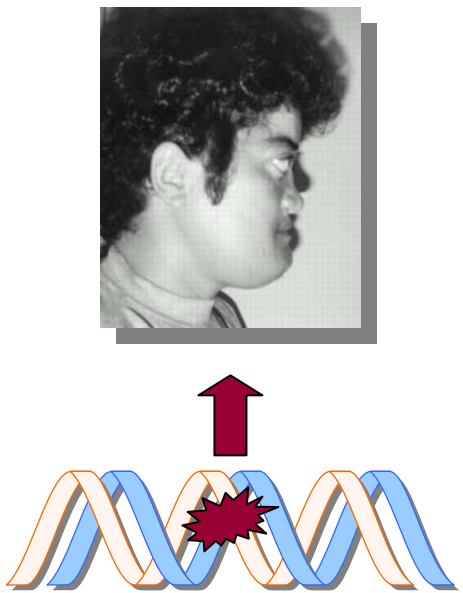
Tian et al. NEJM 2003

Dickkopf-1 (DKK1) y mieloma

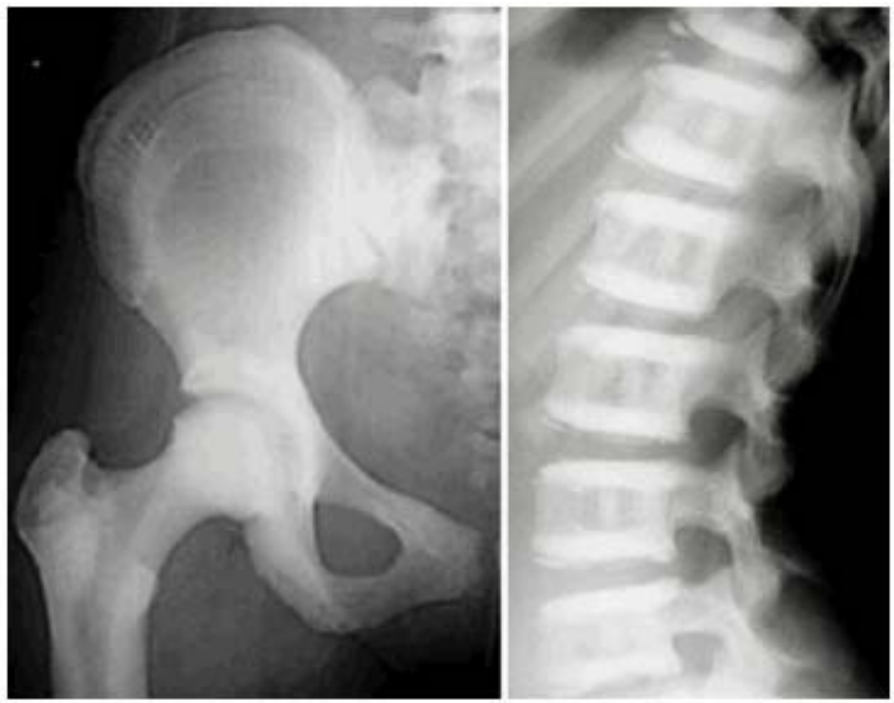


Heath et al JBMR 2009

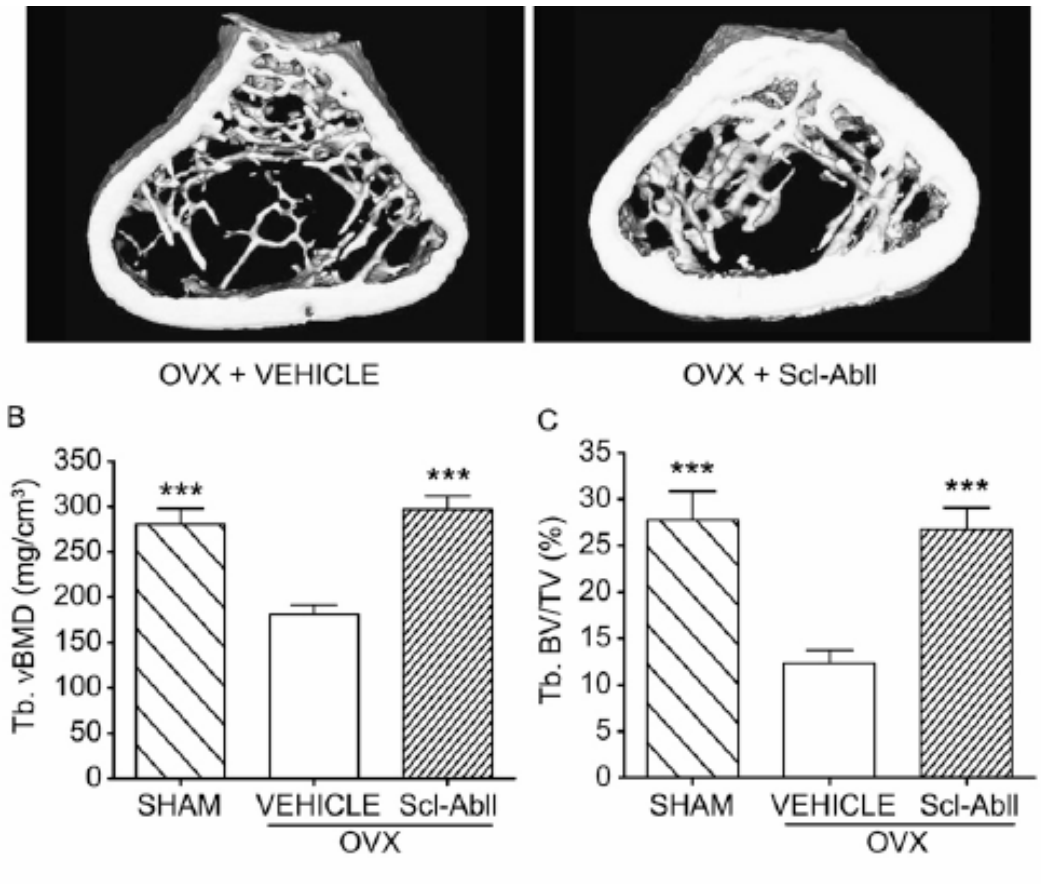
Esclerostina y masa ósea



Enfermedad de Van Buchem
(mutación gen SOST)

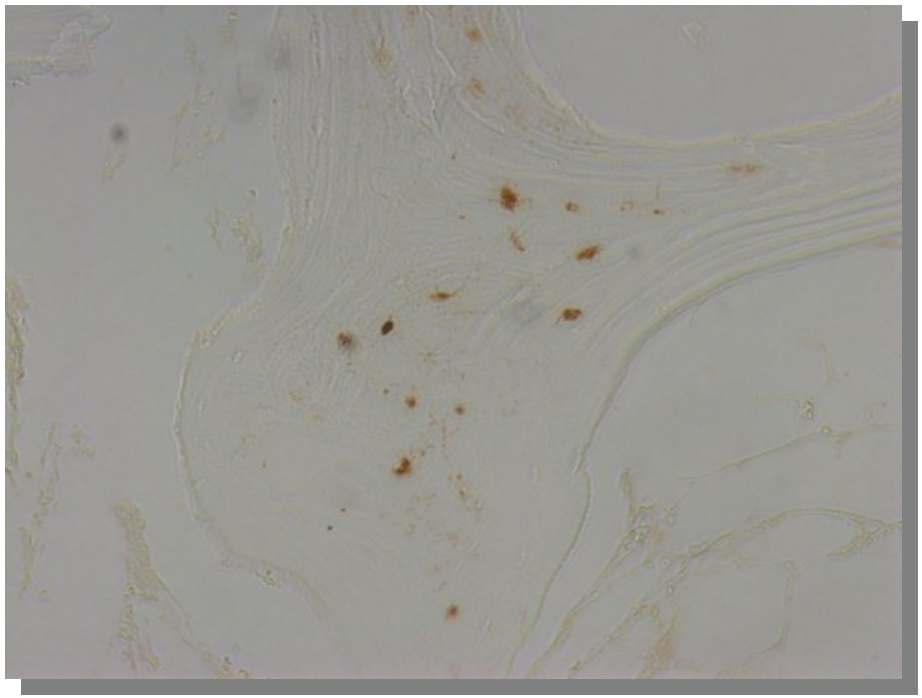


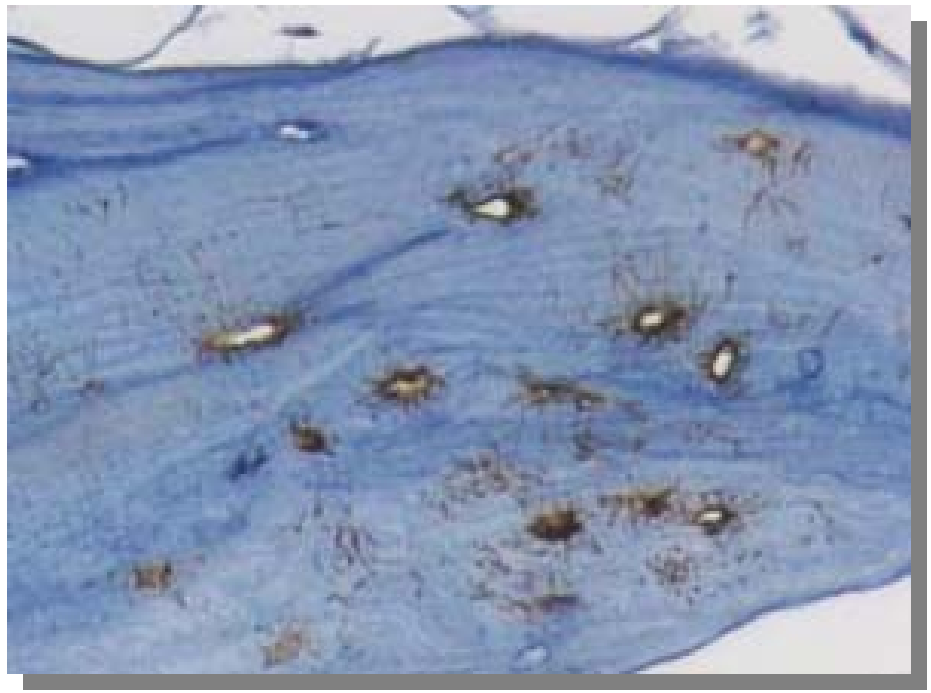
Ac anti-esclerostina en ratas



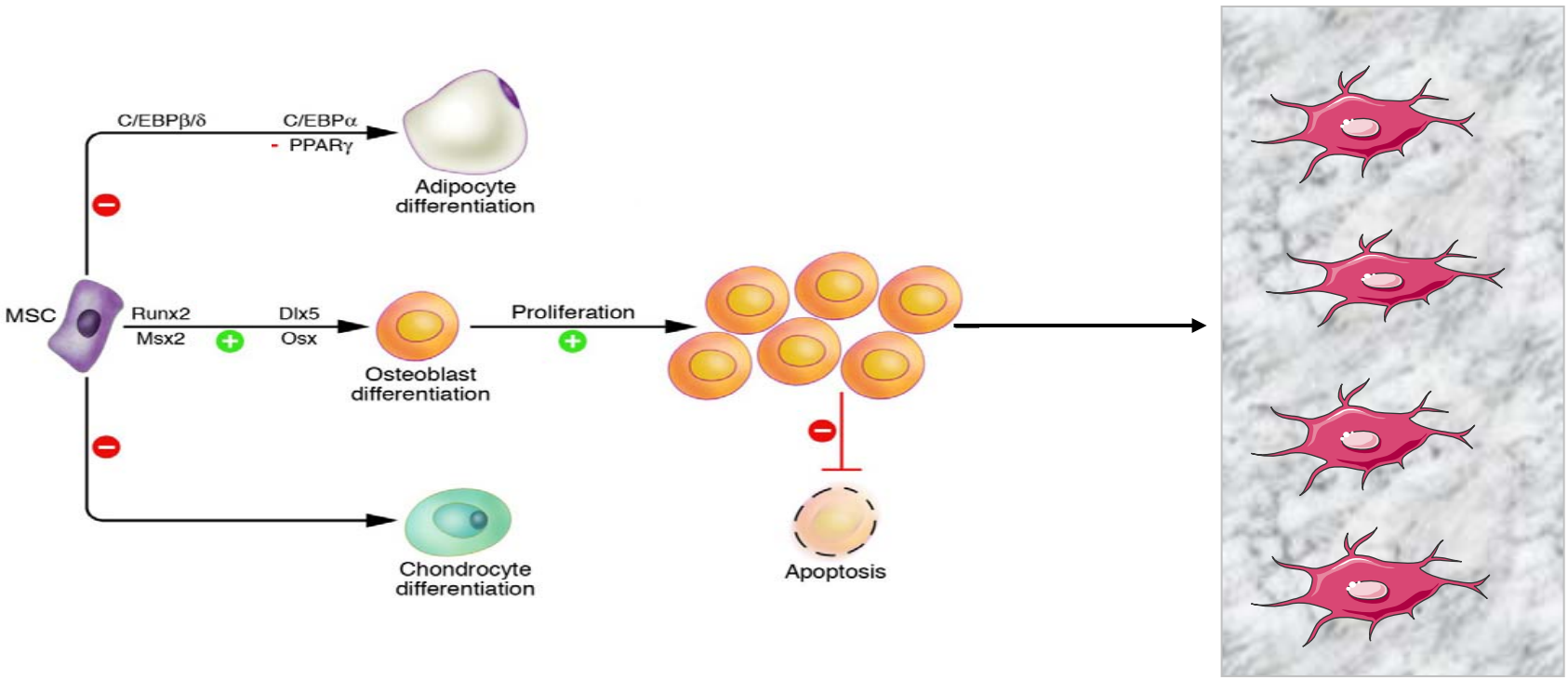
Li et al. JBMR 2009

Esclerostina

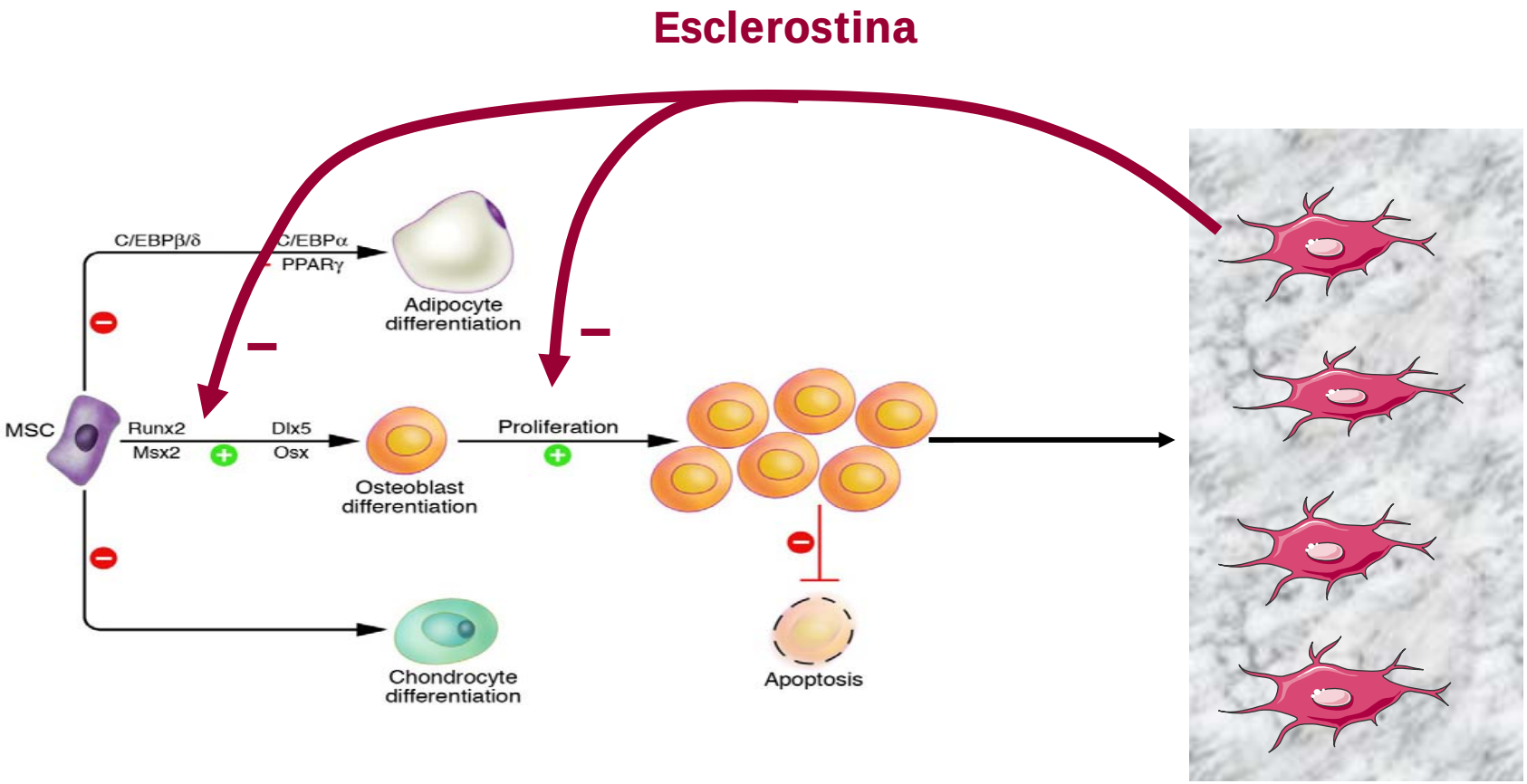




Esclerostina

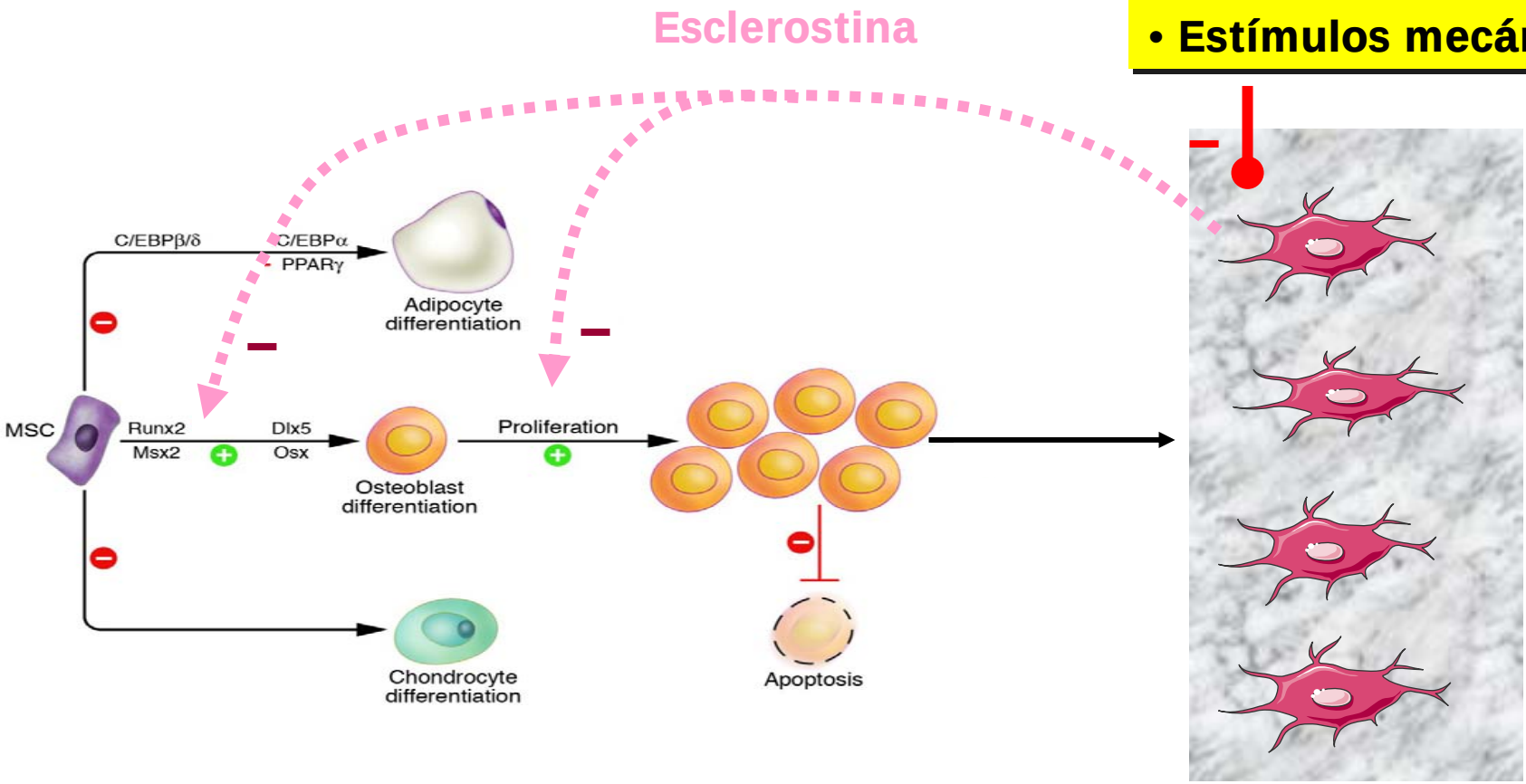


Esclerostina

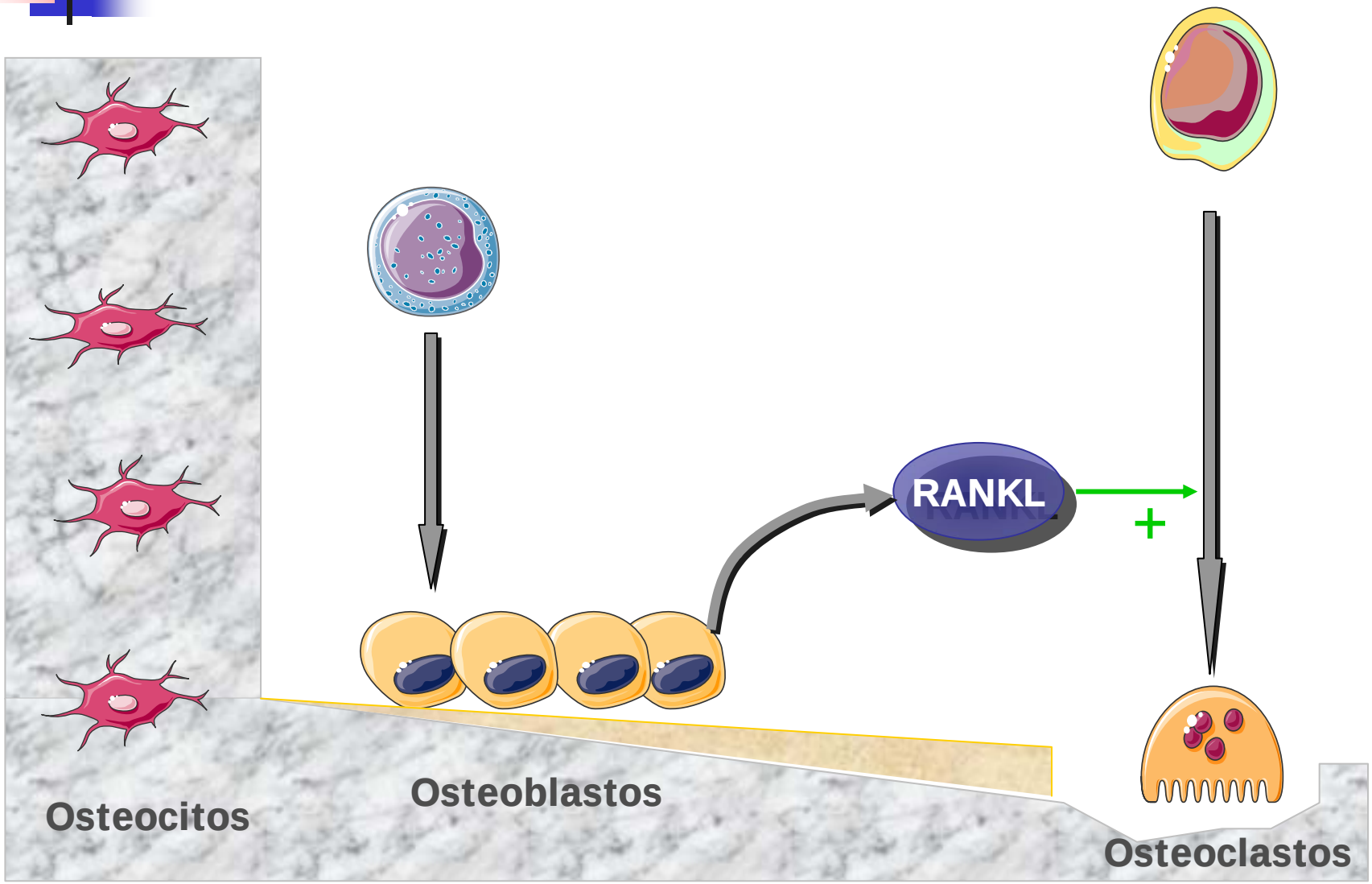


Esclerostina

- **PTH**
- **Estímulos mecánicos**



Dianas para terapias biológicas



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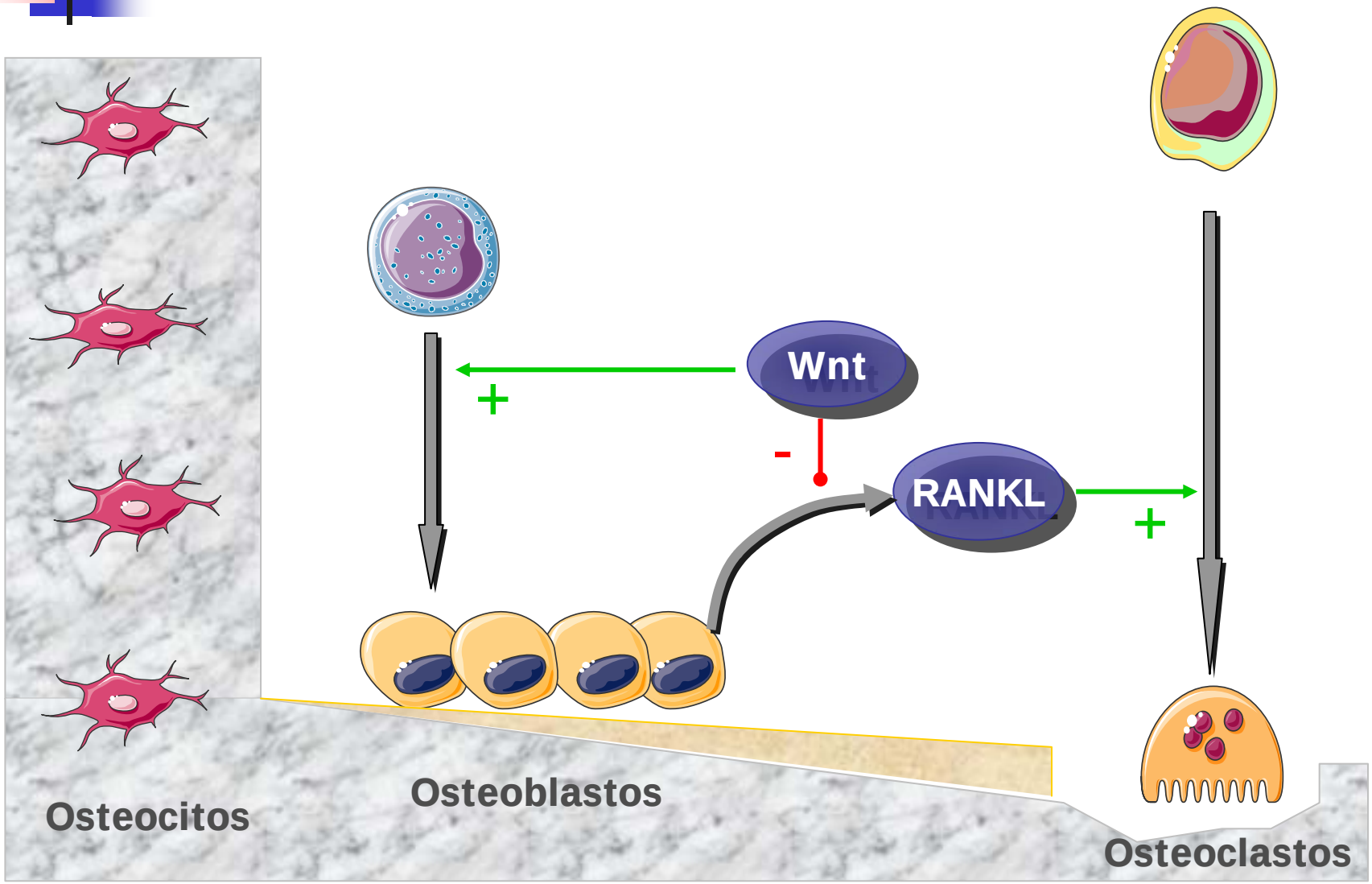
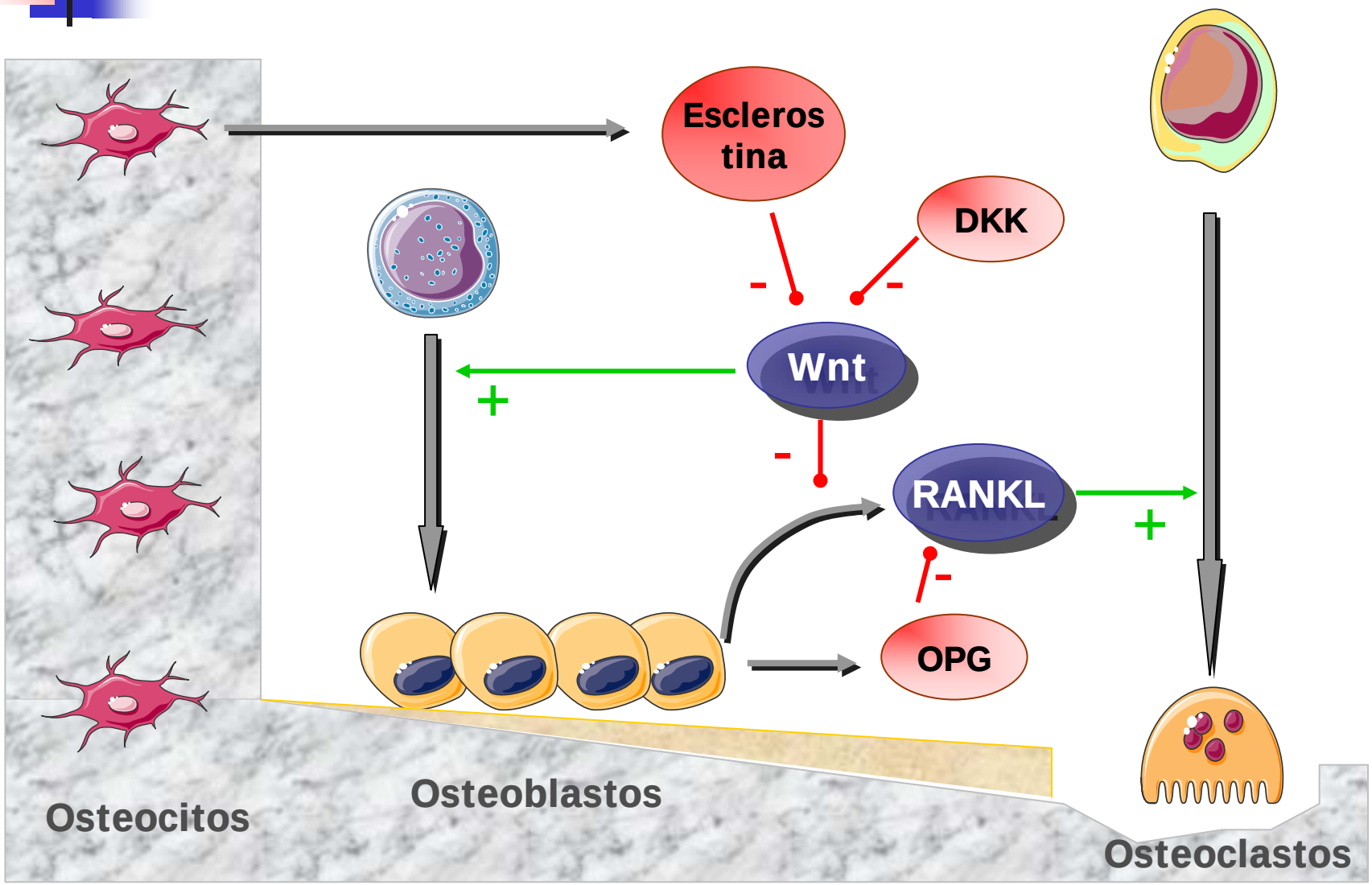


Dianas para terapias biológicas



Dianas para terapias biológicas