SOCIETÀ ITALIANA
G.U.I.D.A.
PER LA GESTIONE UNIFICATA E INTERDISCIPLINARE
DEL DOLORE MUSCOLO-SCHELETRICO E DELL'ALGODISTROFIA

V CONGRESSO NAZIONALE

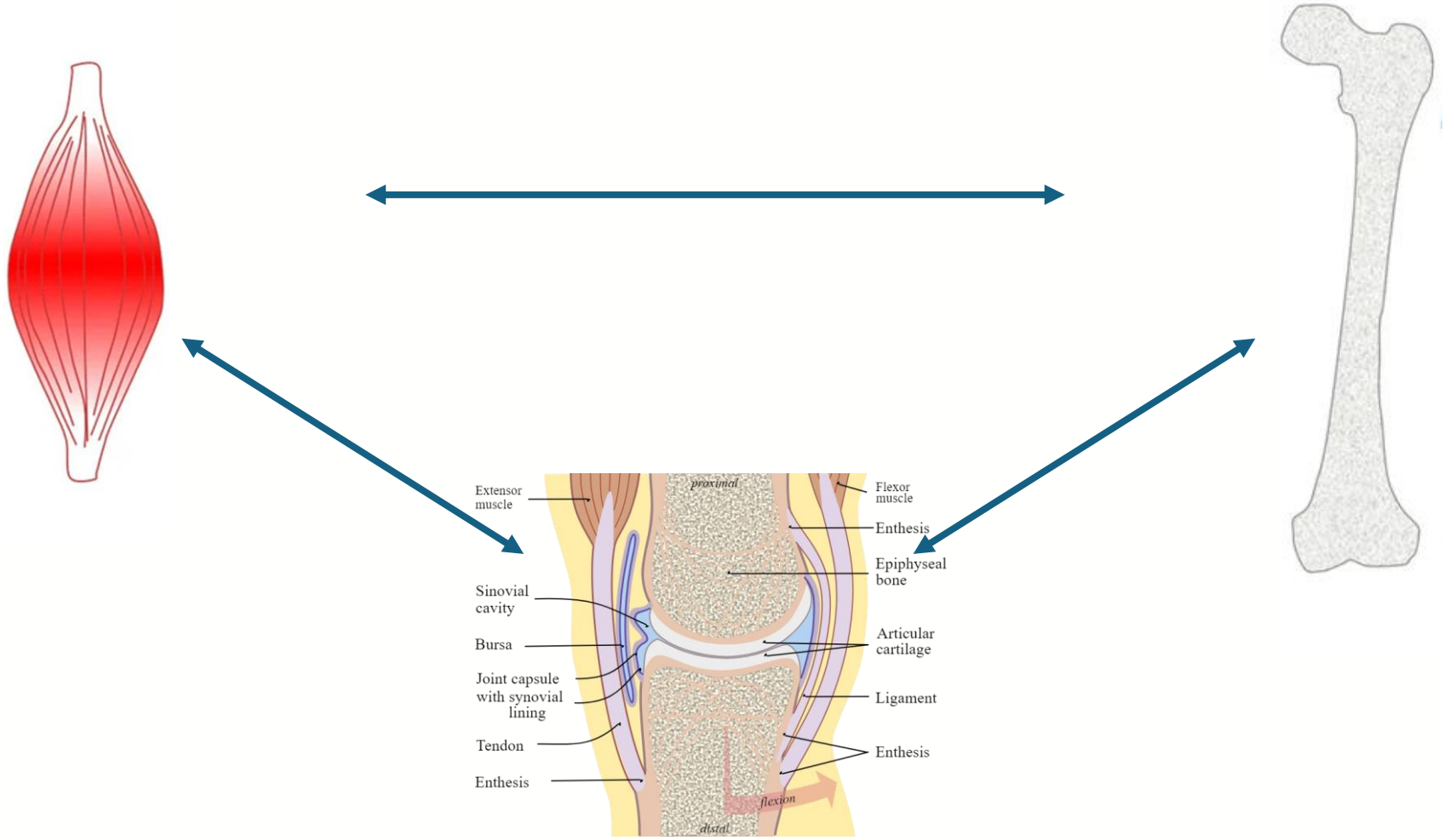
EVERYTHING
YOU NEED TO KNOW

BOLOGNA
ROYAL HOTEL CARLTON
27 Febbraio - 1 Marzo 2025

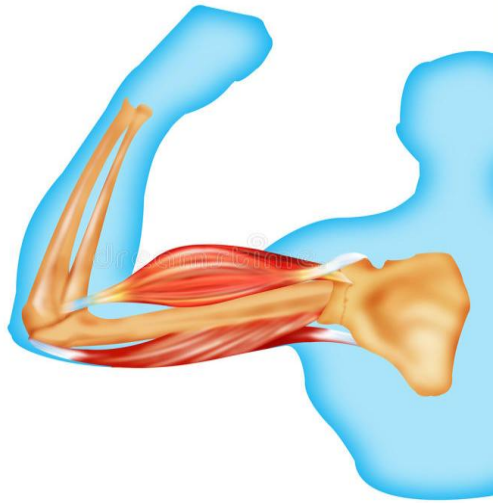
Cross-talk osso, muscolo, articolazione

Andrea Del Fattore,
Head of the Bone Physiopathology Research Unit,
Bambino Gesù Children's Hospital, Rome

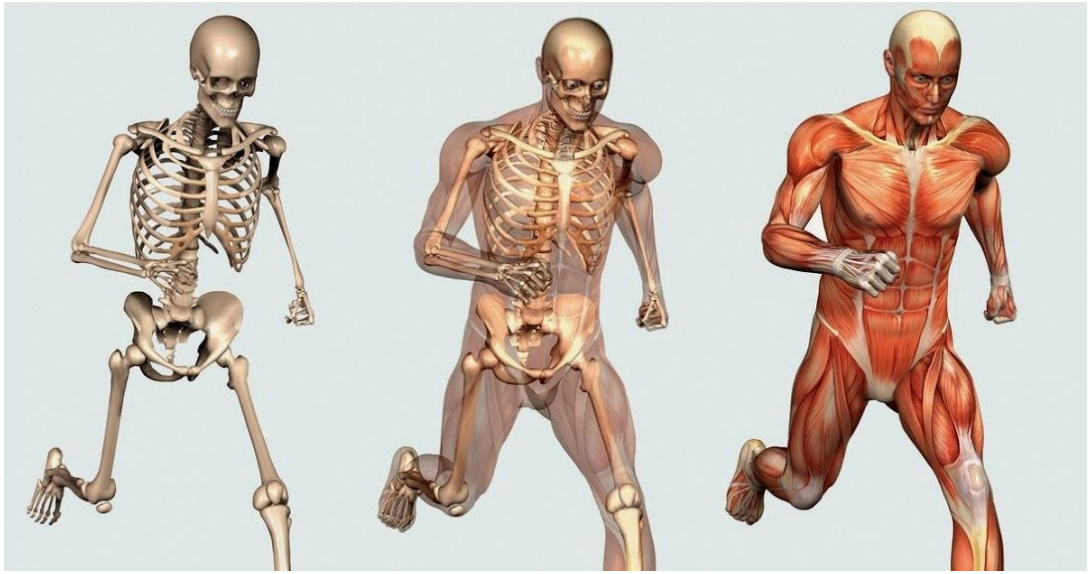
Muscle-Bone-Joint crosstalk

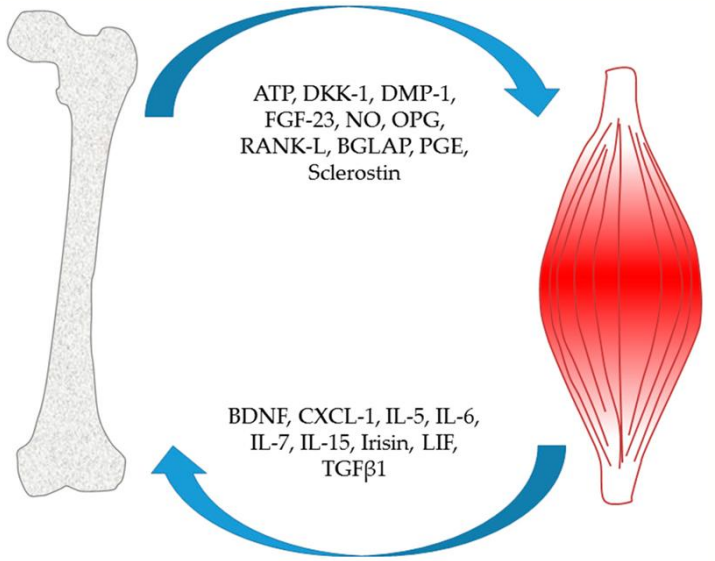


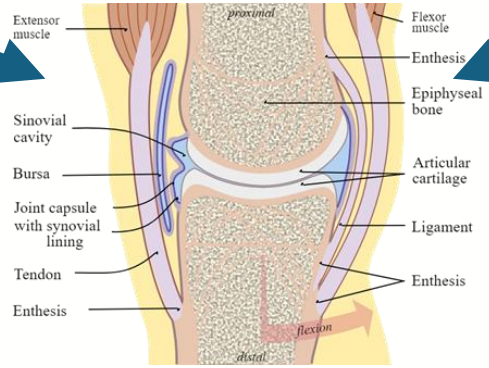
Muscle-Bone-Joint crosstalk



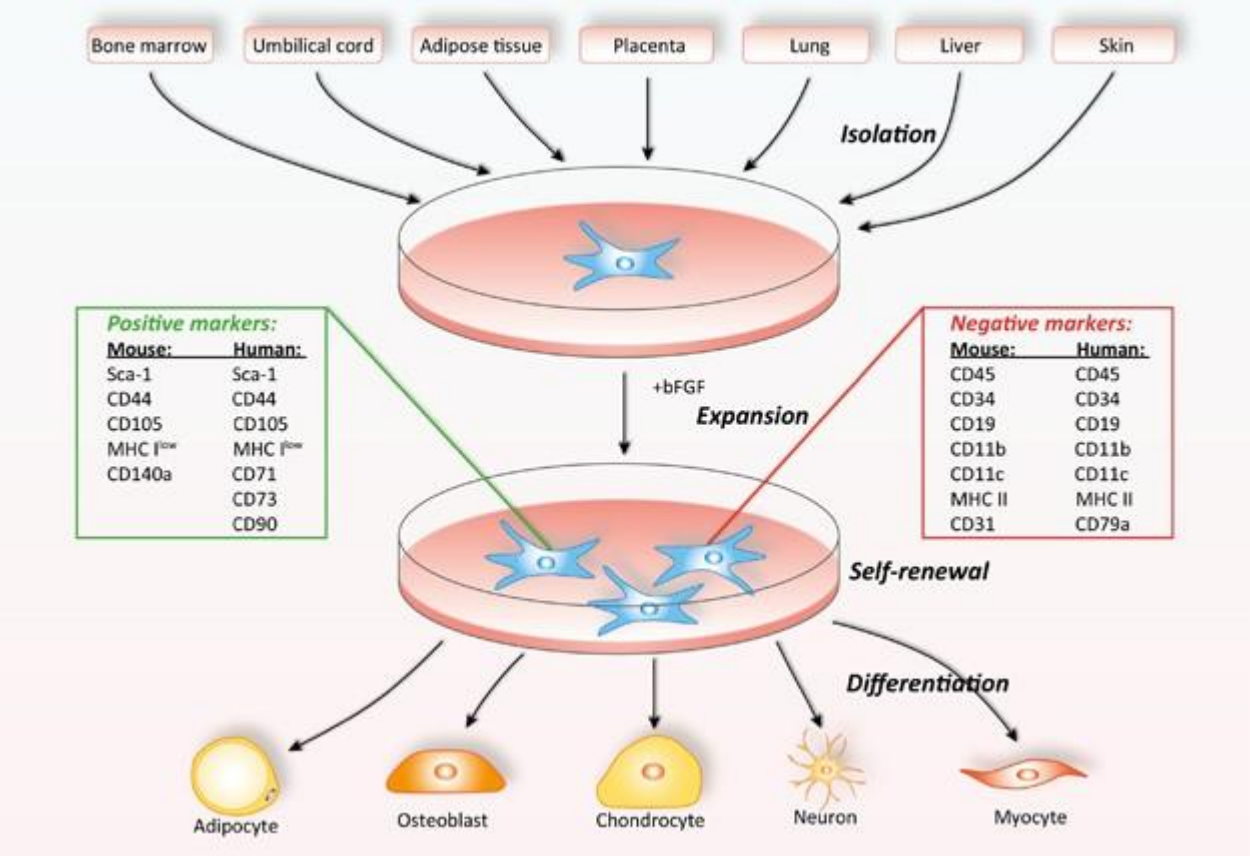
Muscle-Bone-Joint crosstalk





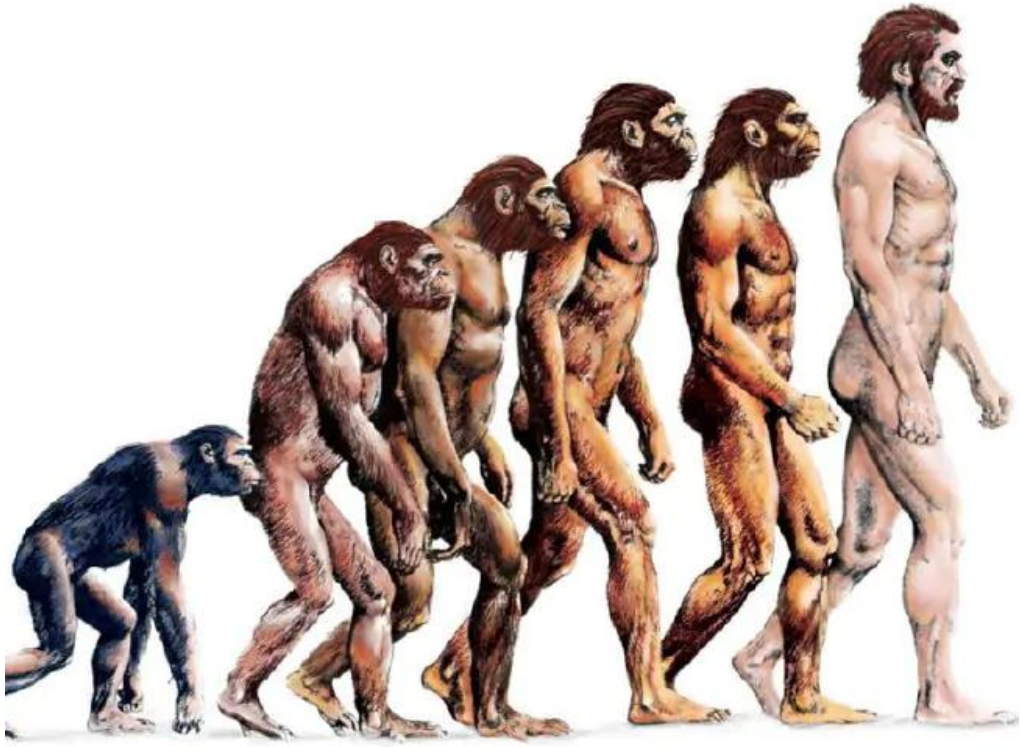


MSC



Chen *et al.* 2016

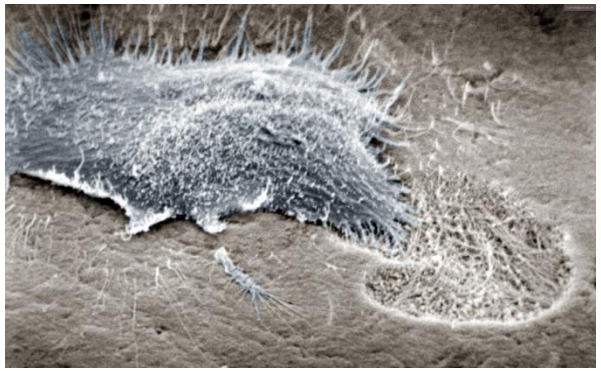
Evolution of Bone Tissue

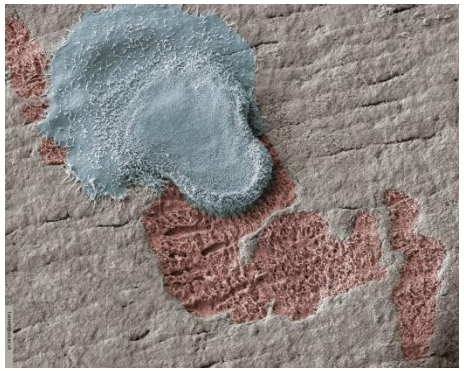


«A survival tool»

Bone tissue

…Bone is the only tissue in our body that contains a cell type, the osteoclast, whose main function is to destroy the tissue in which it resides ……





Bone Re-Modeling

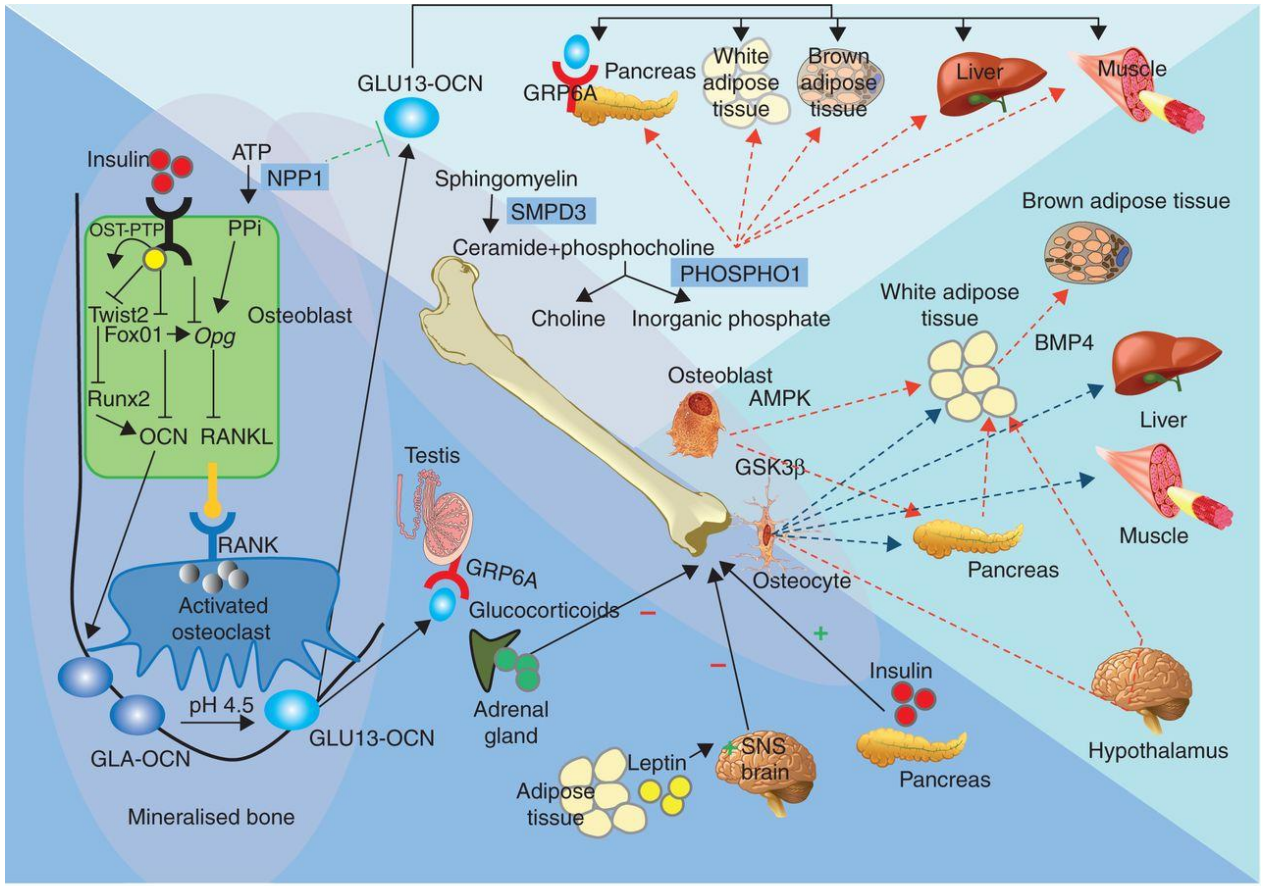
Bone Modeling:

- To allow the growth of Skeleton

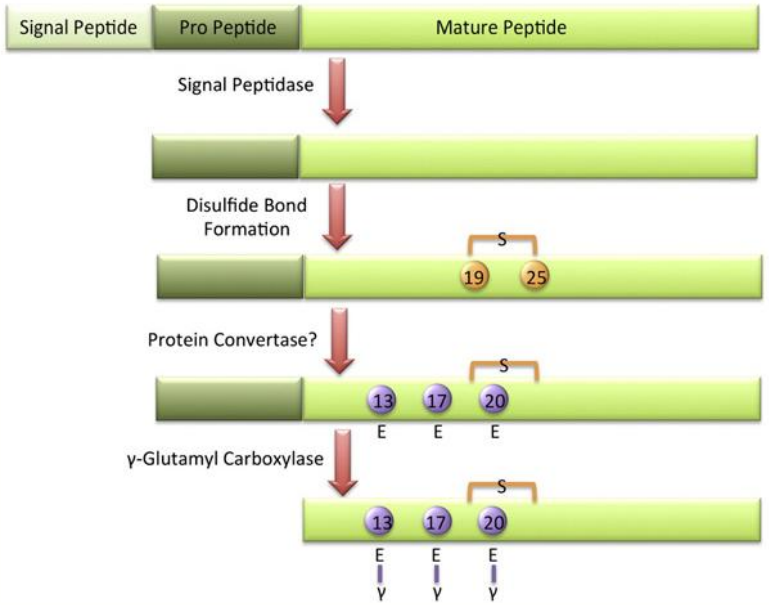
Bone Remodeling:

- To repair micro-fractures
- To substitute ischemic bone with mechanically competent tissue
- To regulate mineral metabolism

The endocrine role of the skeleton



Osteocalcin



Osteocalcin in Human Serum: A Circadian Rhythm

CAREN M. GUNDBERG, MORRI E. MARKOWITZ, MARK MIZRUCHI, JOHN F. ROSEN

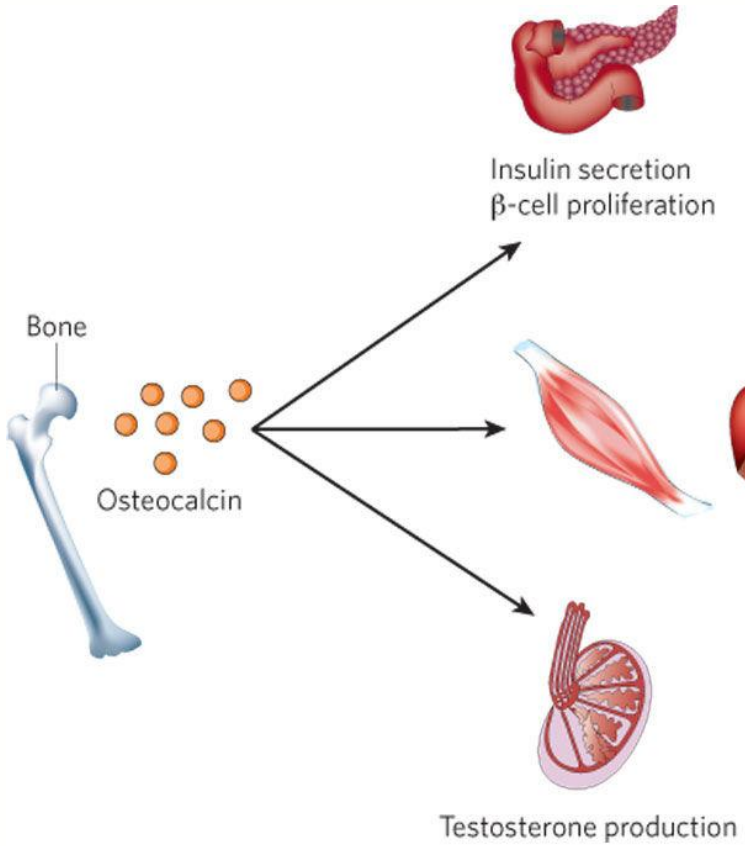
The Journal of Clinical Endocrinology & Metabolism, Volume 60, Issue 4, 1 April 1985, Pages 736–739, https://doi.org/10.1210/jcem-60-4-736
Published: 01 April 1985 **Article history** ▾

Abstract

Osteocalcin, the vitamin K-dependent protein synthesized in bone, is found in blood. The level of circulating osteocalcin has recently been used as an indicator of the rate of bone turnover. We measured serum osteocalcin during 24-h periods in 6 normal 20- to 30-yr-old men and 4 women. Blood was sampled via an indwelling venous catheter every 30 or 60 min for 24 h. Circadian rhythmicity in circulating osteocalcin was found in 9 of the 10 individuals studied. Osteocalcin levels fell during the morning, rose in the afternoon and early evening, and reached a peak nocturnally. There were no consistent correlations between osteocalcin concentrations and circulating levels of ionized calcium, total calcium, or inorganic phosphate in the subjects tested. This study illustrates the importance of regulating the time of blood sampling for osteocalcin determinations in clinical investigations of metabolic bone disease.

Issue Section: Articles

The endocrine role of the Skeleton

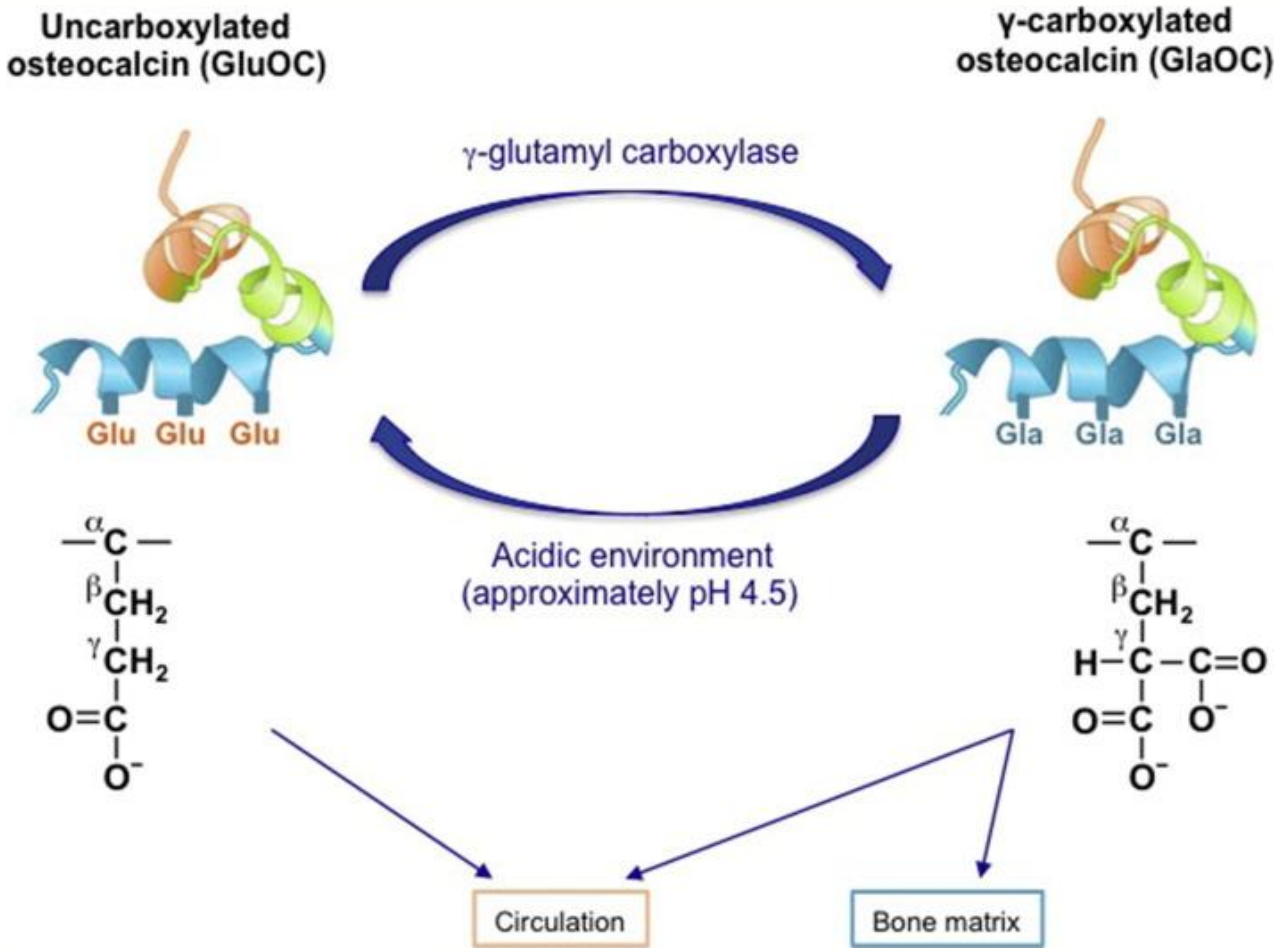


Ferron M, Wei J, Yoshizawa T, Del Fattore A, DePinho RA, Teti A, Ducy P, Karsenty G. **Insulin signaling in osteoblasts integrates bone remodeling and energy metabolism**. **Cell**. 2010

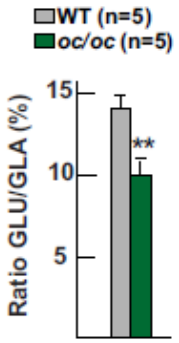
Lee NK, Sowa H, Hinoi E, Ferron M, Ahn JD, Confavreux C, Dacquin R, Mee PJ, McKee MD, Jung DY, Zhang Z, Kim JK, Mauvais-Jarvis F, Ducy P, Karsenty G. **Endocrine regulation of energy metabolism by the skeleton**. **Cell.** 2007

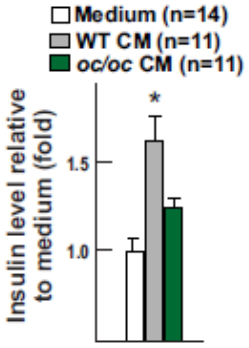
Oury F, Sumara G, Sumara O, Ferron M, Chang H, Smith CE, Hermo L, Suarez S, Roth BL, Ducy P, Karsenty G. **Endocrine regulation of male fertility by the skeleton**. **Cell.** 2011

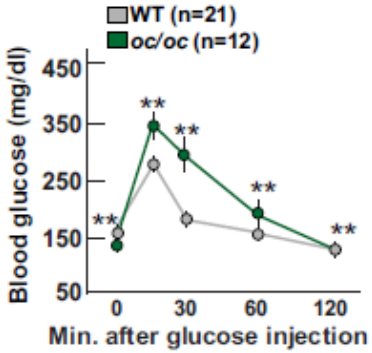
Osteocalcin

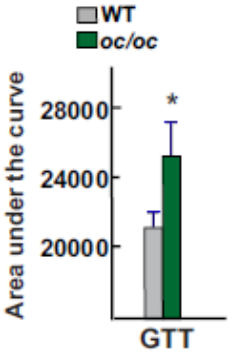


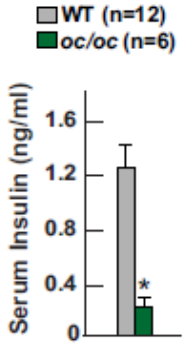
Role of Osteoclasts

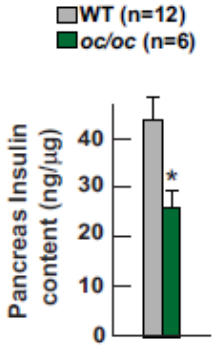


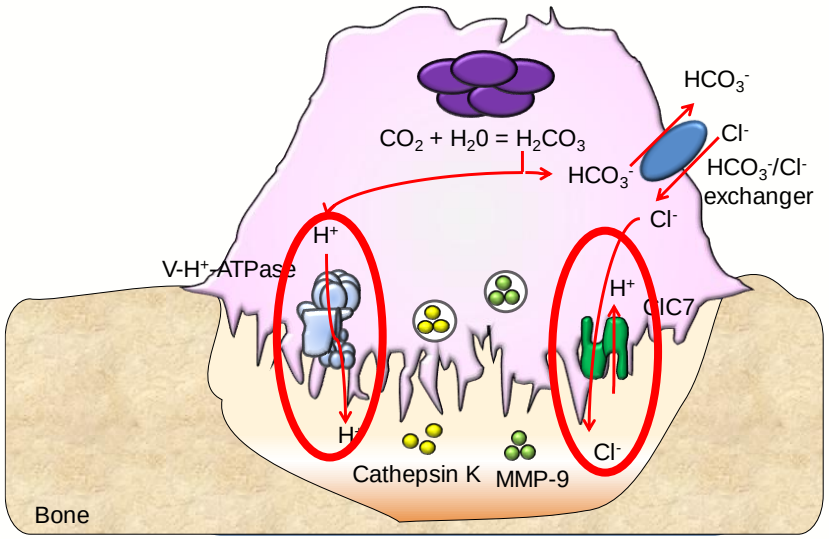








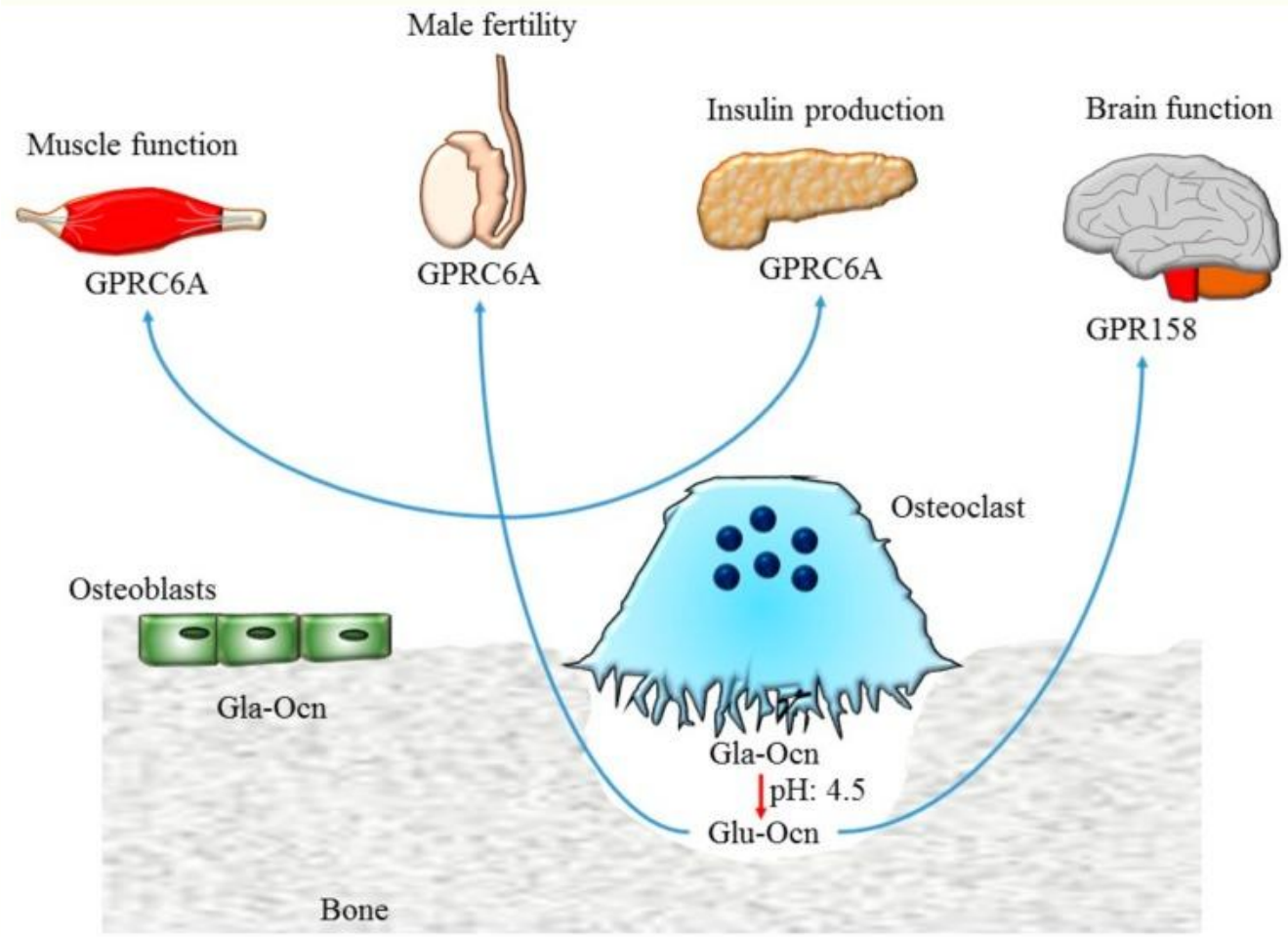




		Age (Years)	Insulin (mU/l)	Osteocalcin ratio GLU/GLA (%)
Males	Controls (n=6-8)	34 ± 7	20.2 ± 5.0	29 ± 8
	ADO-1	45	6.3	4
	ADO-2	47	16.5	1
	ADO-3	34	10.9	14
Females	Controls (n=4-9)	47 ± 16	20.1 ± 2.9	49 ± 18
	ADO-4	64	10	16
	ADO-5	35	9.9	11
	ADO-6	63	11.8	17

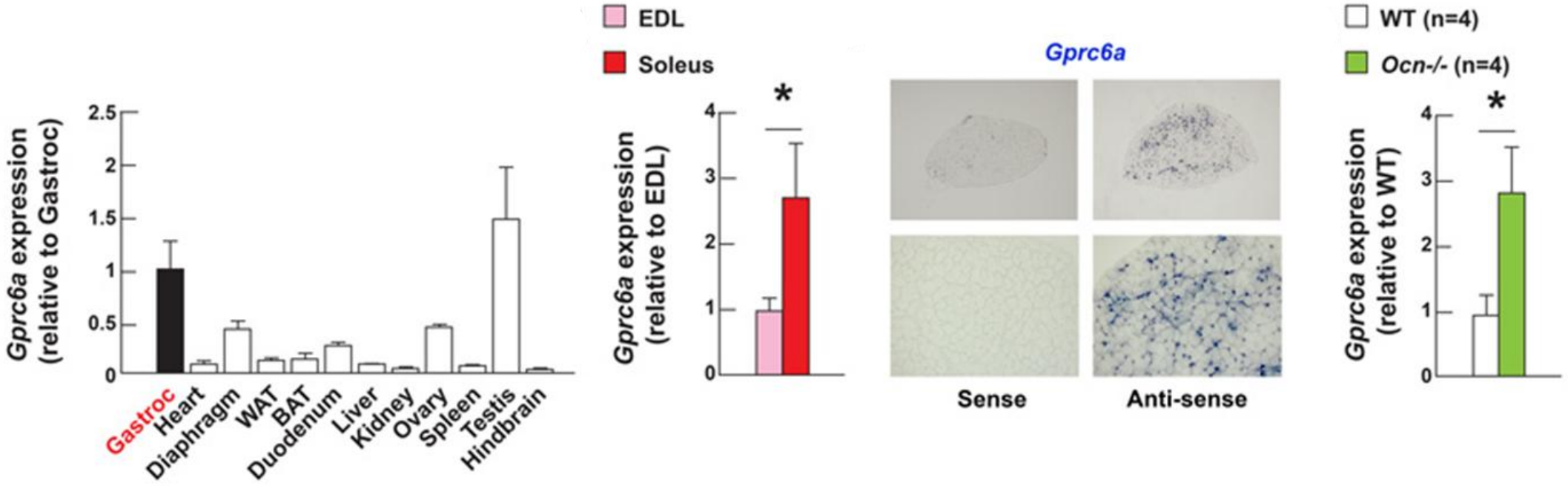
Ferron *et al.* Cell 2010

Osteocalcin Receptors



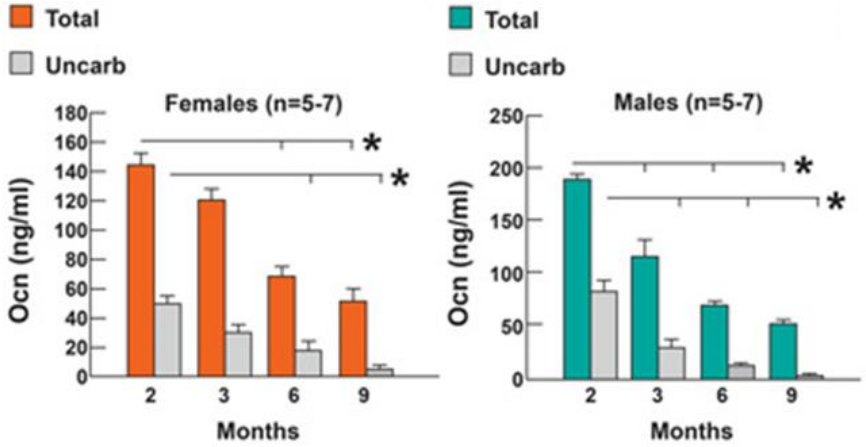
Rossi *et al.* IJMS 2019

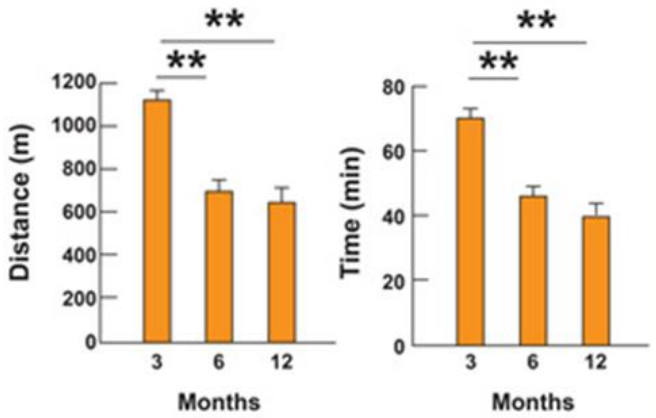
Gprc6a expression - Muscle

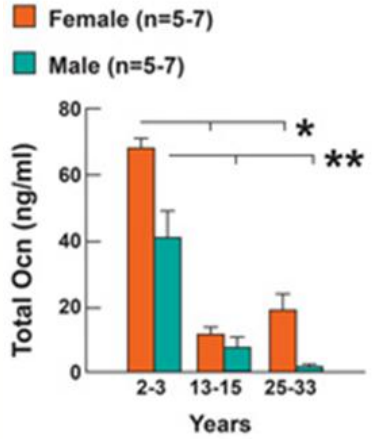


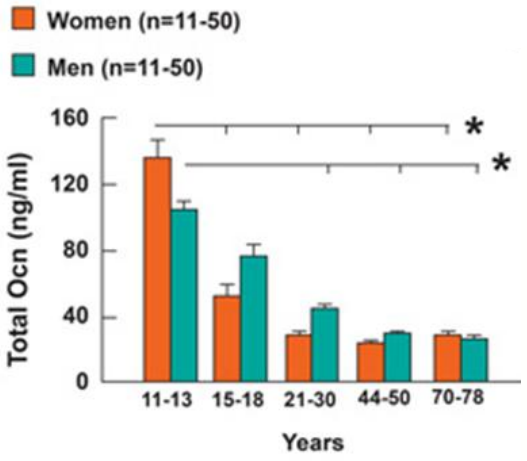
Mera *et al.* Cell Metab. 2016

Osteocalcin levels



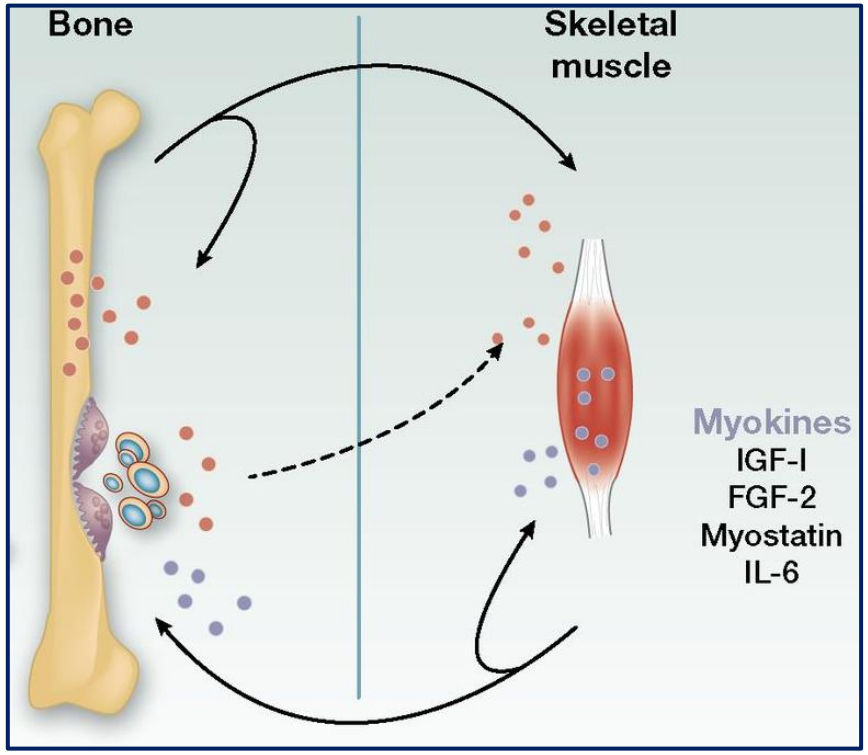






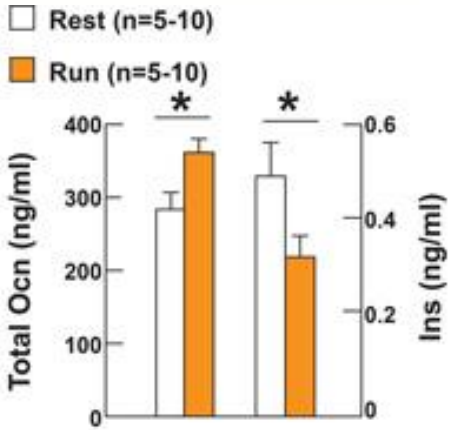
Mera *et al.* Cell Metab. 2016

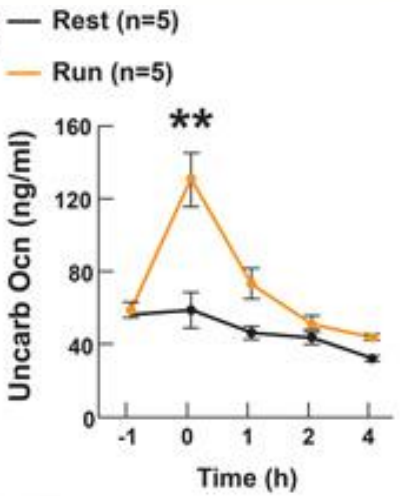
Physical activity

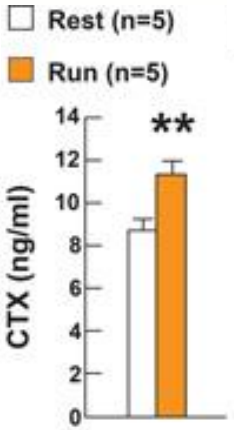


Osteocalcin levels – Physical Activity

40 minuti corsa treadmill 30cm/s



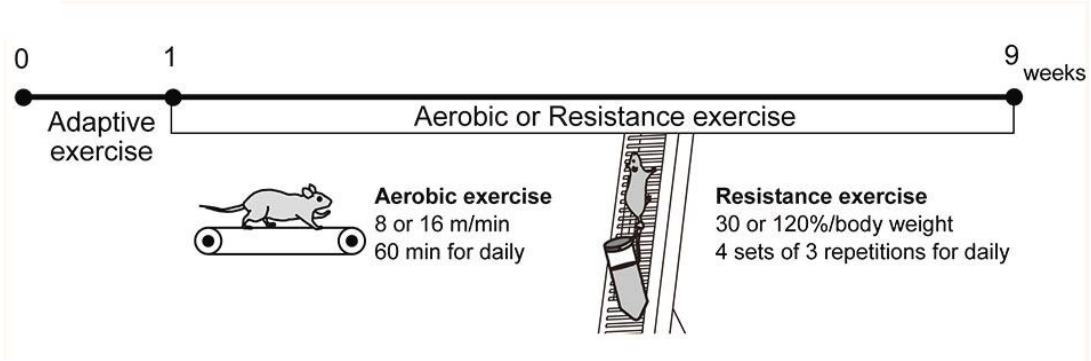


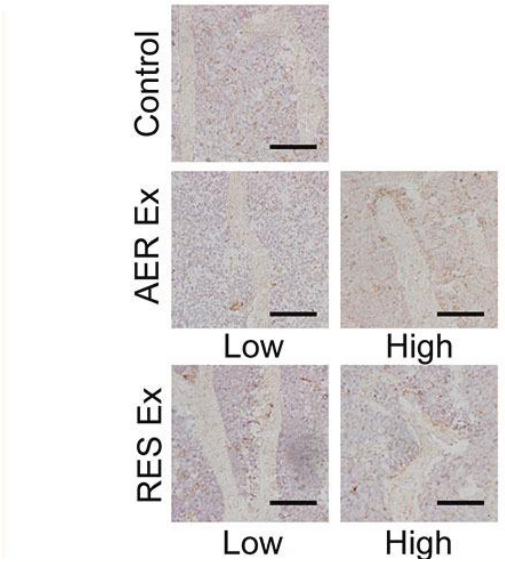


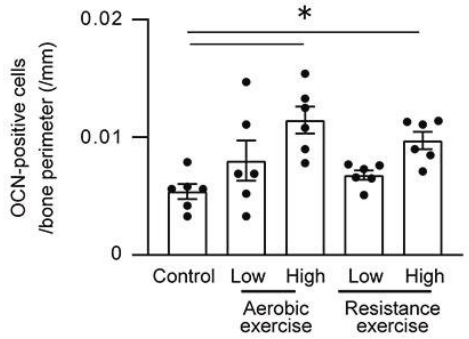
	Rest (n=23)	Run (n=23)	% variation
Total OCN (mg/l)	19.1 ± 1.3	22.0 ± 1*	17.4 ± 4.0
Age (yrs)	21.9 ± 2.4		
BMI (kg/m²)	22.9 ± 1.5		

Mera *et al.* Cell Metab. 2016

Exercise-induced interaction

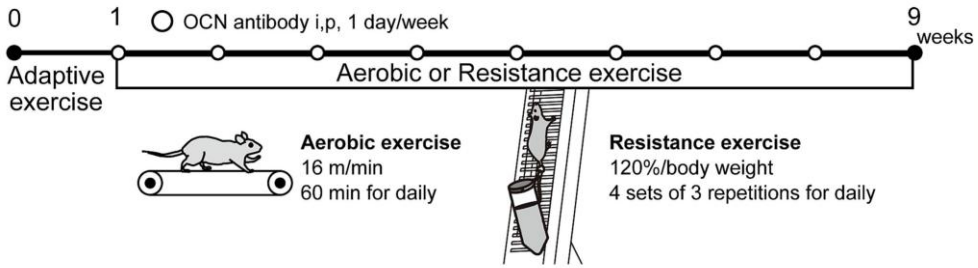


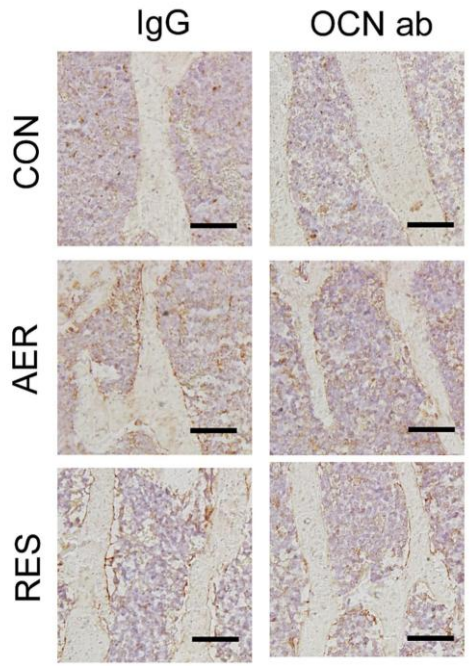


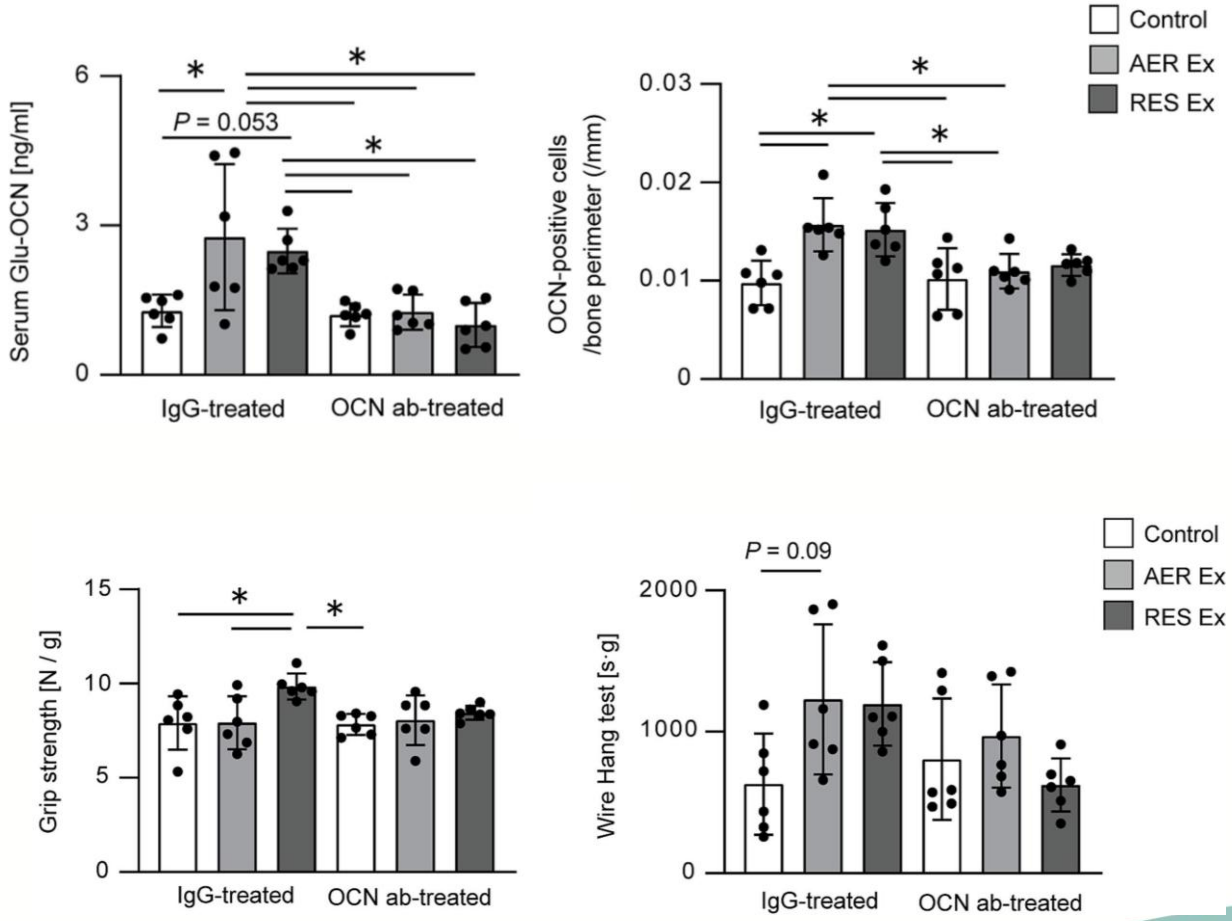


Hatakeyama *et al.* 2025

Exercise-induced interaction

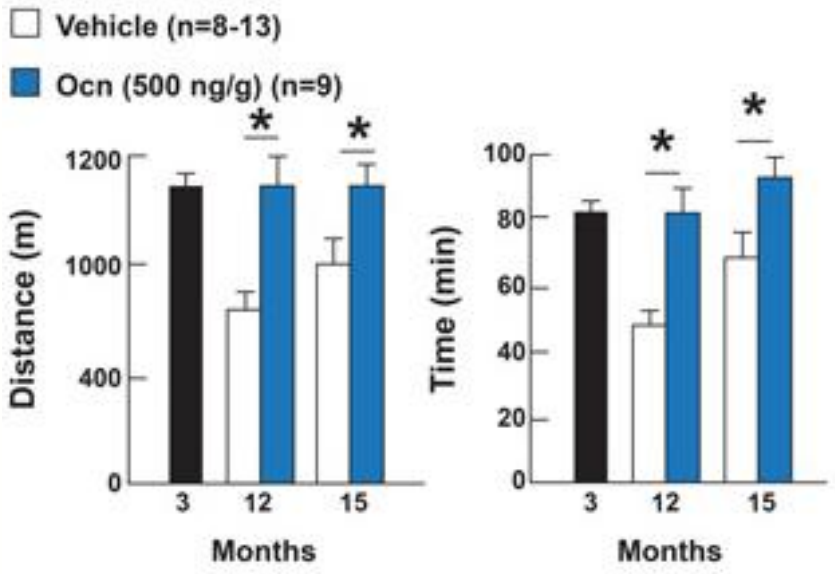






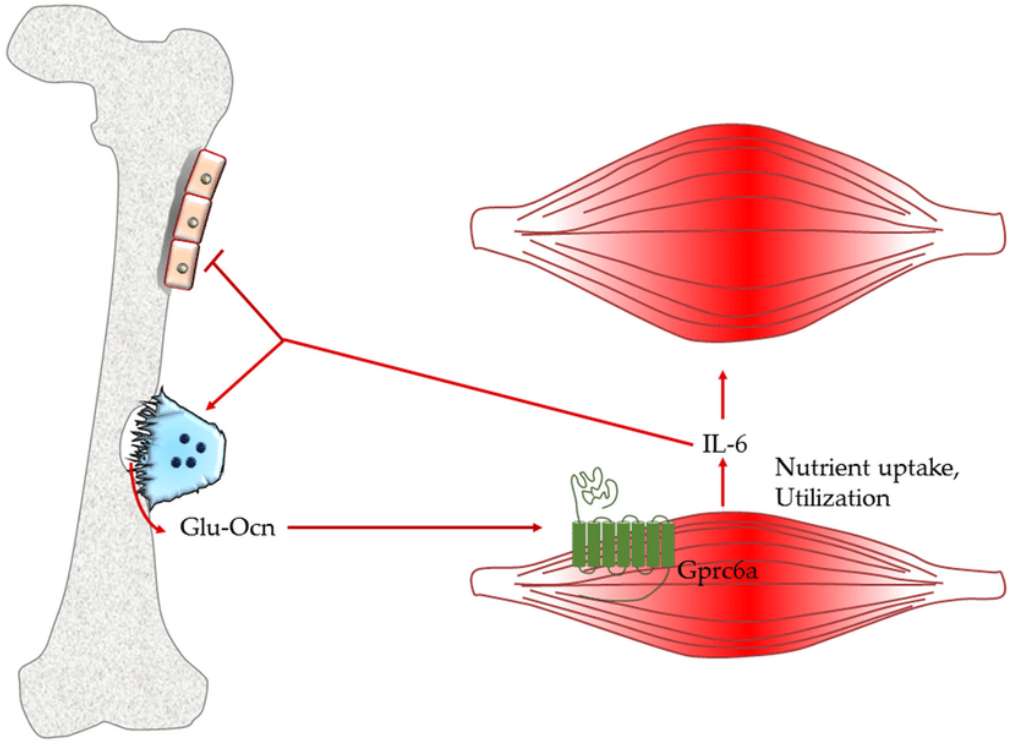
Hatakeyama *et al.* 2025

In vivo treatment with Osteocalcin



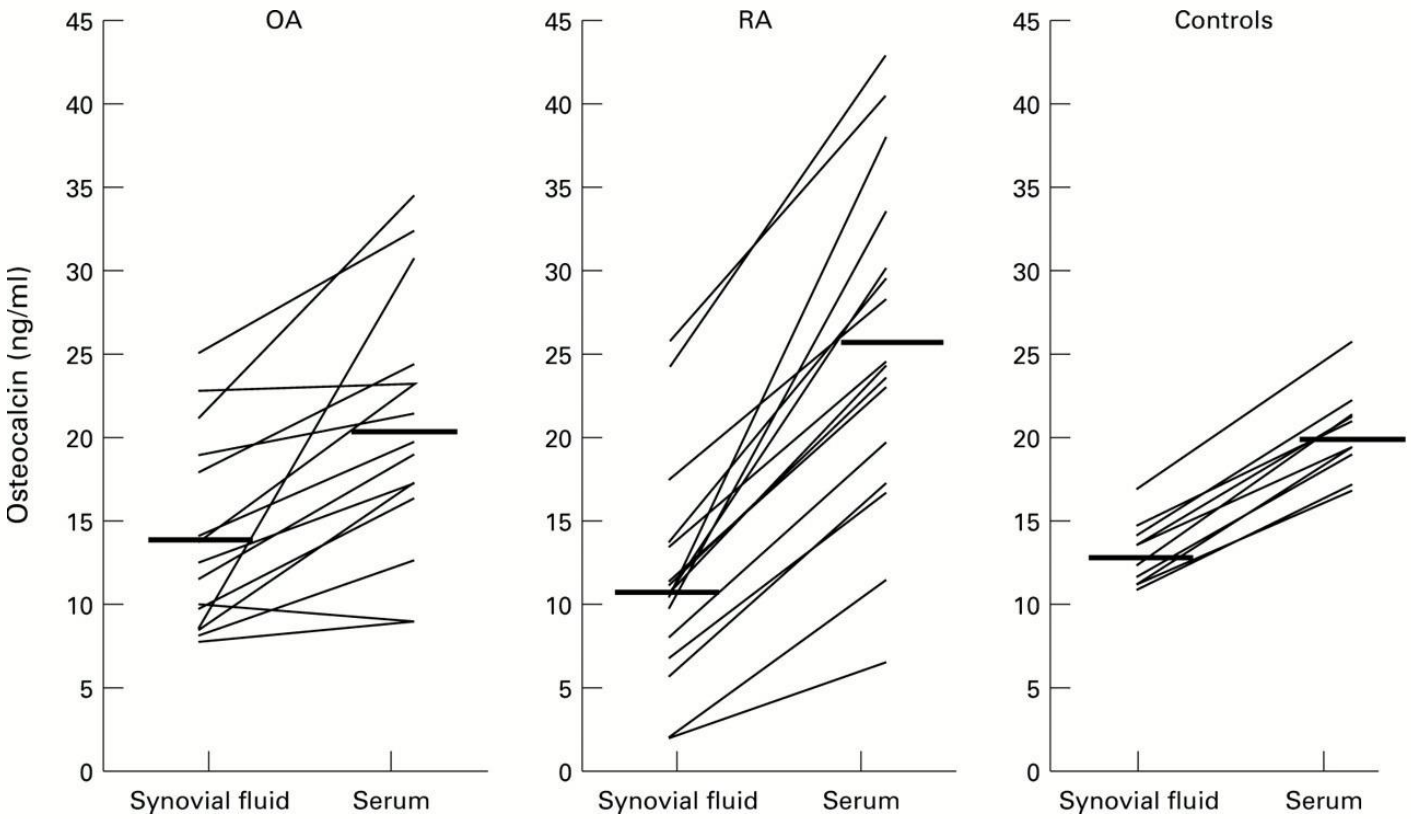
Mera *et al.* Cell Metab. 2016

Osteocalcin levels – Physical Activity



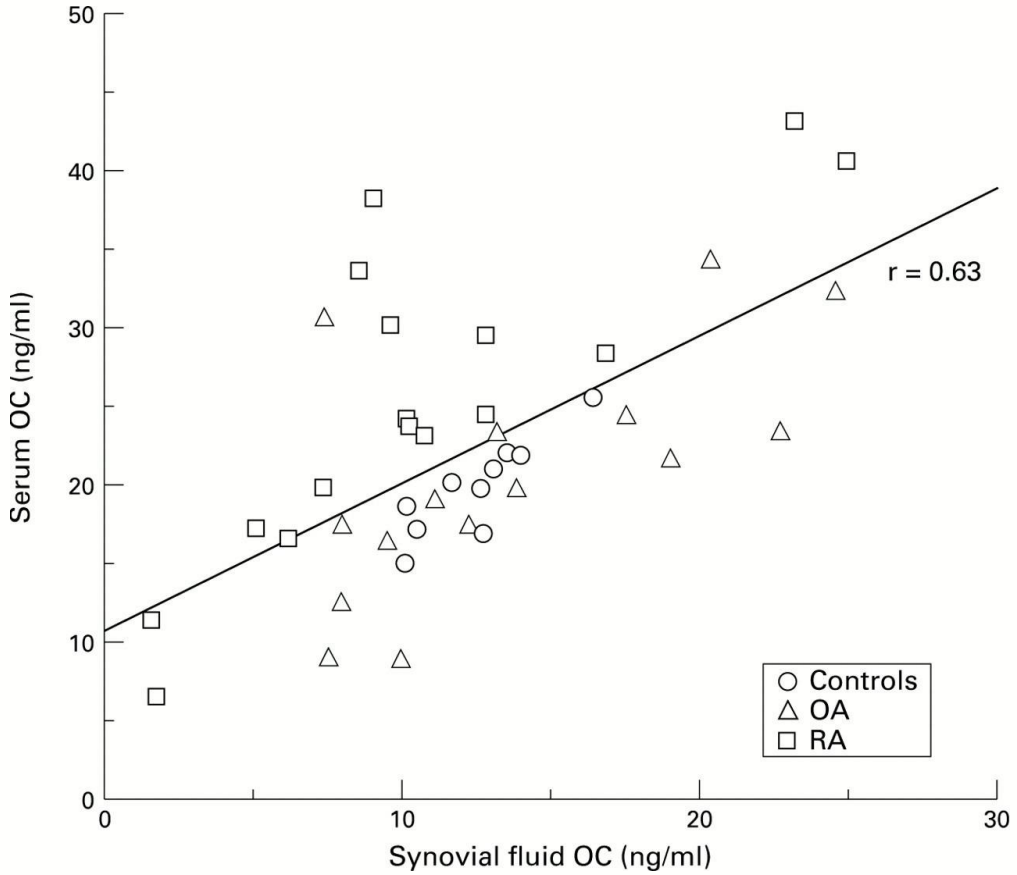
Osteocalcin stimulates nutrient uptake and the secretion of interleukin 6, inducing increase of muscle mass in response to exercise.

Osteocalcin in Synovial fluid



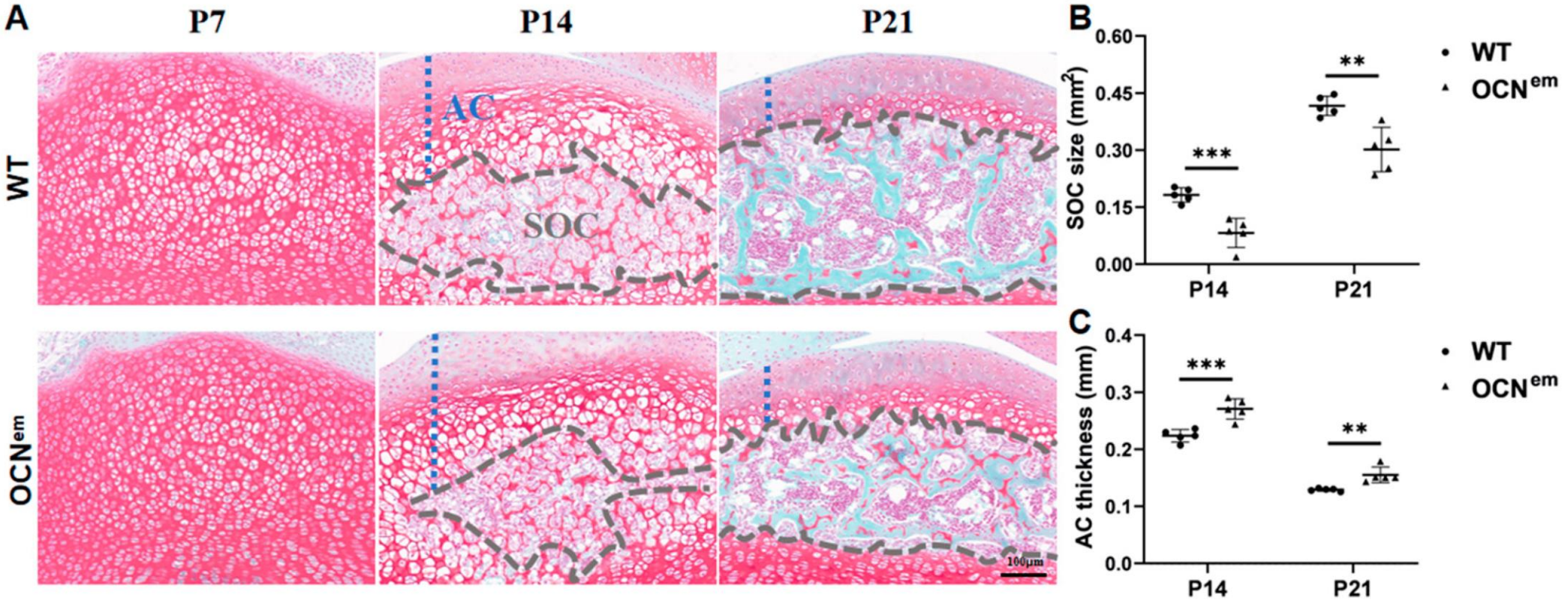
Salisbury *et al.* 1997

Osteocalcin in Synovial fluid



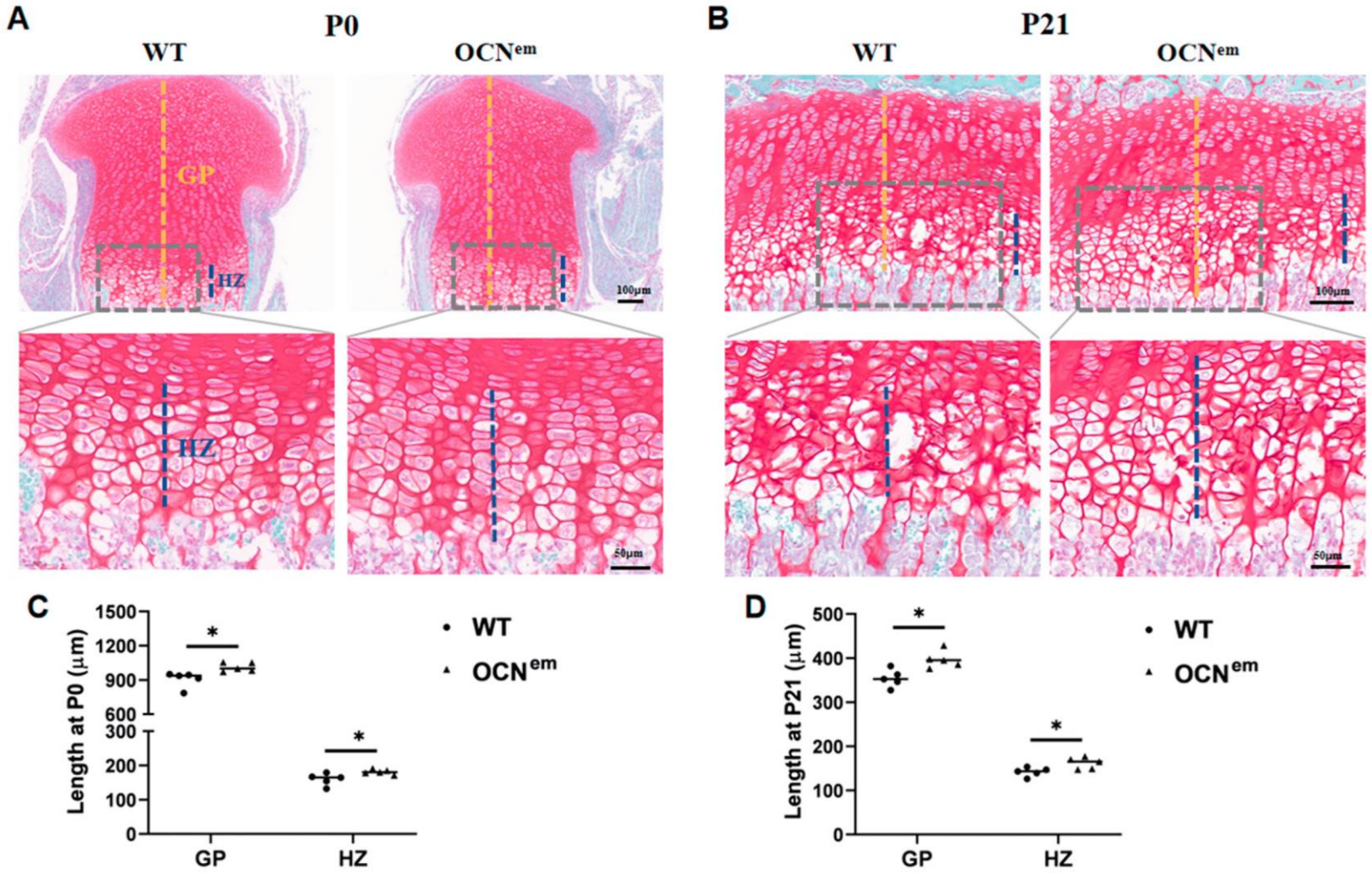
Salisbury *et al.* 1997

Delay formation of secondary ossification centers in OCNem mice



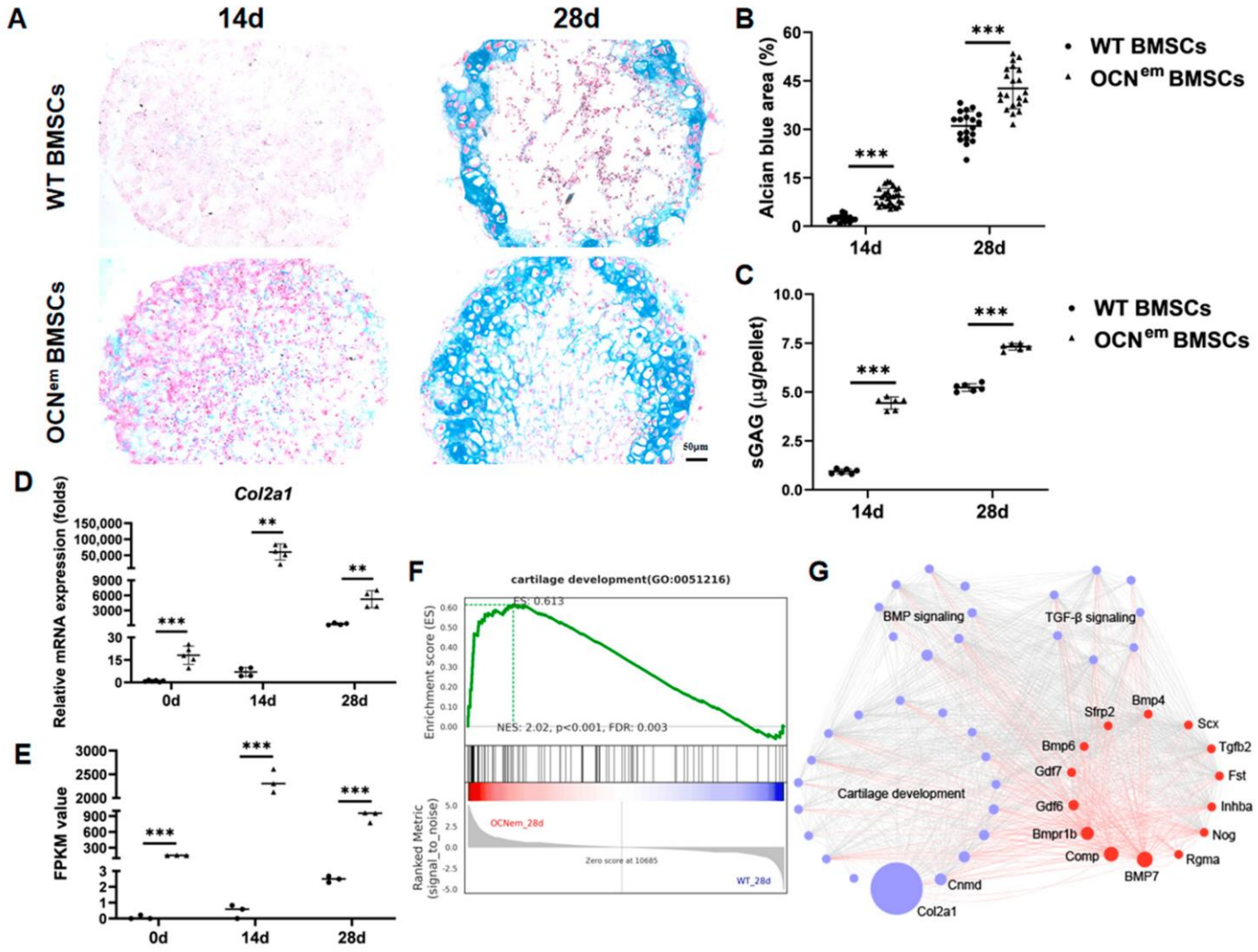
Yu *et al.* 2024

OCNem mice



Yu *et al.* 2024

Osteocalcin - Chondrocytes



Yu *et al.* 2024

Osteocalcin – Be or Not to be a Hormone

An osteocalcin-deficient mouse strain without endocrine abnormalities.

Diegel CR, Hann S, Ayturk UM, Hu JCW, Lim KE, Droscha CJ, Madaj ZB, Foxa GE, Izaguirre I, Transgenics Core VV Paracha N, Pidhaynyy B, Dowd TL, Robling AG, Warman ML, Williams BO.

PLoS Genet. 2020 May 28;16(5):e1008361. doi: 10.1371/journal.pgen.1008361. eCollection 2020 May.

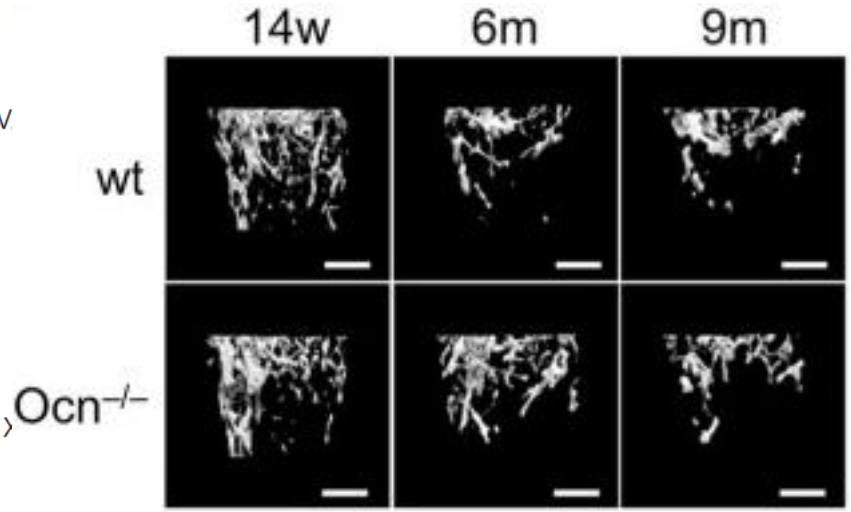
PMID: 32463812 Free PMC article.

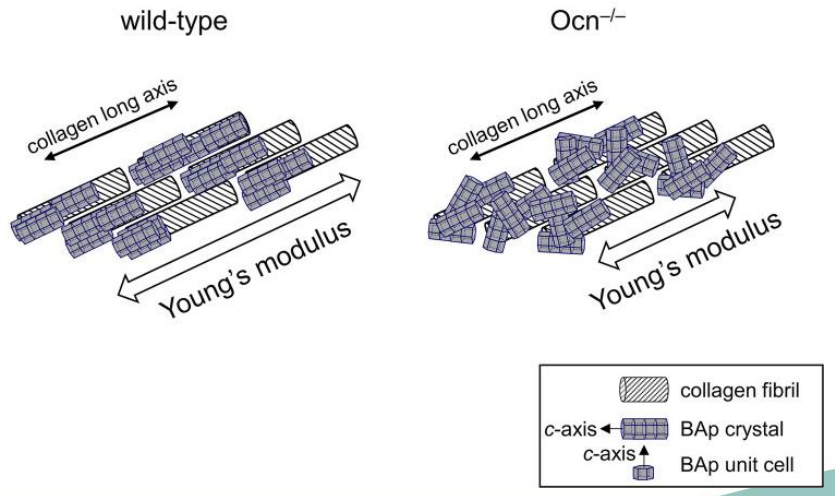
Osteocalcin is necessary for the alignment of apatite crystallites, but not glucose metabolism, testosterone synthesis, or muscle mass.

Moriishi T, Ozasa R, Ishimoto T, Nakano T, Hasegawa T, Miyazaki T, Liu W, Fukuyama R, Wang Y, Komori H, Qin X, Amizuka N, Komori T.

PLoS Genet. 2020 May 28;16(5):e1008586. doi: 10.1371/journal.pgen.1008586. eCollection 2020 May.

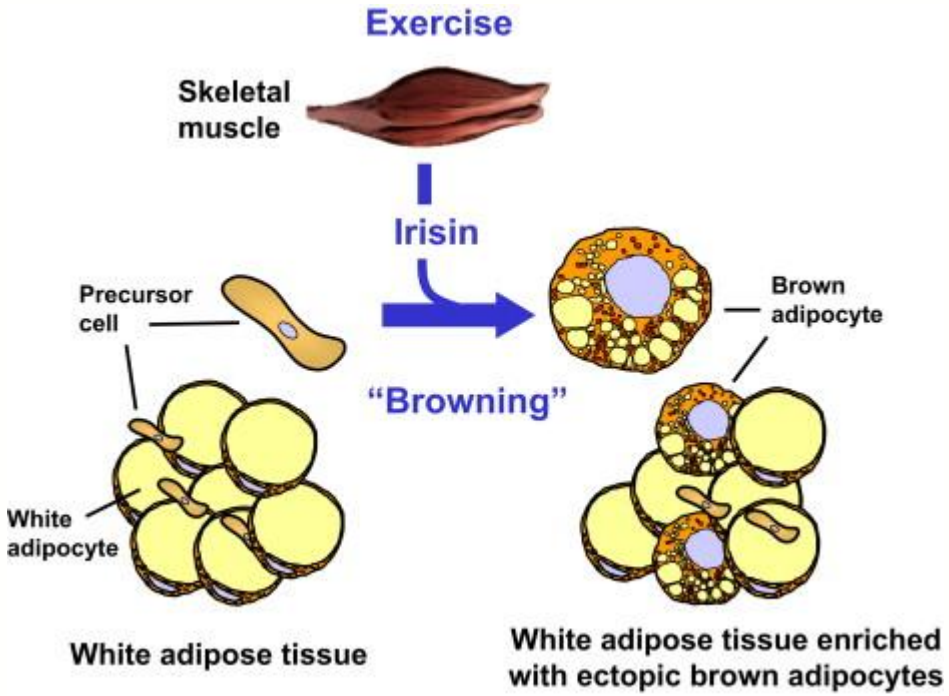
PMID: 32463816 Free PMC article.



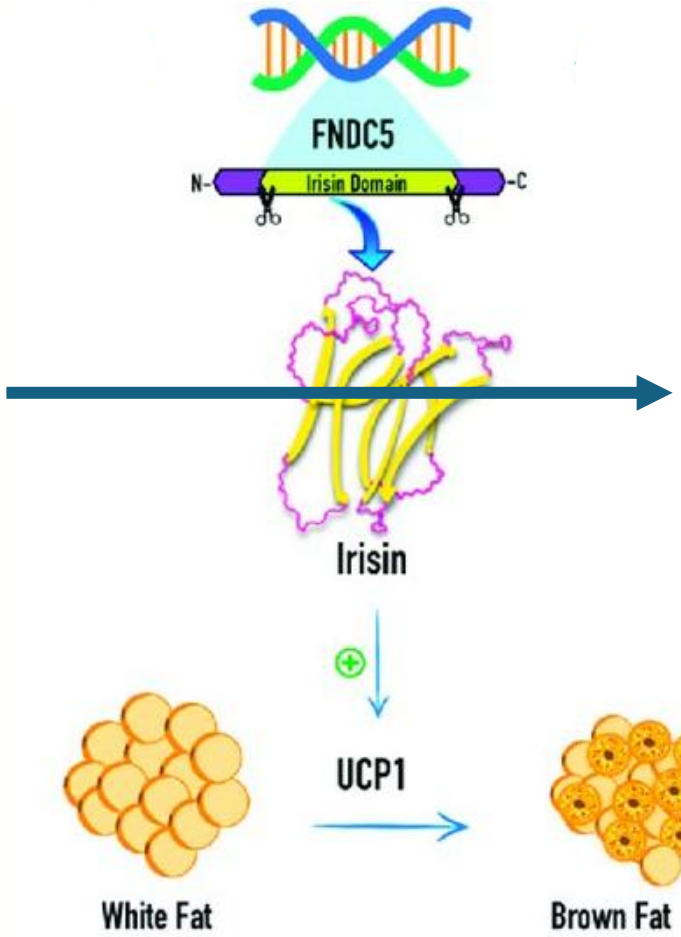


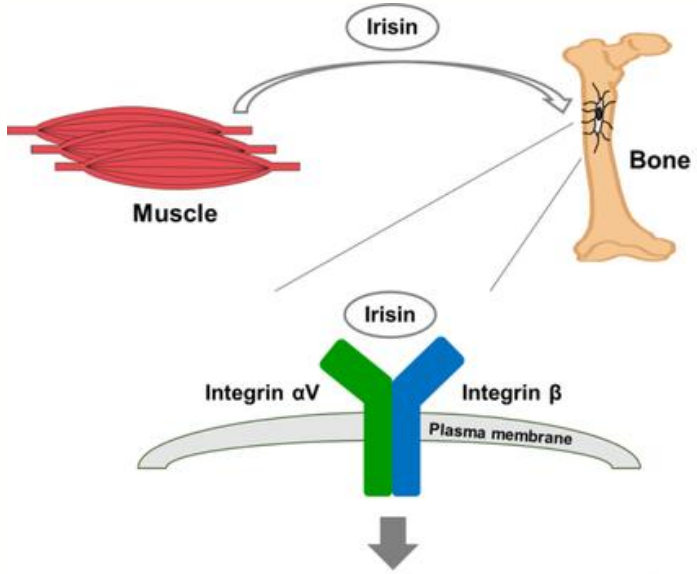
Irisin

- Produced in response to physical exercise
- Identified in 2012 by the Spiegelman lab at Harvard as a new peptide hormone
- Role in the «browning» of adipose tissue

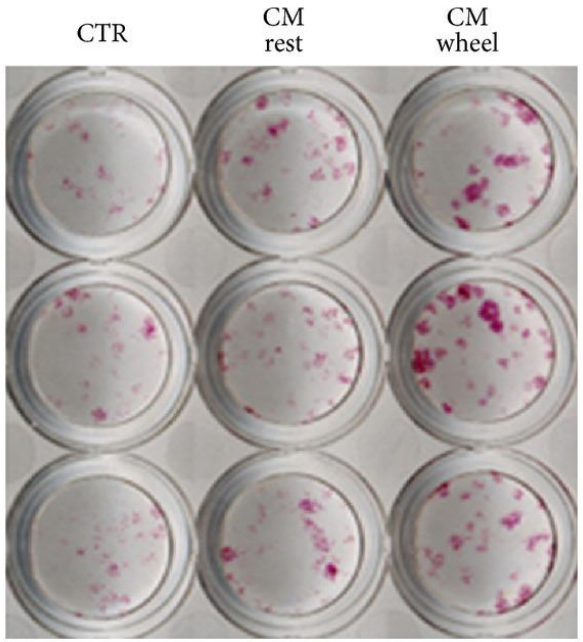


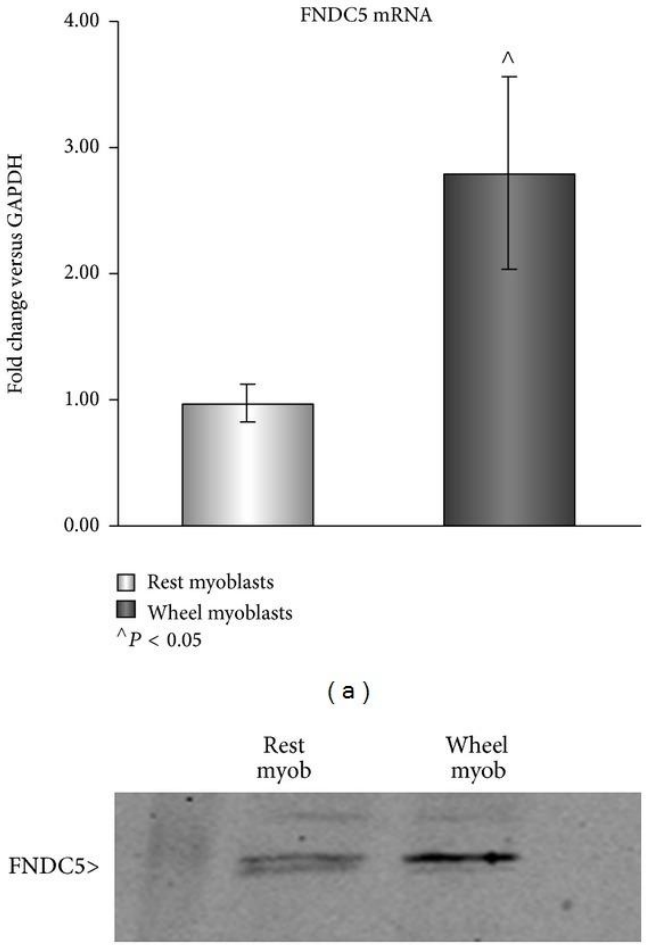
Irisin

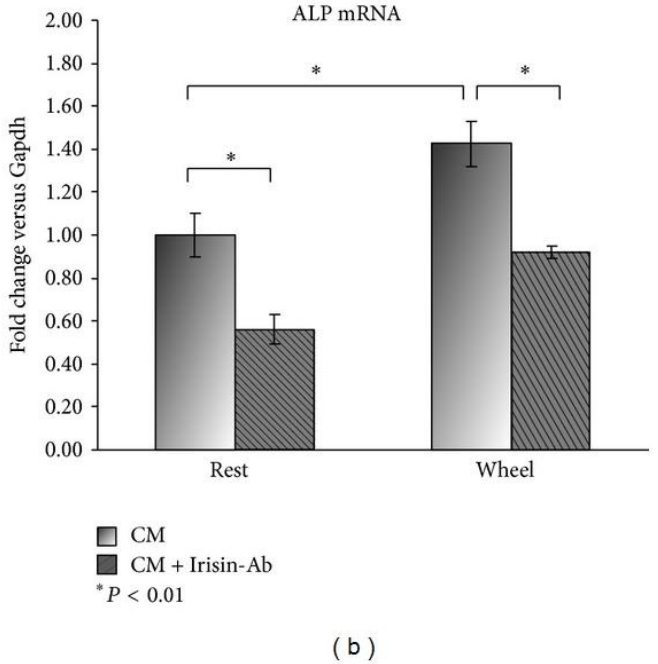

FNDC5
N-
Irisin Domain
-C
Irisin
UCP1
White Fat
Brown Fat


Irisin
Muscle
Bone
Irisin
Integrin αV
Integrin β
Plasma membrane

Irisin stimulates osteoblastogenesis







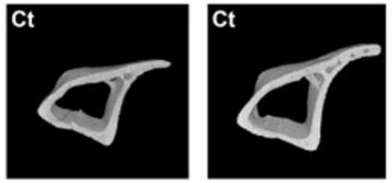
Colaianni *et al.* 2014

Irisin – Cortical bone

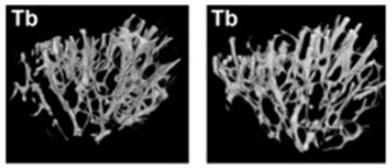
Tibia

A

B



C



D

Injection	Vehicle	r-irisin	*P value*
TMD Cortical (gHA/cm³)	1.01 ±0.02	1.08 ±0.01	*0.01*
pMOI (mm⁴)	0.42 ±0.02	0.50 ±0.01	*0.01*
Ct.BS (mm²)	14.13 ±0.26	15.20 ±0.27	*0.02*
Ct.Pm (mm)	12.01 ±0.23	12.89 ±0.26	*0.03*
Tt.Area (mm²)	1.71 ±0.02	1.80 ±0.03	*0.04*
Marrow Area (mm²)	0.96 ±0.02	1.05 ±0.03	*0.03*
Ct.Th (mm)	0.13 ±0.004	0.12 ±0.01	*0.62*
BMD (gHA/cm³)	0.13 ±0.01	0.14 ±0.01	*0.37*
BV/TV (%)	51.13 ±2.26	44.32 ±2.60	*0.07*
Tb.Th (µm)	31.71 ±0.80	32.21 ±1.60	*0.78*
Tb.N (1/µm)	0.002 ±0.0001	0.001 ±0.0001	*0.09*
Tb.Sp (µm)	218.97 ±7.11	235.55 ±11.47	*0.23*

Vertebrae

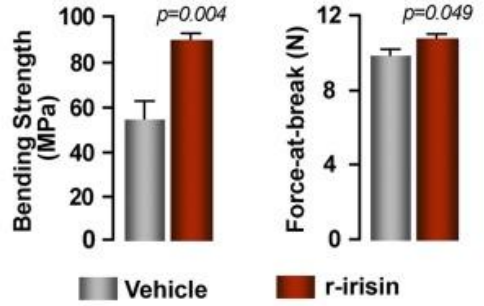
E

	Vehicle	r-irisin
BV/TV (%)	18.2 ± 1.15	17.6 ± 0.2
Tb.N (1/mm)	25.3 ± 0.7	26.1 ± 0.3
Tb.Th (mm)	0.7 ± 0.1	0.7 ± 0.0
Tb.Sp (mm)	3.3 ± 0.1	3.2 ± 0.0

Colaianni *et al.* 2015

Irisin stimulates bone formation

A



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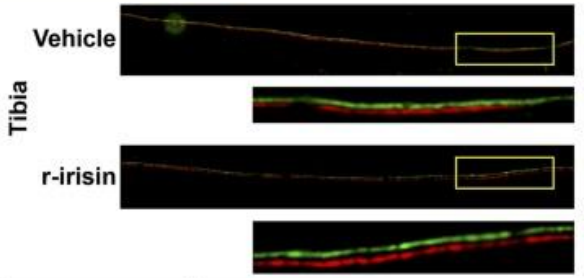
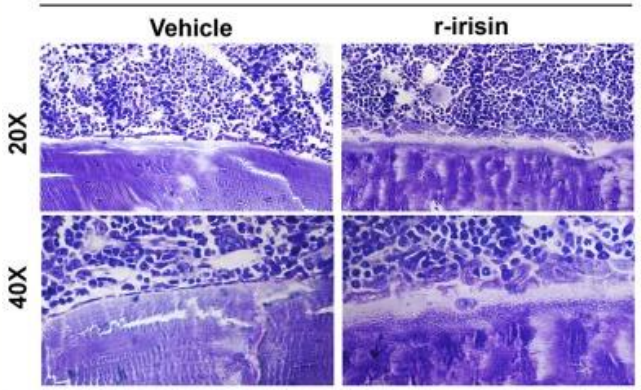


	Vehicle	r-irisin	*P-value*
MS/BS	0.03 ± 0.00	0.04 ± 0.01	*0.399*
MAR (μm/day)	1.45 ± 0.11	2.48 ± 0.09	*0.002*
BFR ($\mu m^3/\mu m^2$/day)	0.06 ± 0.01	0.11 ± 0.00	*0.002*

C

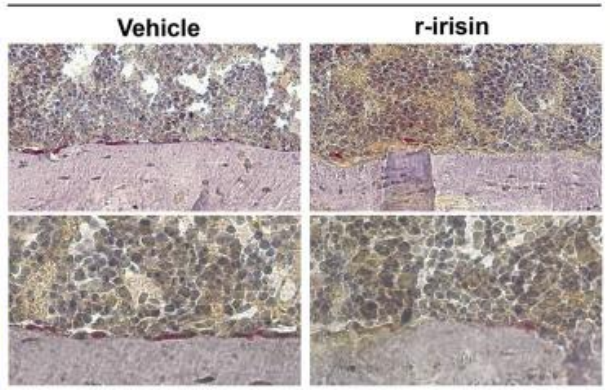
Tibia Osteoblast



	Vehicle	r-irisin	*P-value*
Ob.N/BPm (mm^{-1})	17.17 ± 5.87	36.36 ± 3.23	*0.0496*

D

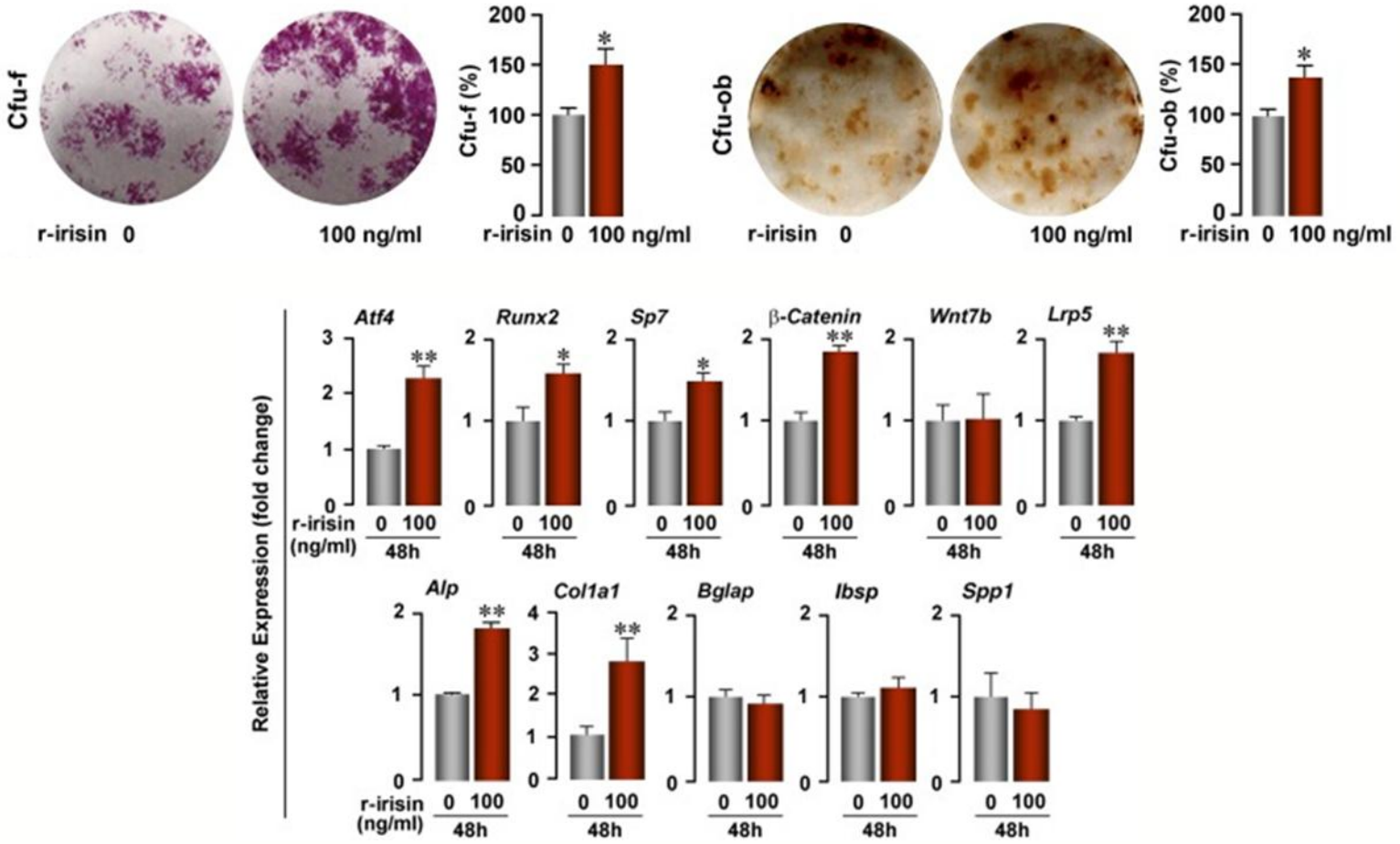
Tibia Osteoclast



	Vehicle	r-irisin	*P-value*
Oc.N/BPm (mm^{-1})	5.00 ± 1.20	1.56 ± 0.33	*0.0503*

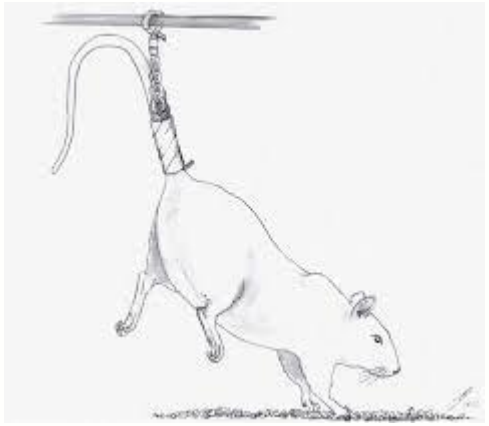
Colaianni *et al.* 2015

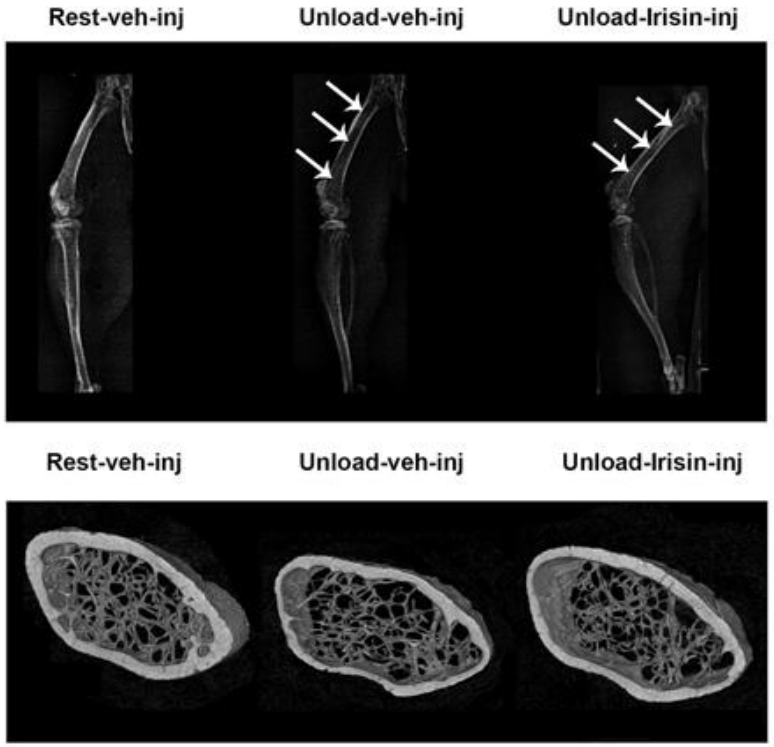
Irisin stimulates osteoblast differentiation



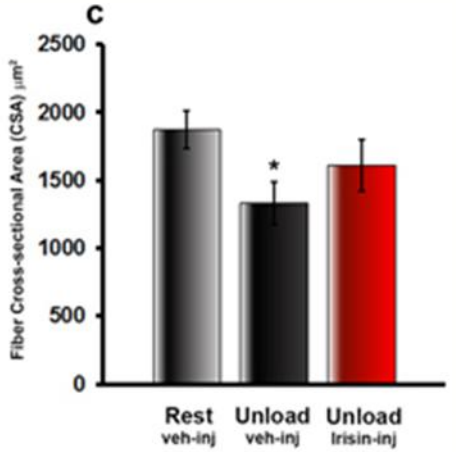
Colaianni *et al.* 2015

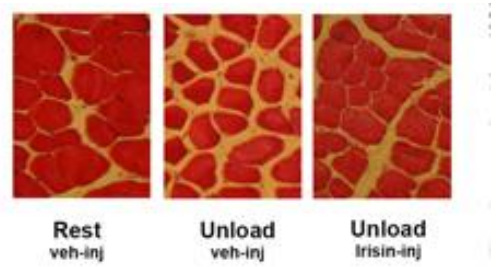
Irisin prevents Bone Loss and Muscle atrophy





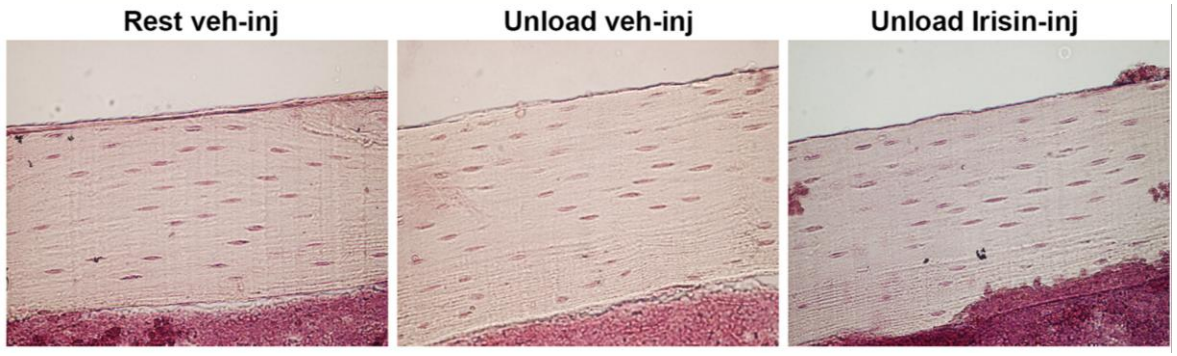
Cortical			
BMD (mg HA/cm³)	1.12 ± 0.004	1.07 ± 0.015 **	1.12 ± 0.005 ^^
Ct. Th. (μm)	140.32 ± 1.81	127.58 ± 8.94 **	130.32 ± 2.04 **
Trabecular			
BMD (mg HA/cm³)	0.084 ± 0.005	0.051 ± 0.009 **	0.070 ± 0.005
BV/TV (%)	3.65 ± 0.31	1.58 ± 0.52 **	2.75 ± 0.18

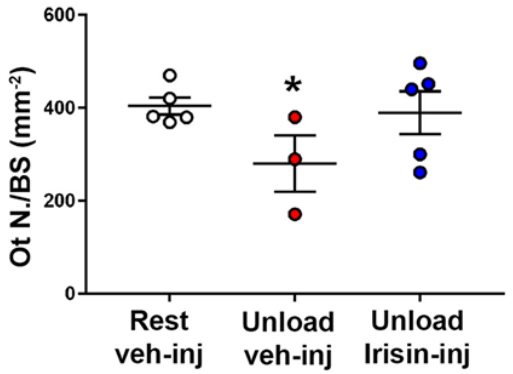


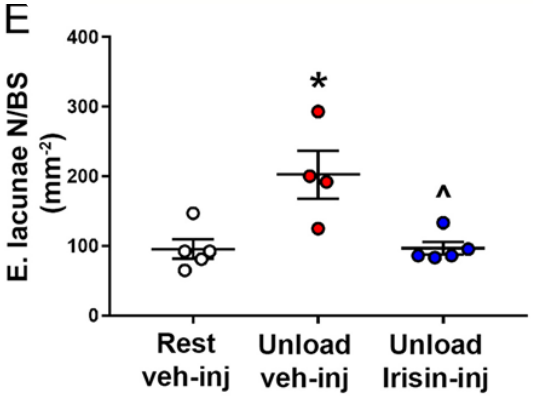


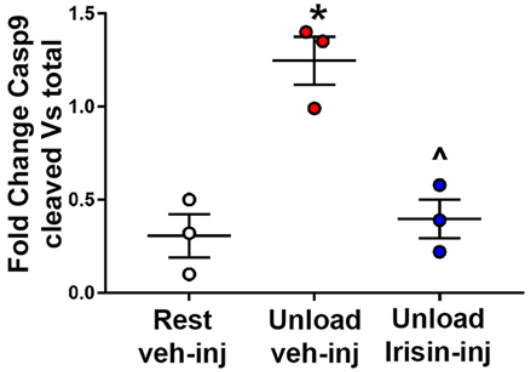
Colaianni *et al.* 2017

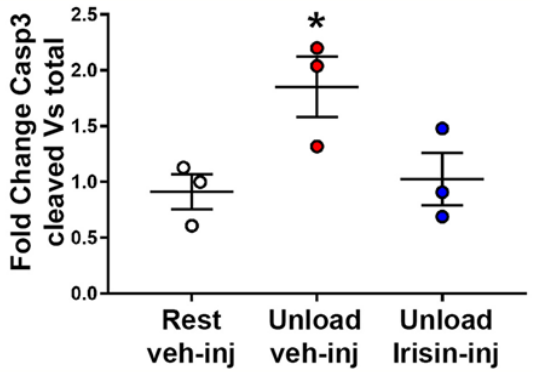
Irisin prevents Osteocyte apoptosis





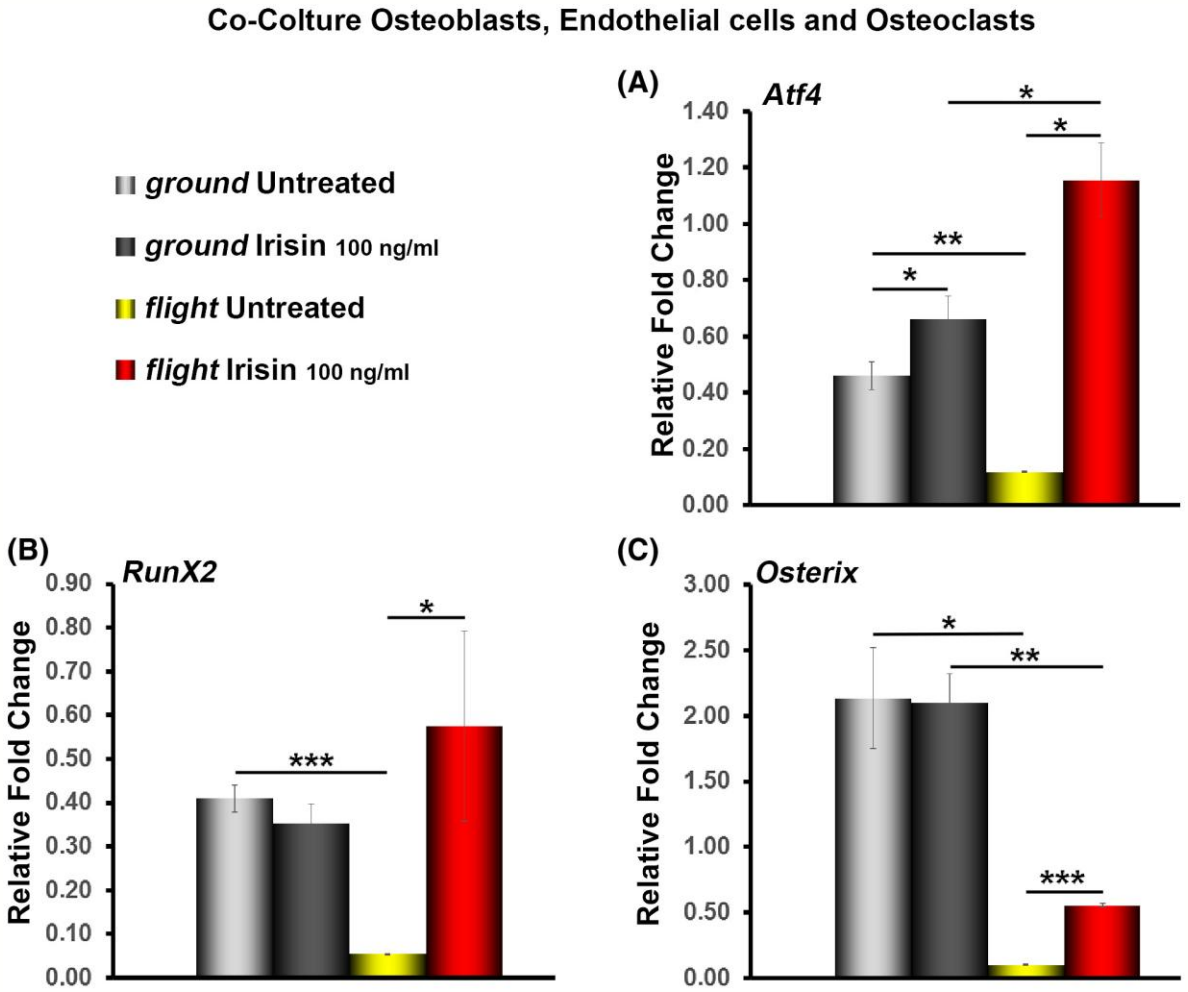






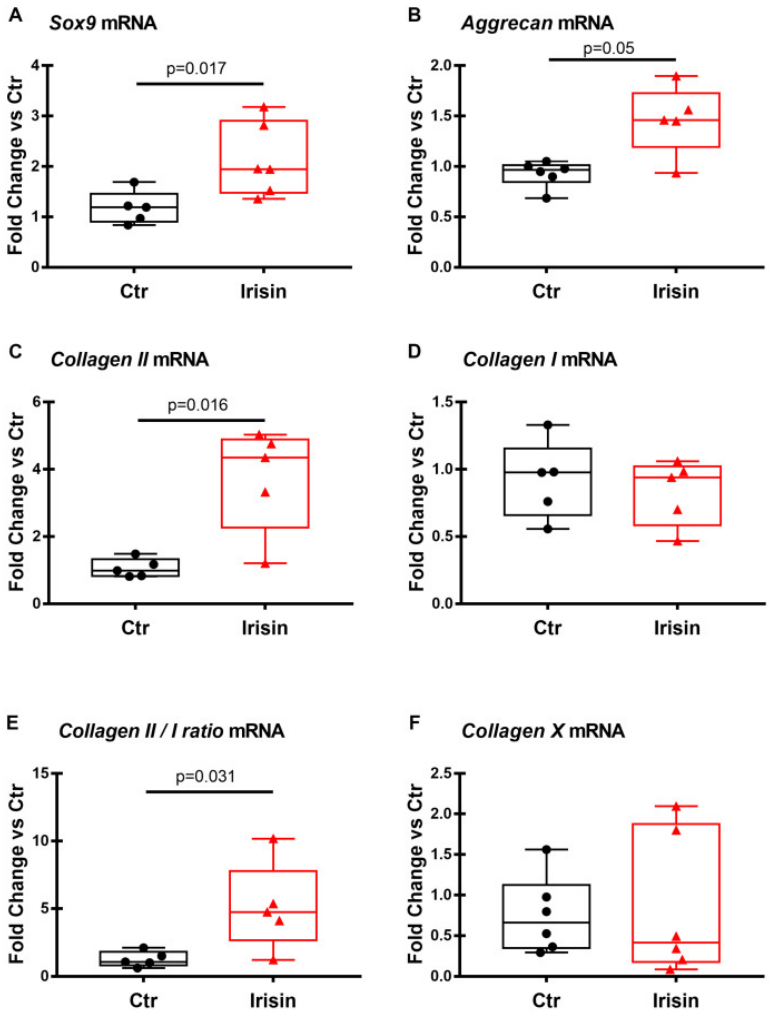
Storlino *et al.* 2020

Irisin - Microgravity



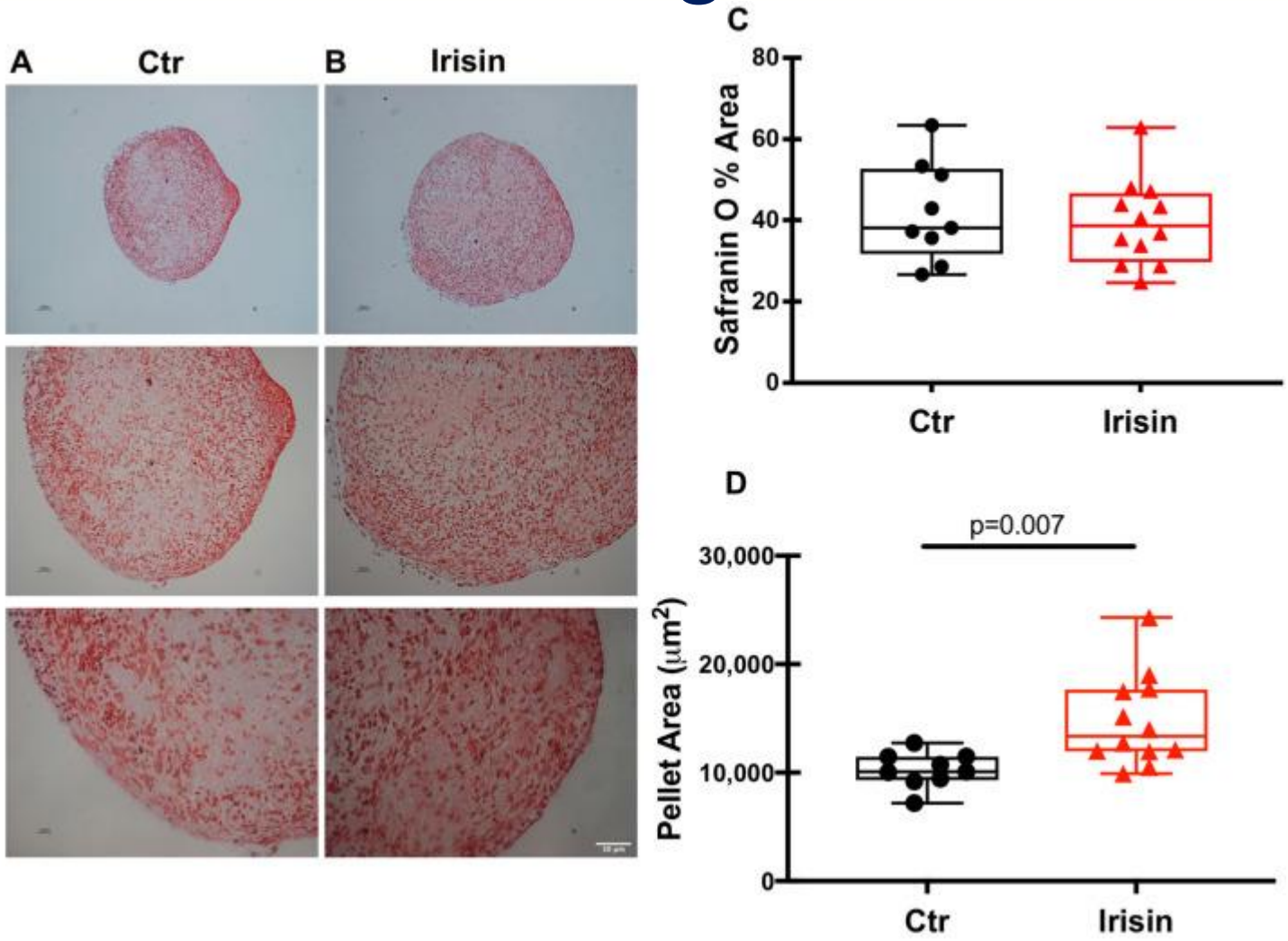
Colucci *et al.* 2020

Irisin - Chondrogenic markers



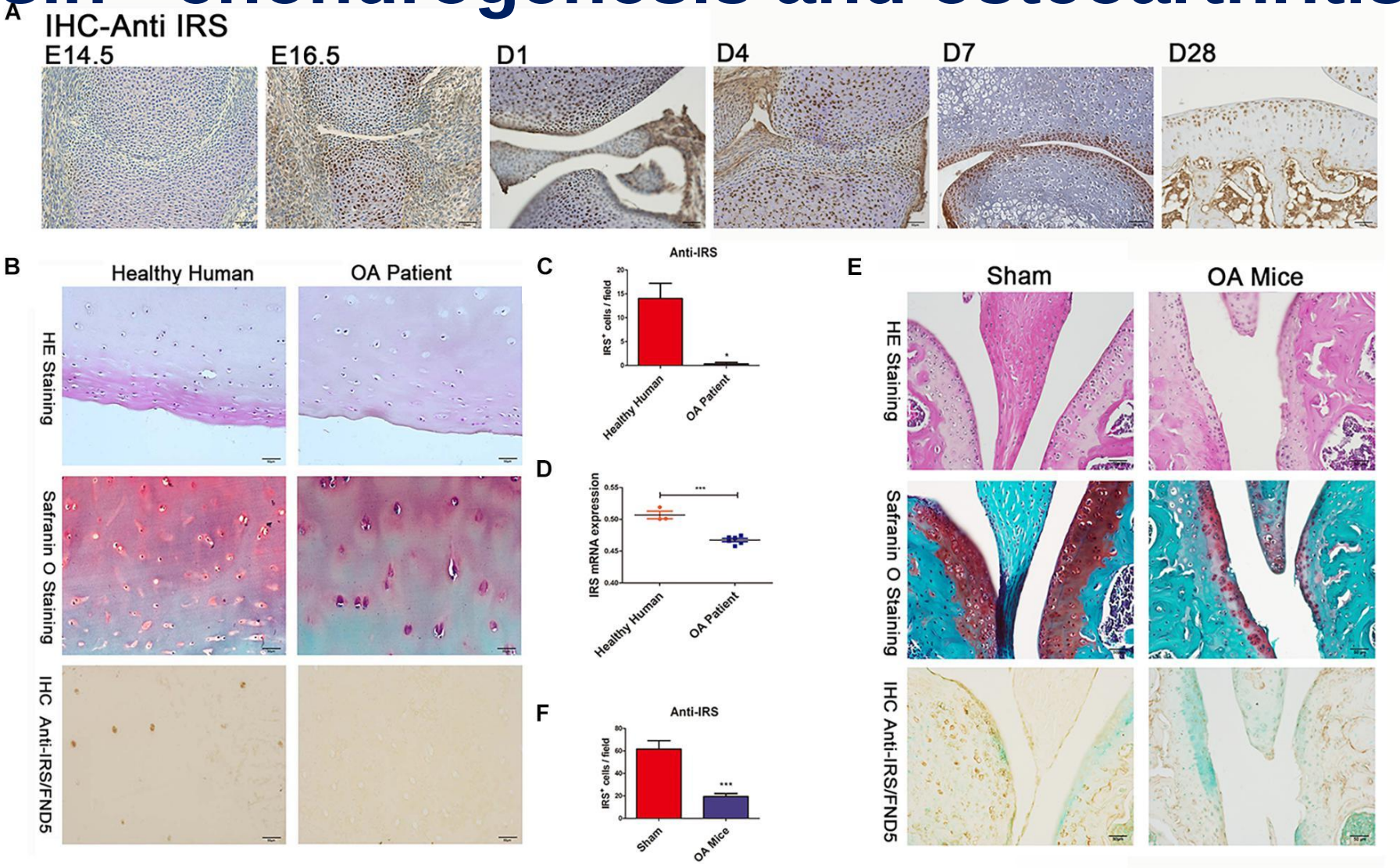
Posa *et al*. 2023

Irisin - Chondrogenic markers



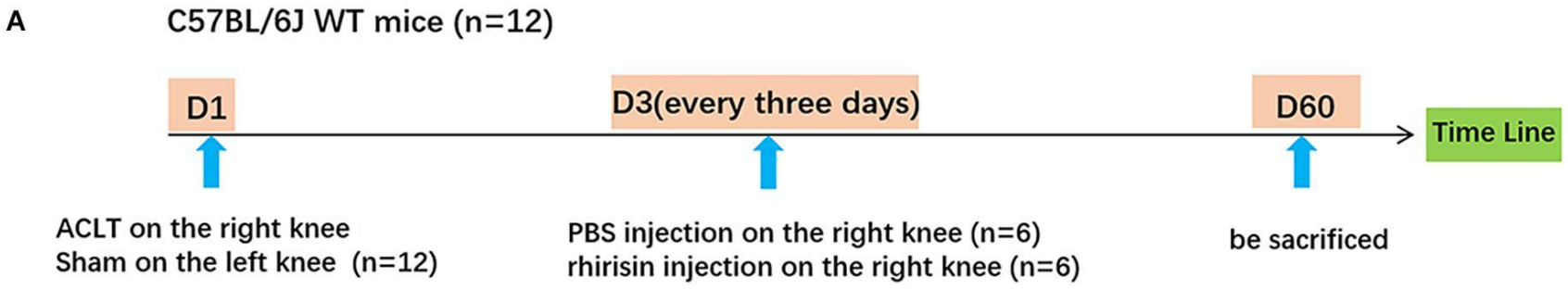
Posa *et al*. 2023

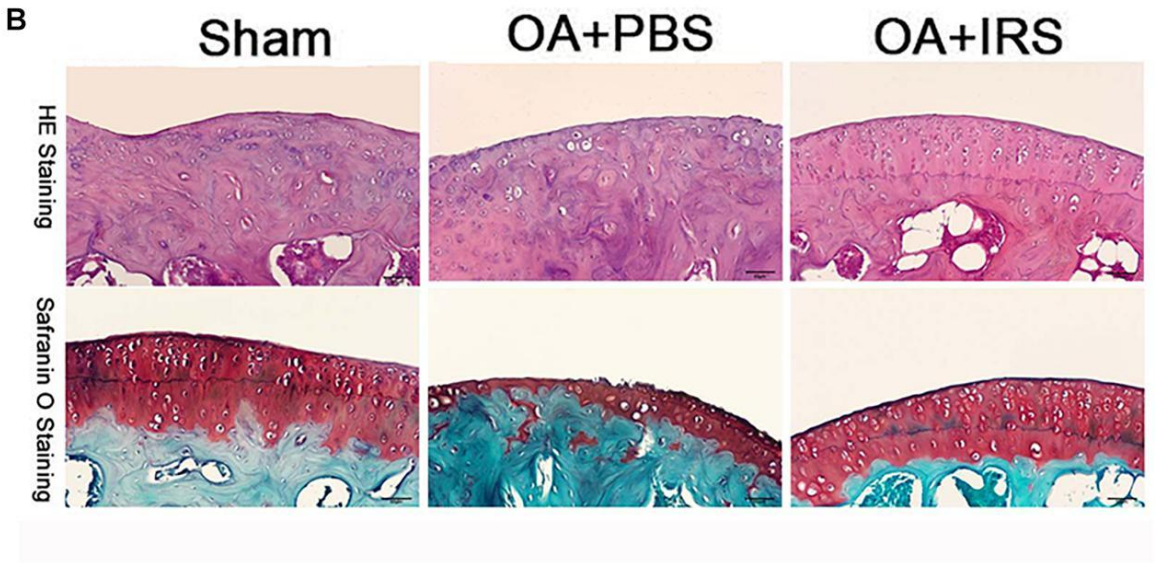
Irisin - chondrogenesis and osteoarthritis (OA)

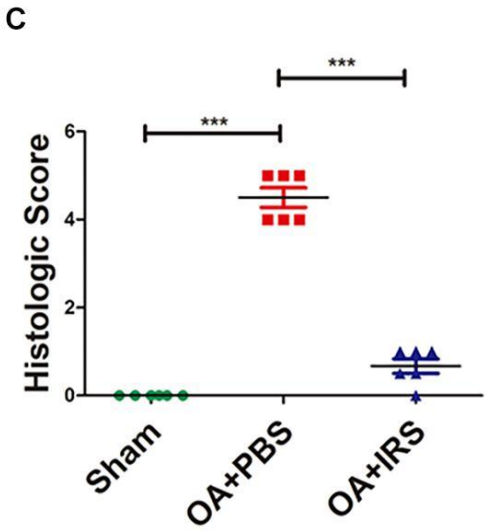


Li *et al*. 2021

Irisin inhibits cartilage degradation

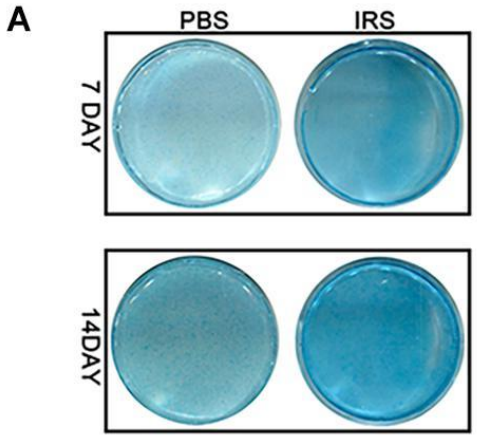


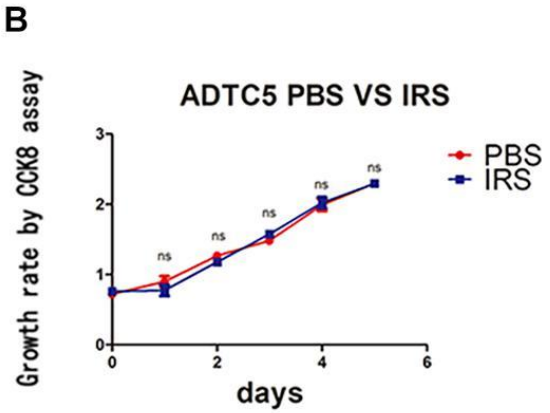


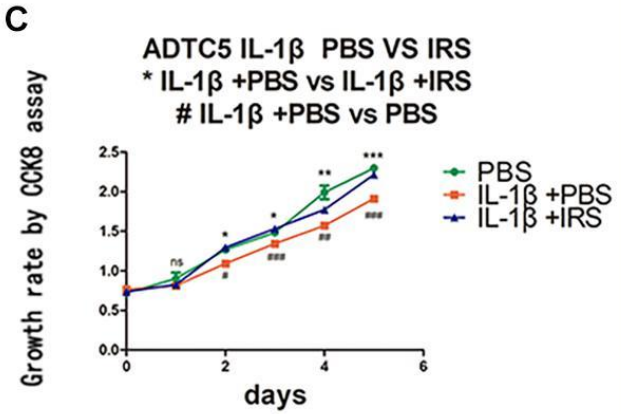


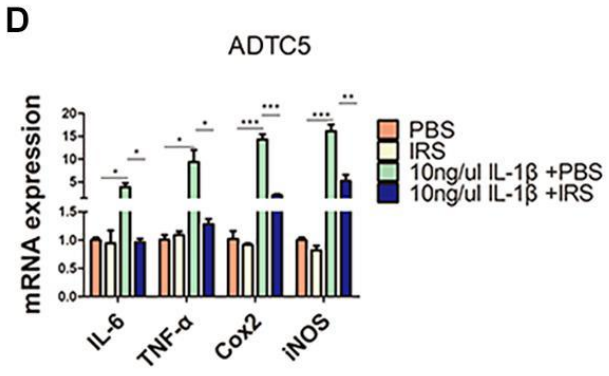
Li *et al*. 2021

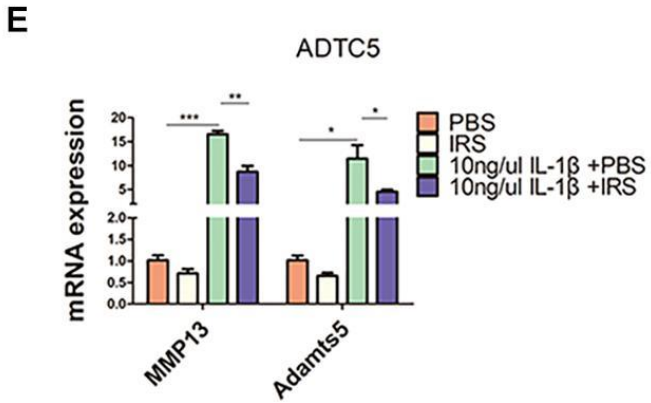
Irisin inhibits Inflammation in ADTC5 Cells

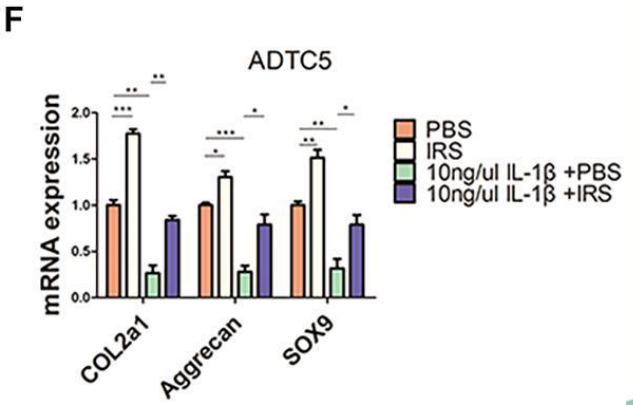












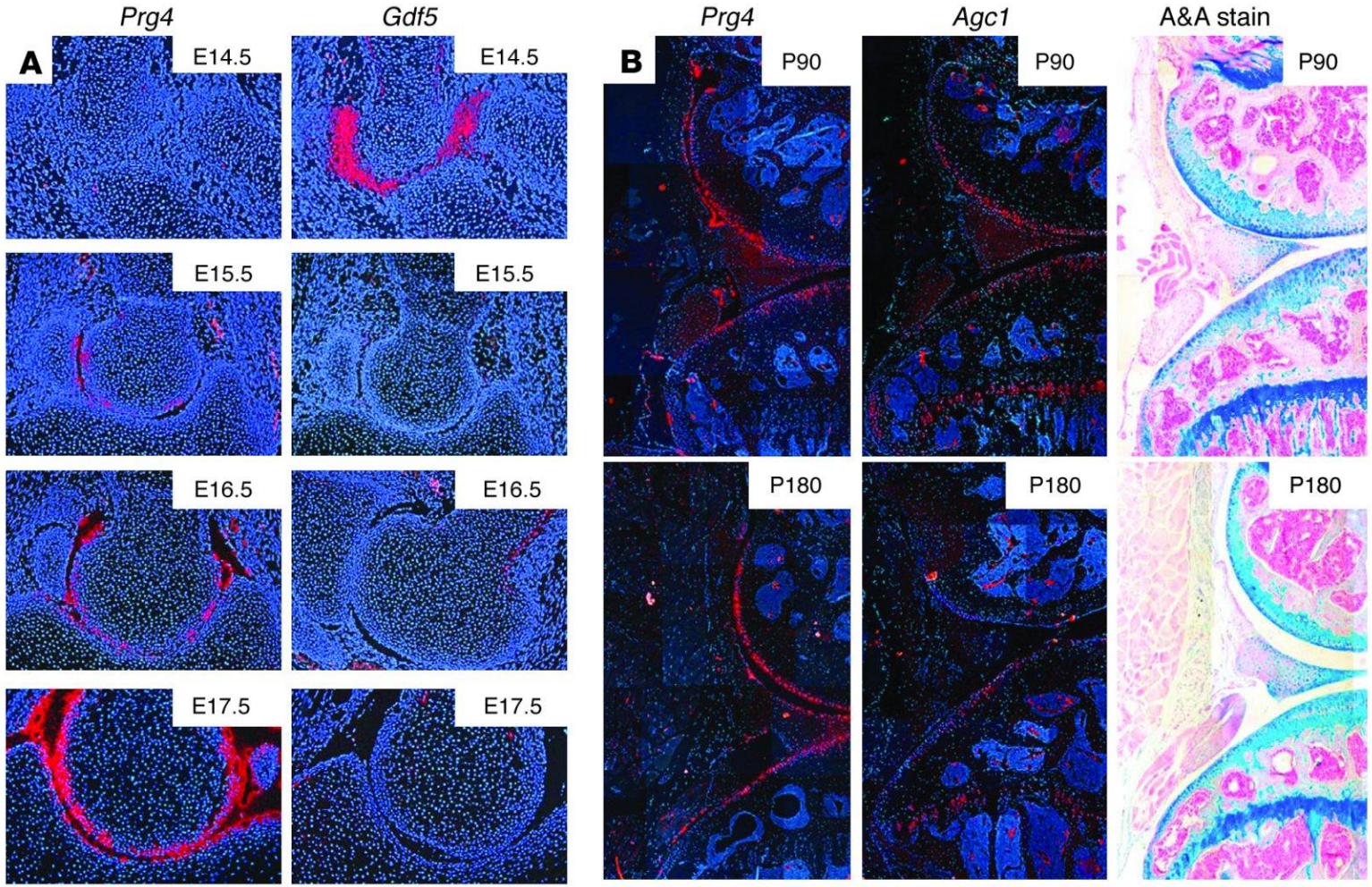
Li *et al*. 2021

PRG4 (Proteoglycan-4)

- Also known as lubricin, is a mucin-like glycoprotein found in many areas of the body, including the superficial zone and surface of articular cartilage.

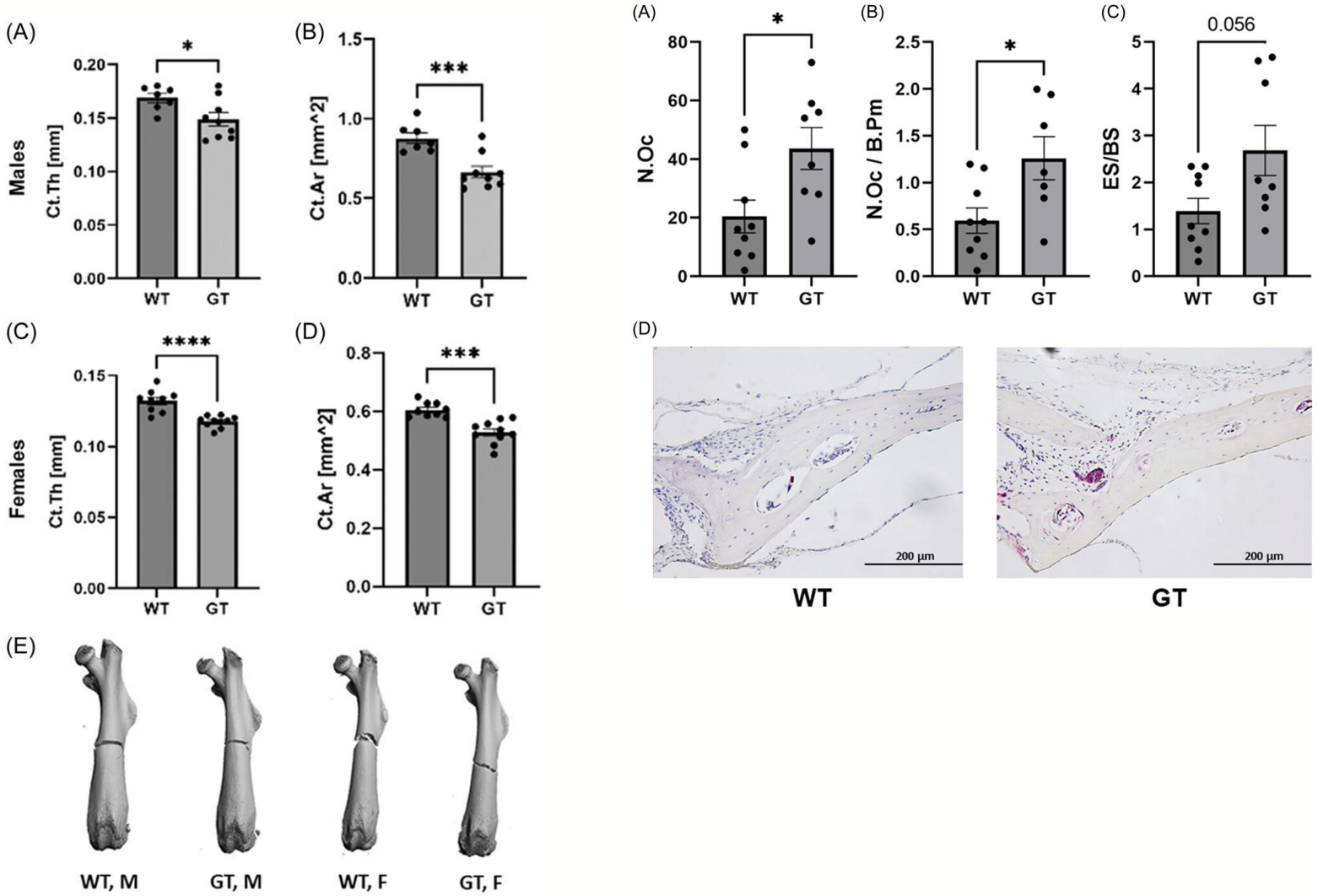
- Boundary lubricant between articulating cartilage surfaces, but also has demonstrated anti-inflammatory properties, including in synovial fluid, on synovial macrophages, systemically in an osteoarthritis rat model, and in human corneal epithelial cells following TNF-induced inflammation.

PRG4



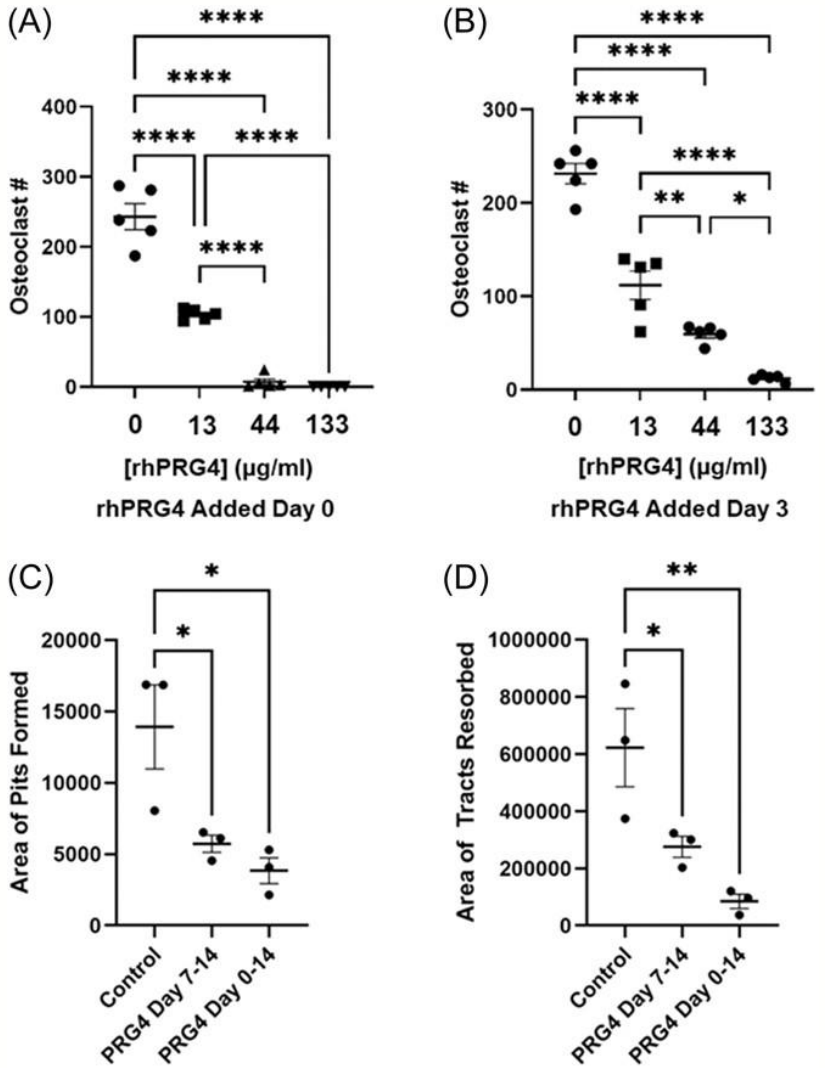
Rhee et al. 2005

PRG4 deficient mice



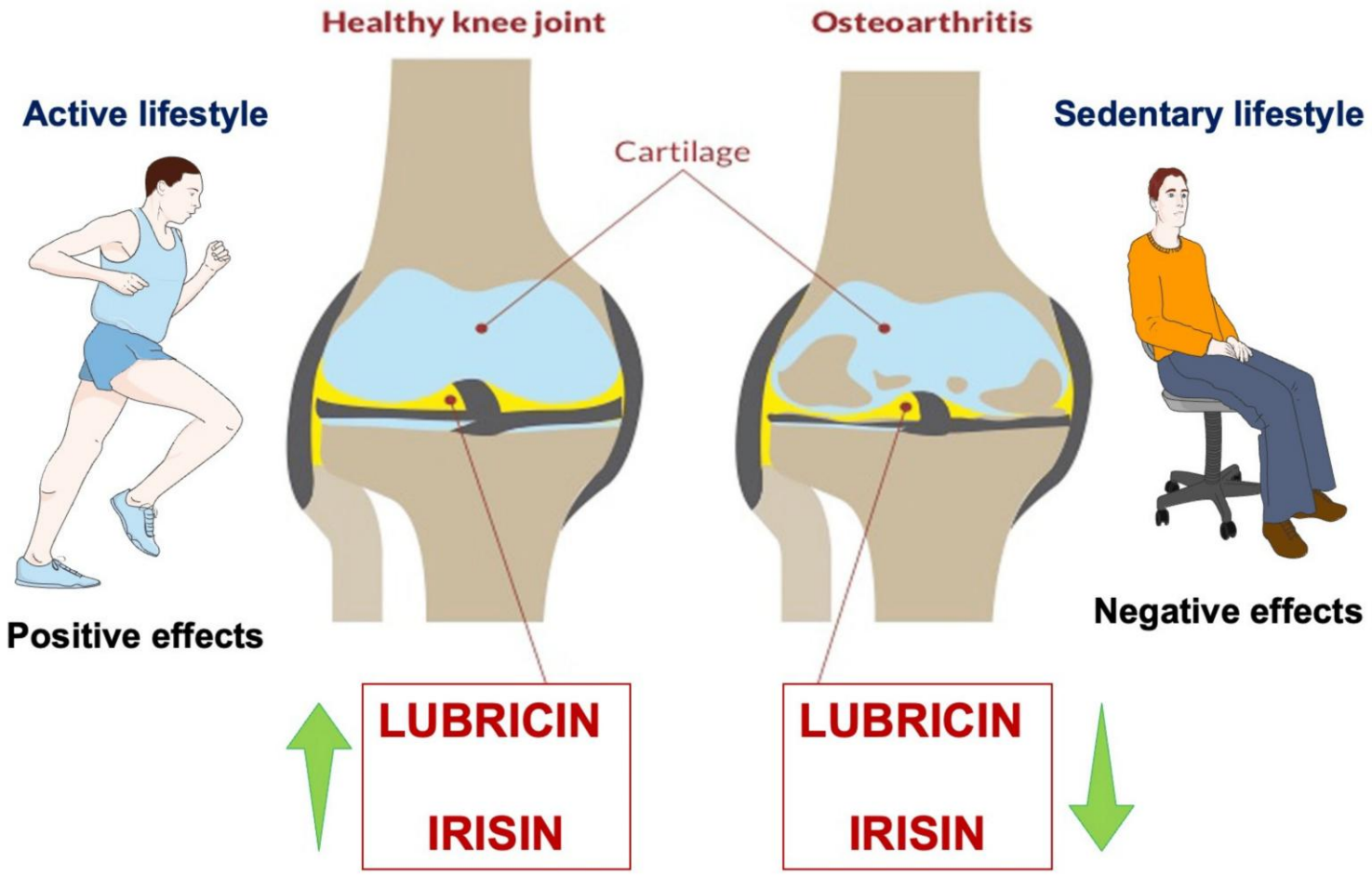
Tanguay *et al.* 2023

PRG4 treatment – *In vitro* osteoclastogenesis



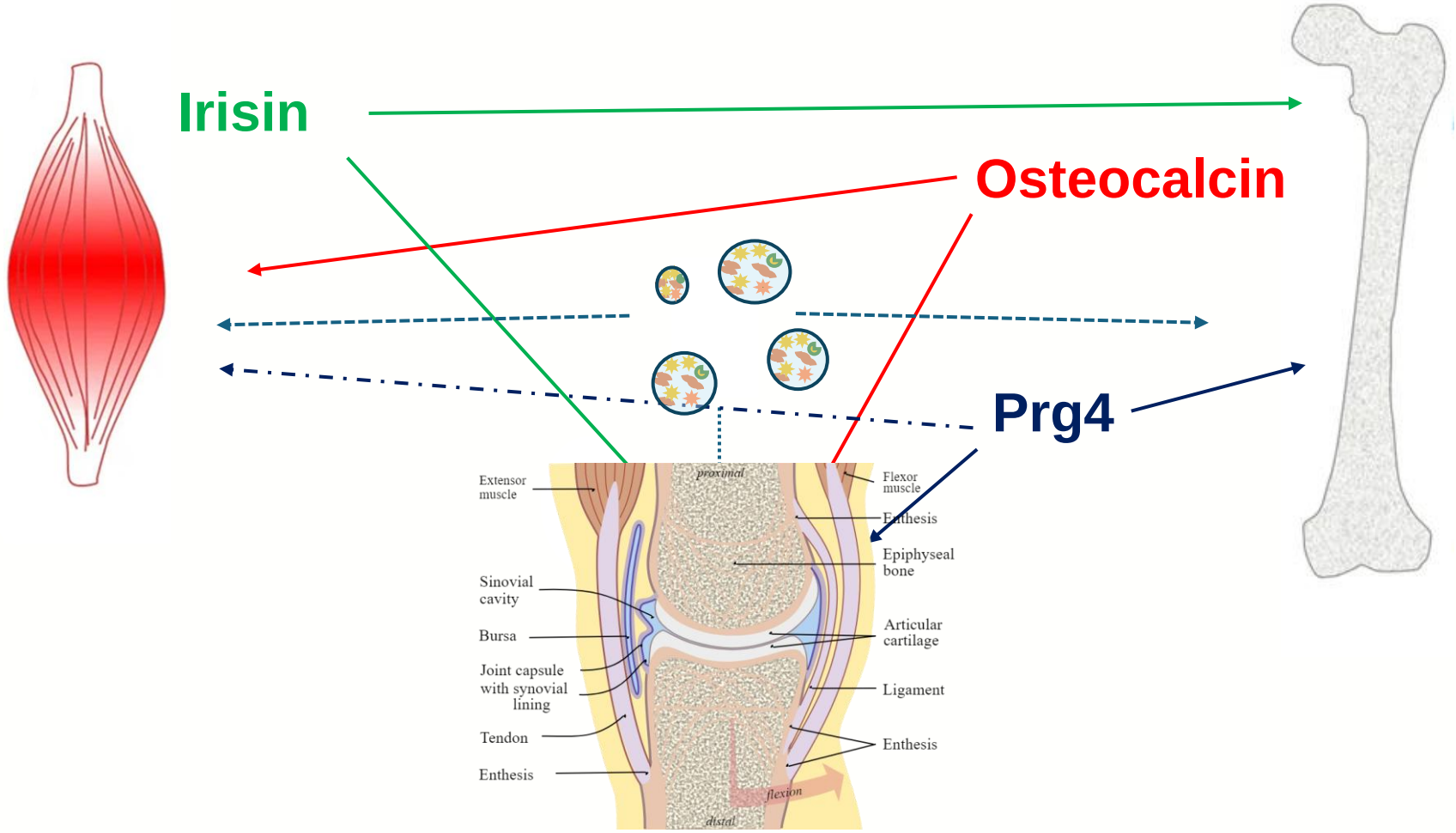
Tanguay *et al.* 2023

PRG4 - Exercise



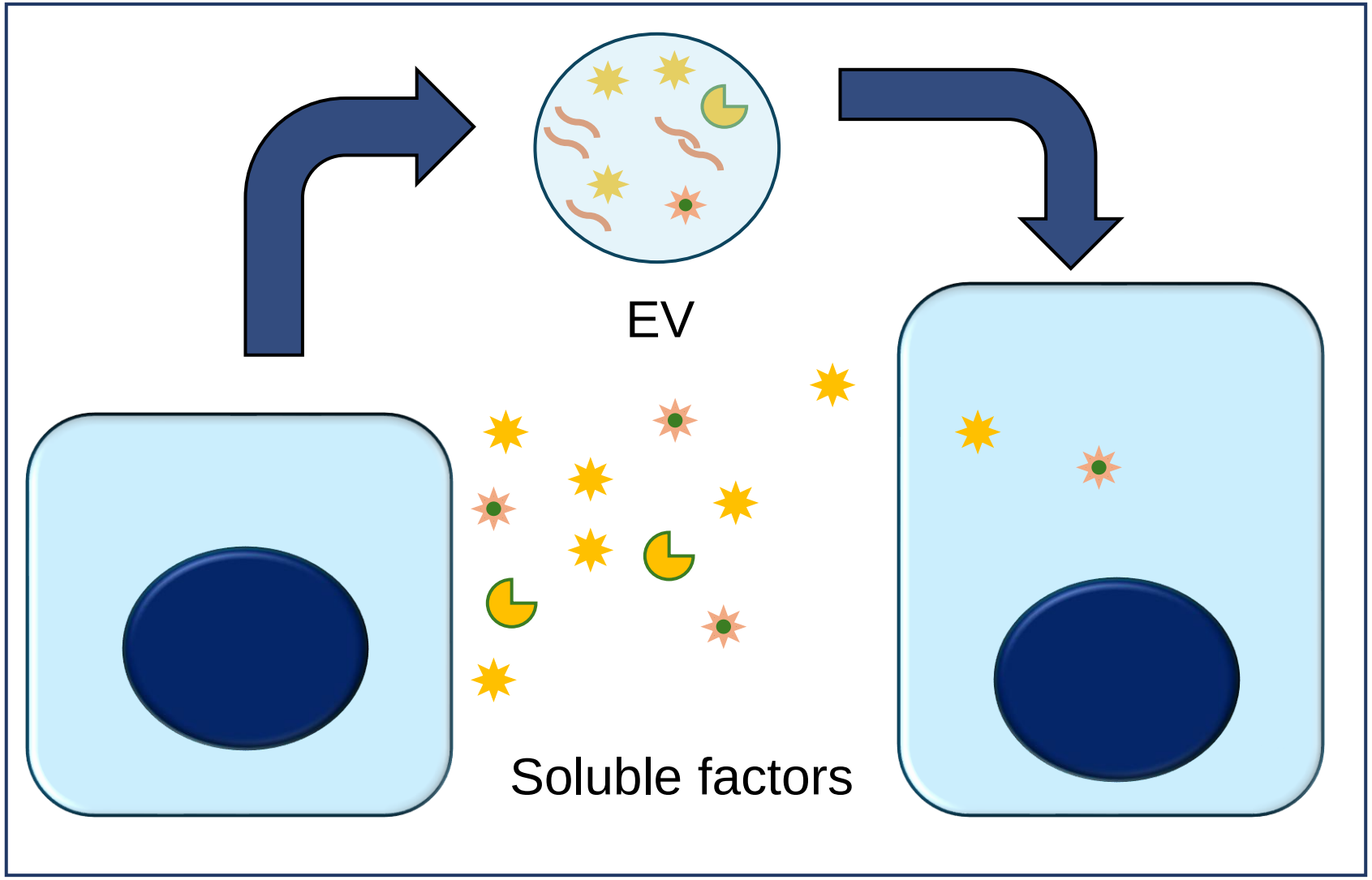
Roggio *et al.* 2023

Muscle-Bone-Joint crosstalk

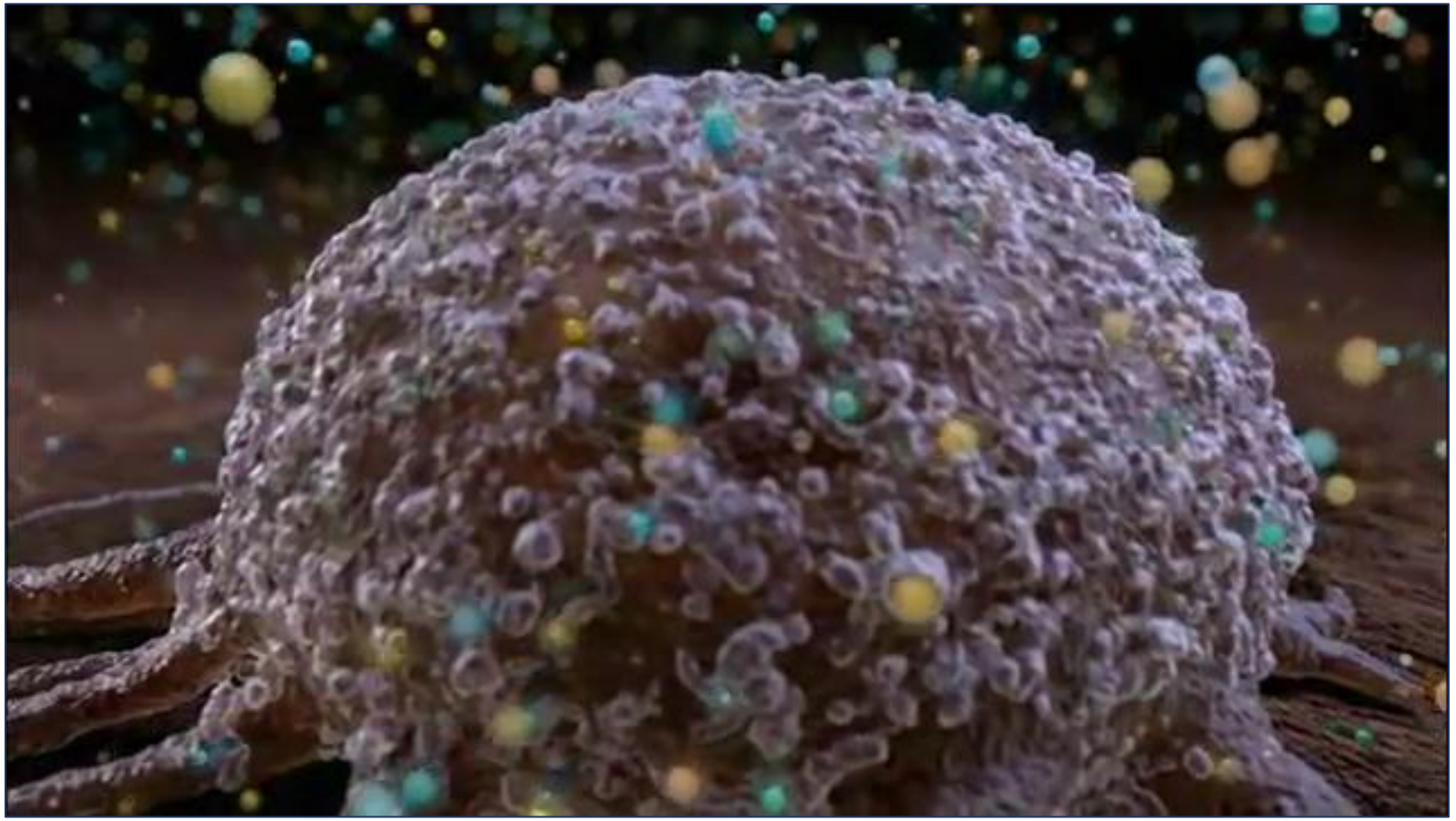


Thank you

Secretome



Extracellular vesicles



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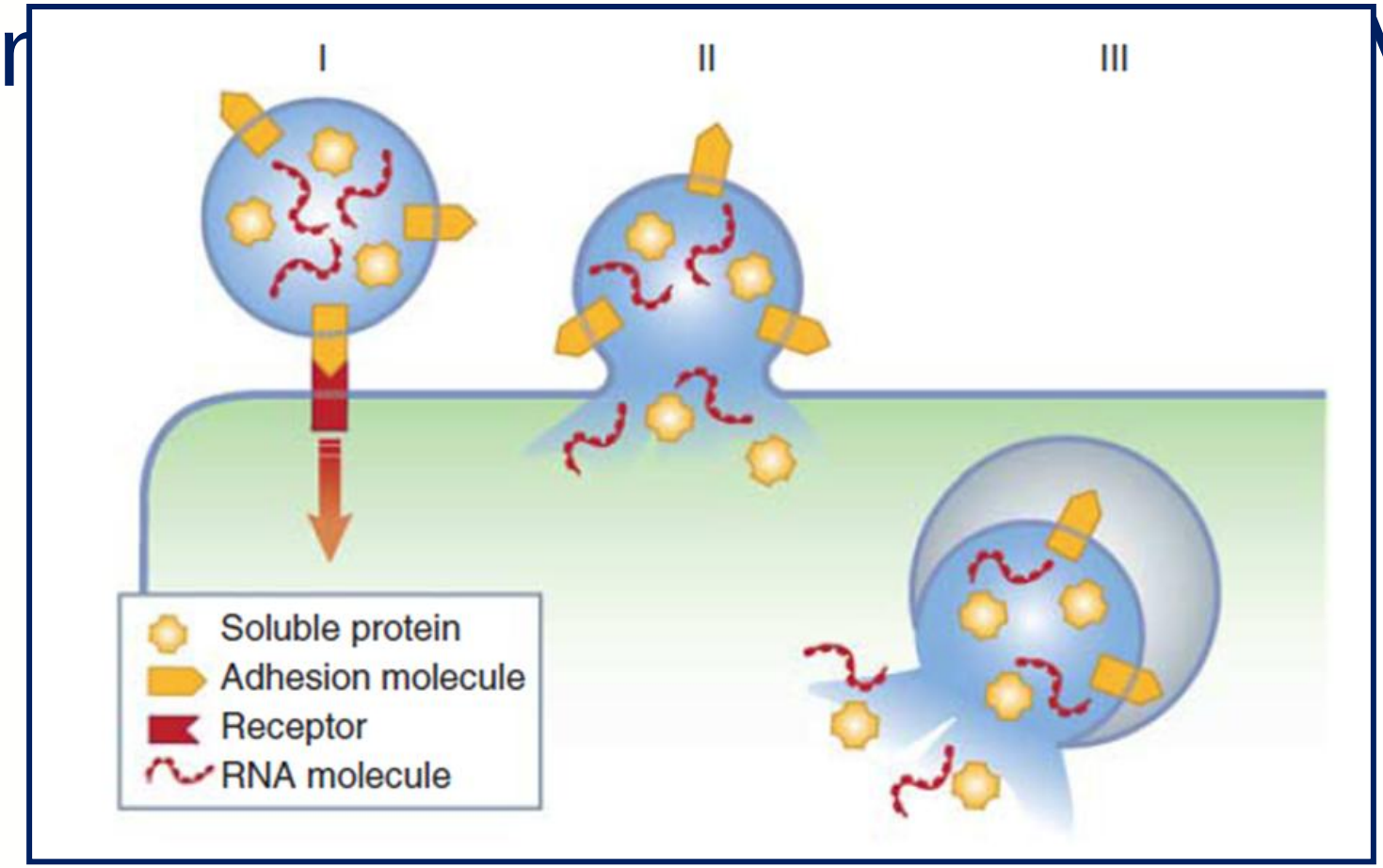
I
II
III
Soluble protein
Adhesion molecule
Receptor
RNA molecule

V

bers –

frontiers in Physiology

MINI REVIEW
published: 30 May 2018
doi: 10.3389/fphys.2018.00628

Osteoclast-Derived Extracellular Vesicles: Novel Regulators of Osteoclastogenesis and Osteoclast–Osteoblasts Communication in Bone Remodeling

Feng-Lai Yuan†, Qian-yuan Wu†, Zong-Ning Miao†, Ming-Hui Xu, Rui-Sheng Xu, Dong-Lin Jiang, Jun-Xing Ye, Fei-hu Chen, Ming-Dong Zhao*, Hao-jue Wang* and Xia Li*

International Journal of *Molecular Sciences*

MDPI

Review

The Role of Extracellular Vesicles in Bone Metastasis

Michela Rossi [1], Giulia Battafarano [1], Matteo D'Agostini [2] and Andrea Del Fattore [1,*]

1 Bone Physiopathology Group, Multifactorial Disease and Complex Phenotype Research Area, Bambino Gesù Children's Hospital, 00165 Rome, Italy; michela1.rossi@opbg.net (M.R.); giulia.battafarano@opbg.net (G.B.)
2 Clinical Laboratory, Bambino Gesù Children's Hospital, 00165 Rome, Italy; matteo.dagostini@opbg.net
* Correspondence: andrea.delfattore@opbg.net; Tel.: +39-06-6859-2938

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Critical Reviews in Oral Biology & Medicine

Emerging Role of Extracellular Vesicles in Bone Remodeling

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journals.sagepub.com/home/jdr

M. Liu[1], Y. Sun[2], and Q. Zhang[1]

ORIGINAL ARTICLE

JBMR®

Osteoblast-Derived Extracellular Vesicles Are Biological Tools for the Delivery of Active Molecules to Bone

Alfredo Cappariello,[1] Alexander Loftus,[1] Maurizio Muraca,[2] Antonio Maurizi,[1] Nadia Rucci,[1] and Anna Teti[1]

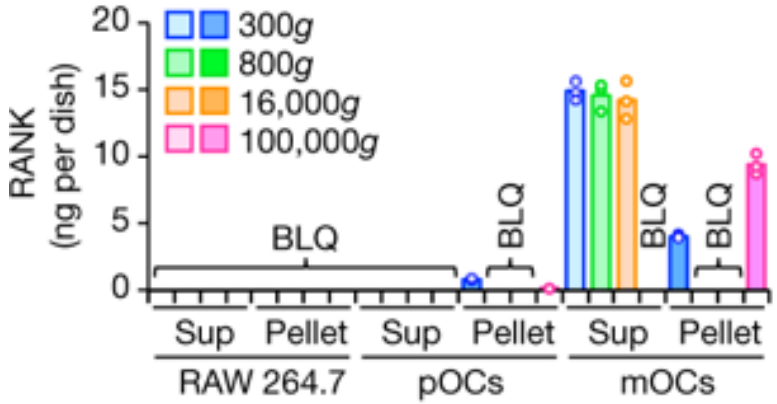
Aquila, L'Aquila, Italy
aly

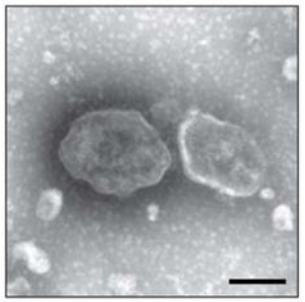
RESEARCH ARTICLE

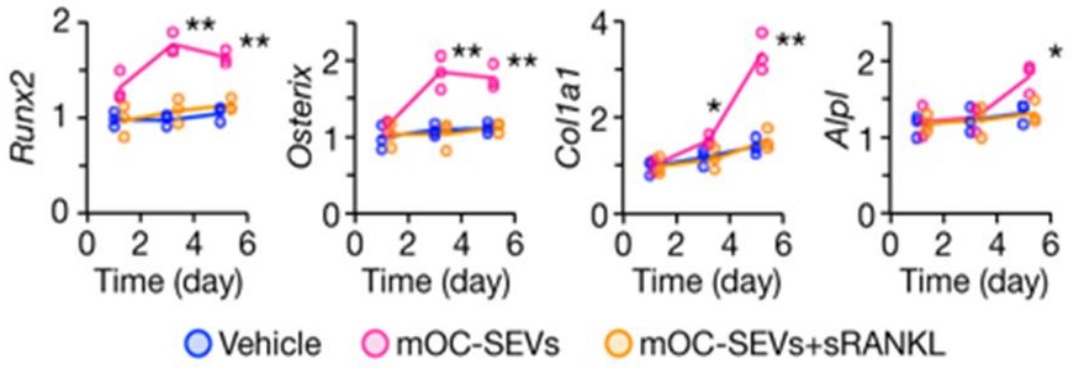
JBMR®

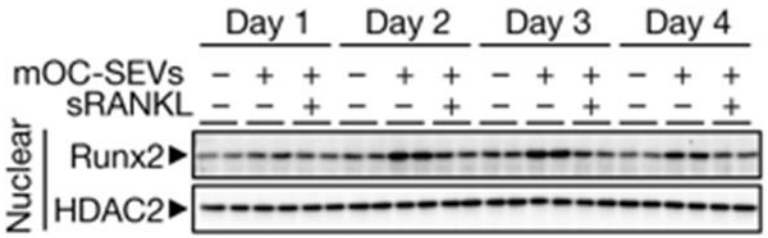
Characterization of Extracellular Vesicles in Osteoporotic Patients Compared to Osteopenic and Healthy Controls

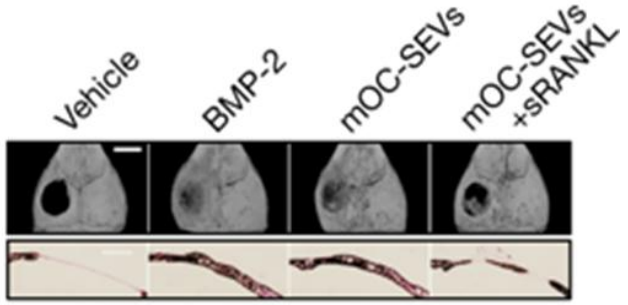
Jessica Pepe,[1#] Michela Rossi,[2#] Giulia Battafarano,[2] Pamela Vernocchi,[3] Federica Conte,[4] Valeria Marzano,[3] Eda Mariani,[5] Stefano Levi Mortera,[3] Cristiana Cipriani,[1] Ippolita Rana,[6] Paola Sabrina Buonuomo,[6] Andrea Bartuli,[6] Viviana De Martino,[1] Simone Pelle,[7] Luisa Pascucci,[8] Renato Maria Toniolo,[9] Lorenza Putignani,[10] Salvatore Minisola,[1#] and Andrea Del Fattore[2#]

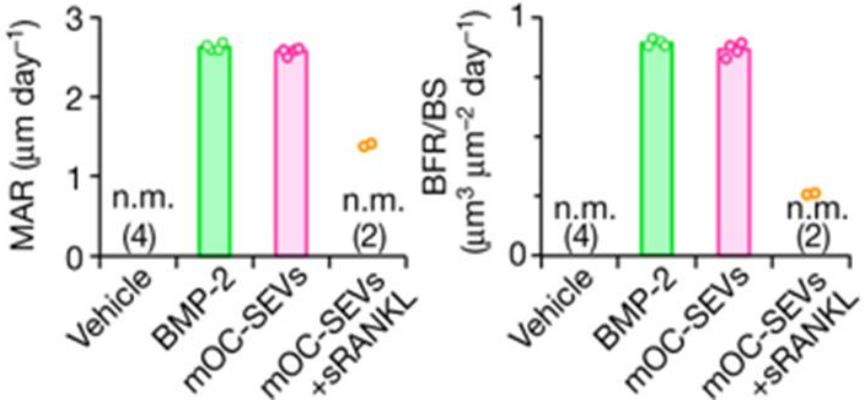






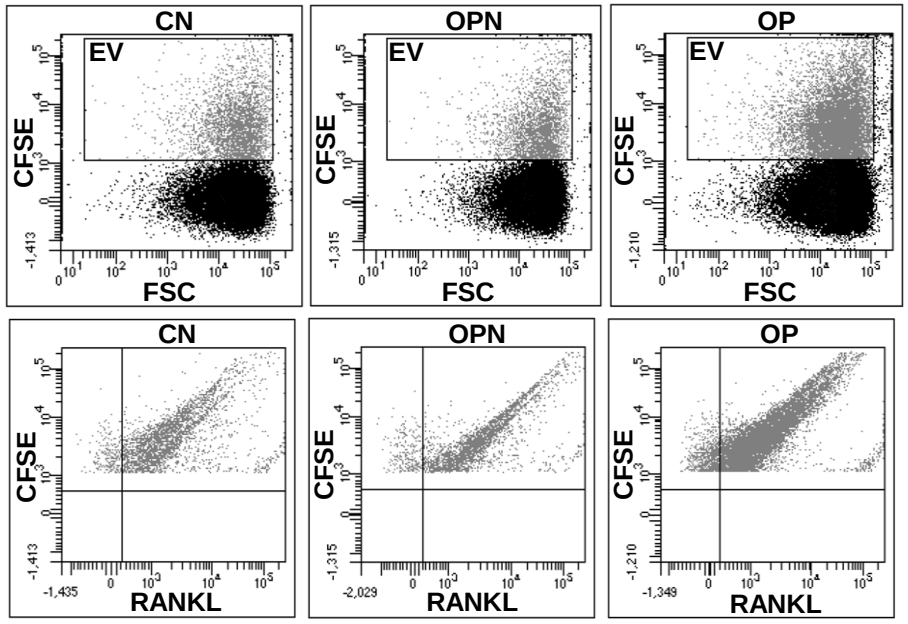


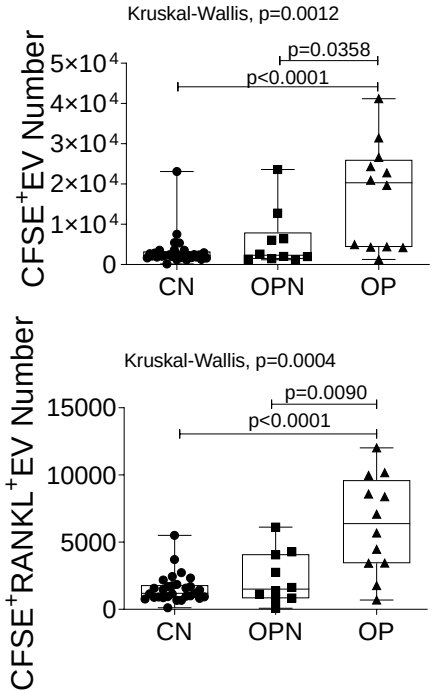


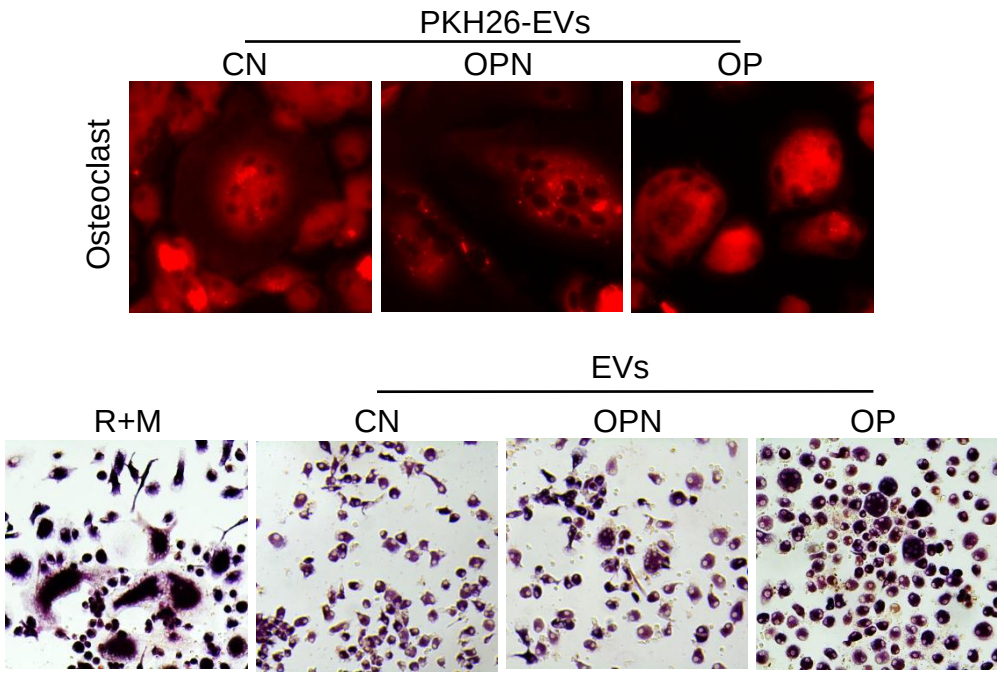


Ikebuchi *et al*. Nature Communications 2018

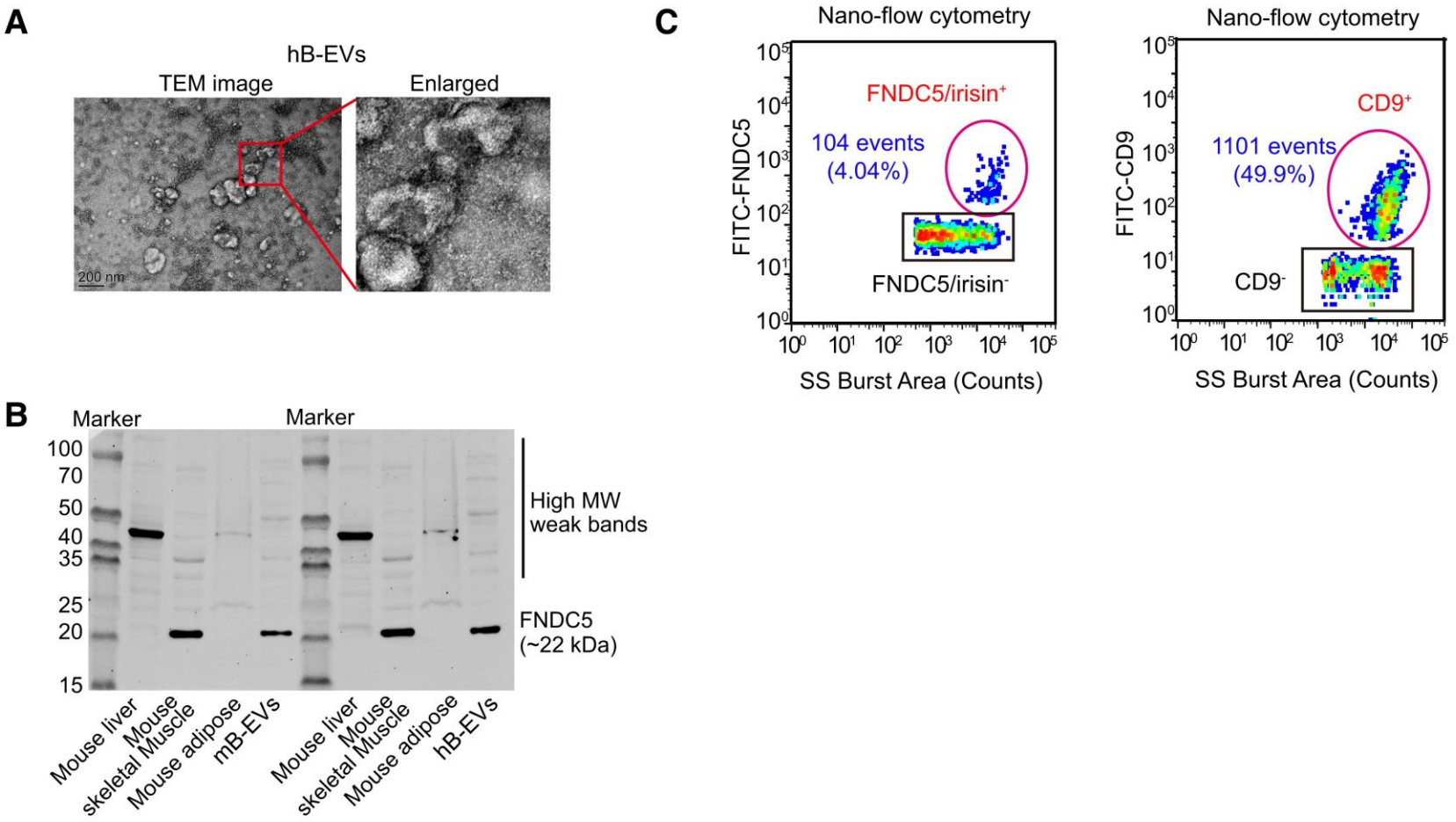
Circulating RANKL EV







Rossi *et al.* JBMR 2022



Chi *et al.* European Heart Journal 2022

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- Principali fattori articolari che influenzano sia osso che muscolo ✅ IL-6 (Interleuchina-6)Secreta dalle cellule sinoviali e dal liquido sinoviale.Effetti sul muscolo: promuove la sintesi proteica e la crescita muscolare (in condizioni fisiologiche).Effetti sull'osso: può stimolare l'attività osteoblastica e favorire la rigenerazione ossea, ma in eccesso può attivare osteoclasti e aumentare il riassorbimento osseo. ✅ IL-15Prodotta dalla membrana sinoviale.Effetti sul muscolo: stimola l'anabolismo muscolare e la sintesi proteica.Effetti sull'osso: promuove la formazione ossea e inibisce il riassorbimento da parte degli osteoclasti. ✅ TGF-β (Fattore di crescita trasformante beta)Rilasciato dalla cartilagine e dal liquido sinoviale.Effetti sul muscolo: coinvolto nella rigenerazione muscolare, ma in eccesso può promuovere fibrosi.Effetti sull'osso: regola il rimodellamento osseo, stimolando gli osteoblasti e inibendo il riassorbimento osseo. ✅ VEGF (Fattore di crescita dell'endotelio vascolare)Espressa dalle cellule sinoviali e dalla cartilagine.Effetti sul muscolo: stimola l'angiogenesi e migliora l'apporto di ossigeno e nutrienti ai muscoli.Effetti sull'osso: favorisce la vascolarizzazione ossea, essenziale per la formazione e la rigenerazione dell'osso. ✅ Osteopontina (OPN)Prodotta dalla cartilagine articolare e dalle cellule sinoviali.Effetti sul muscolo: coinvolta nella riparazione muscolare e nella regolazione dell'infiammazione.Effetti sull'osso: stimola l'attività osteoblastica e la mineralizzazione ossea. ✅ LeptinaSecreta dal liquido sinoviale e dalle cellule sinoviali.Effetti sul muscolo: regola il metabolismo energetico e la sensibilità insulinica nel muscolo.Effetti sull'osso: stimola la formazione ossea attraverso l'attivazione degli osteoblasti. ✅ AdiponectinaPresente nel liquido sinoviale e derivata dalle cellule sinoviali.Effetti sul muscolo: migliora l'ossidazione degli acidi grassi e la sensibilità insulinica, favorendo la funzione muscolare.Effetti sull'osso: modula il metabolismo osseo e promuove la formazione ossea.

- Patients with a loss-of-function mutation in the *PRG4* gene are affected by a condition known as Camptodactyly-Arthropathy-Coxa vara-Pericarditis (CACP), which is characterized by joint disease, pericardial effusion, and, notably, low bone mass (osteopenia), among other symptoms.[1]

Lubricin mRNA expression during elbow joint formation and in adult knee joints. (A) Pseudo-colored pictures showing Prg4 mRNA expression (red) and cell nuclei (blue) in the developing mouse elbow joint from E14.5–E17.5. Cavitation between the humerus and ulna begins at E14.5. Gdf5 is still strongly expressed in the presumptive joint mesenchyme, but Prg4 is not expressed at that time. Prg4 mRNA expression is detected at the forming joint surfaces from E15.5, after cavitation has begun, whereas Gdf5 expression is no longer detected in the joint area. Expression of Prg4 at the cartilage surfaces and adnexal structures increases further as maturation proceeds. (B) Pseudo-colored pictures showing Prg4 or Agc1 mRNA expression (red) and cell nuclei (blue) in 3-month-old (P90) and 6 month-old (P180) mouse knee joints. Alizarin red and Alcian blue–stained (A&A-stained) adjacent sections are included for orientation. Prg4 expression persists throughout adult life at the articular cartilage surface and within the synovium but is not detectable in the growth plate cartilage. Agc1 is expressed in articular and growth plate cartilage.

SOCIETÀ ITALIANA

G.U.I.D.A.

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DEL DOLORE MUSCOLO-SCHELETRICO E DELL'ALGODISTROFIA