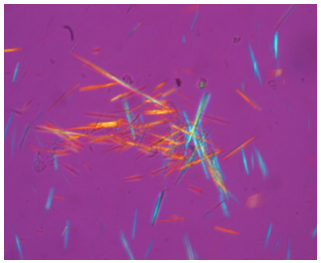
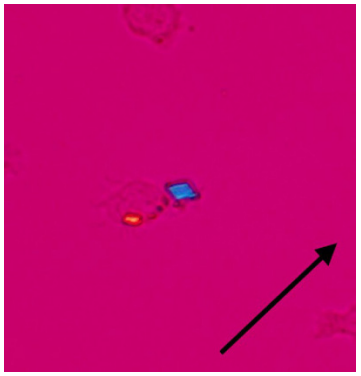
Crystals and Osteoarthritis

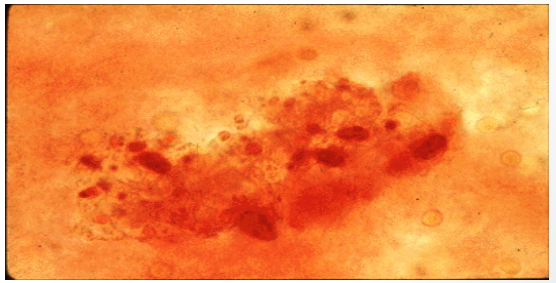
Ann K. Rosenthal, MD
Will and Cava Ross Professor of Medicine
Medical College of Wisconsin

Objectives

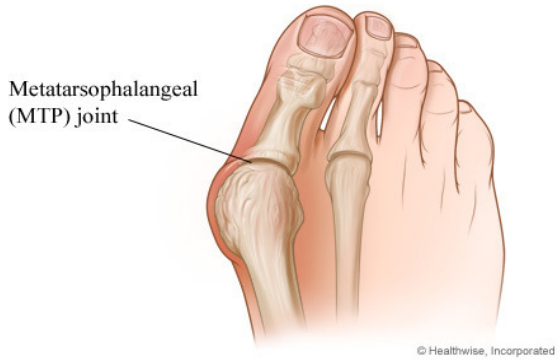
- Review epidemiologic evidence for an etiologic connection between OA and crystals
- Discuss relationship between crystal formation and OA
- Learn how crystal-induced damage worsens OA







Gout prefers joints affected by osteoarthritis



Roddy, E., W. Zhang, and M. Doherty, *Are joints affected by gout also affected by osteoarthritis?* Annals of the Rheumatic Diseases, 2007. **66**(10): p. 1374-7

Gout is associated with knee OA

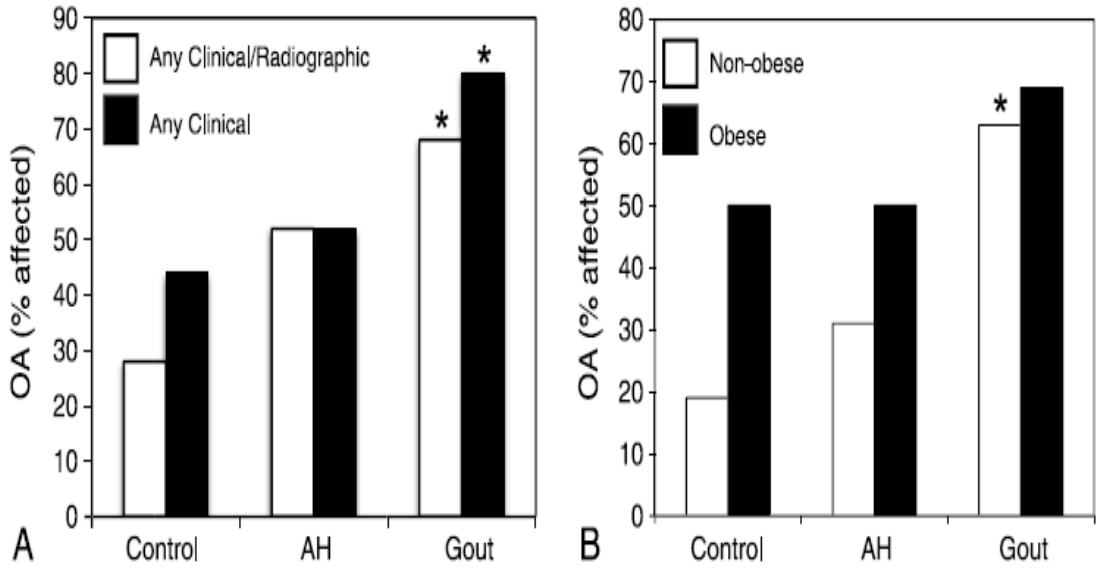
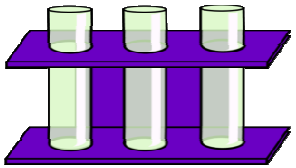


FIGURE 2. Prevalence of knee OA and impact of BMI on knee OA among the control, AH, and gout groups. A, Presence of gout predicts increased prevalence of knee OA. Control, AH, and gout subjects were assessed for presence of knee OA using ACR Clinical/Radiographic or Clinical OA criteria, as indicated (*$P < 0.05$ vs control group). B, Presence of gout predicts increased prevalence of knee OA among nonobese patients. Control, AH, and gout subjects were stratified into nonobese (BMI <30 kg/m^2) and obese (BMI ≥30 kg/m^2) subgroups, and the prevalence of knee OA (ACR Clinical/Radiographic criteria) was determined for each subgroup (*$P < 0.05$ vs corresponding control group).

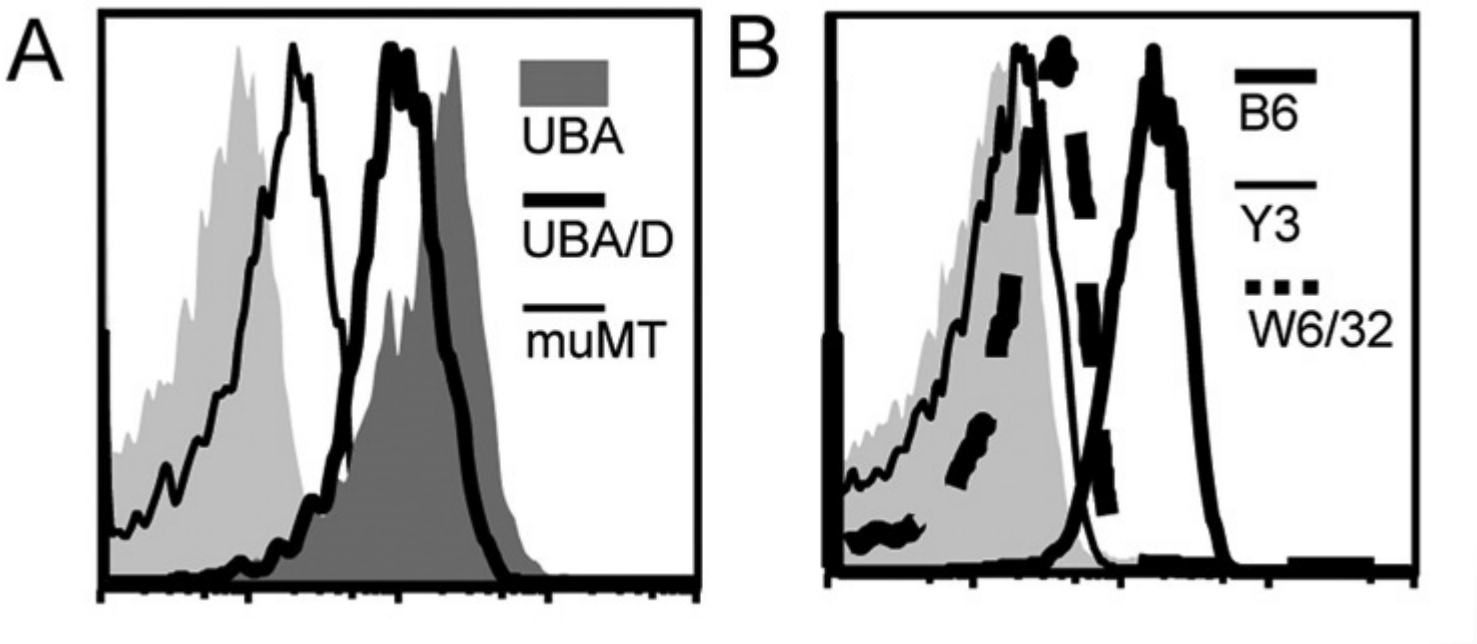
Howard et al . (*J Clin Rheumatol* 2015;21: 63–71)

Crystal formation in gout

- MSU crystal formation occurs in solution
- Promoted by:
  - Cool temperatures
  - acidic pH
  - decreased oxygen saturation
  - Ca2+
  - Gouty synovial fluid
  - Serum
  - Collagen
  - mechanical trauma
  - ? Cartilage matrix components

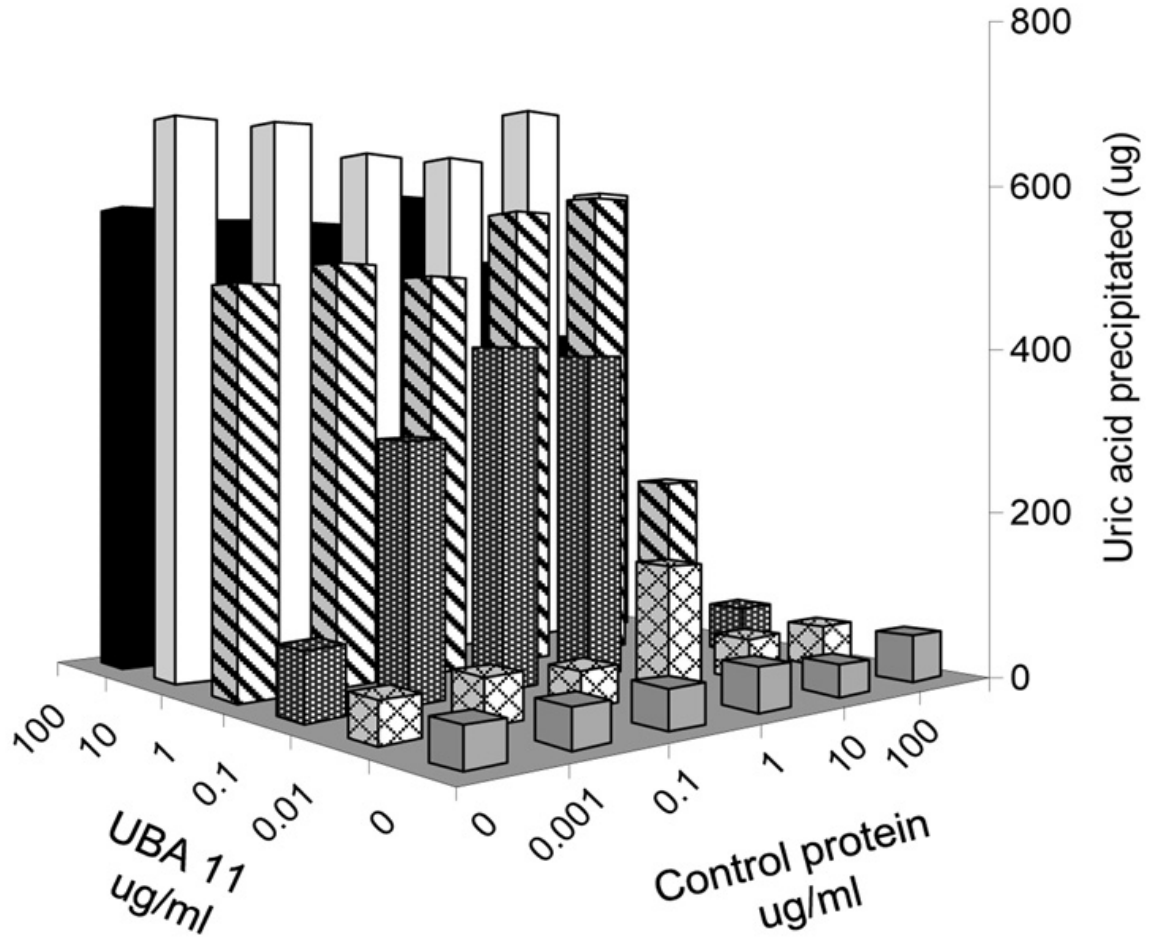


Immunoglobulins bind to MSU crystals



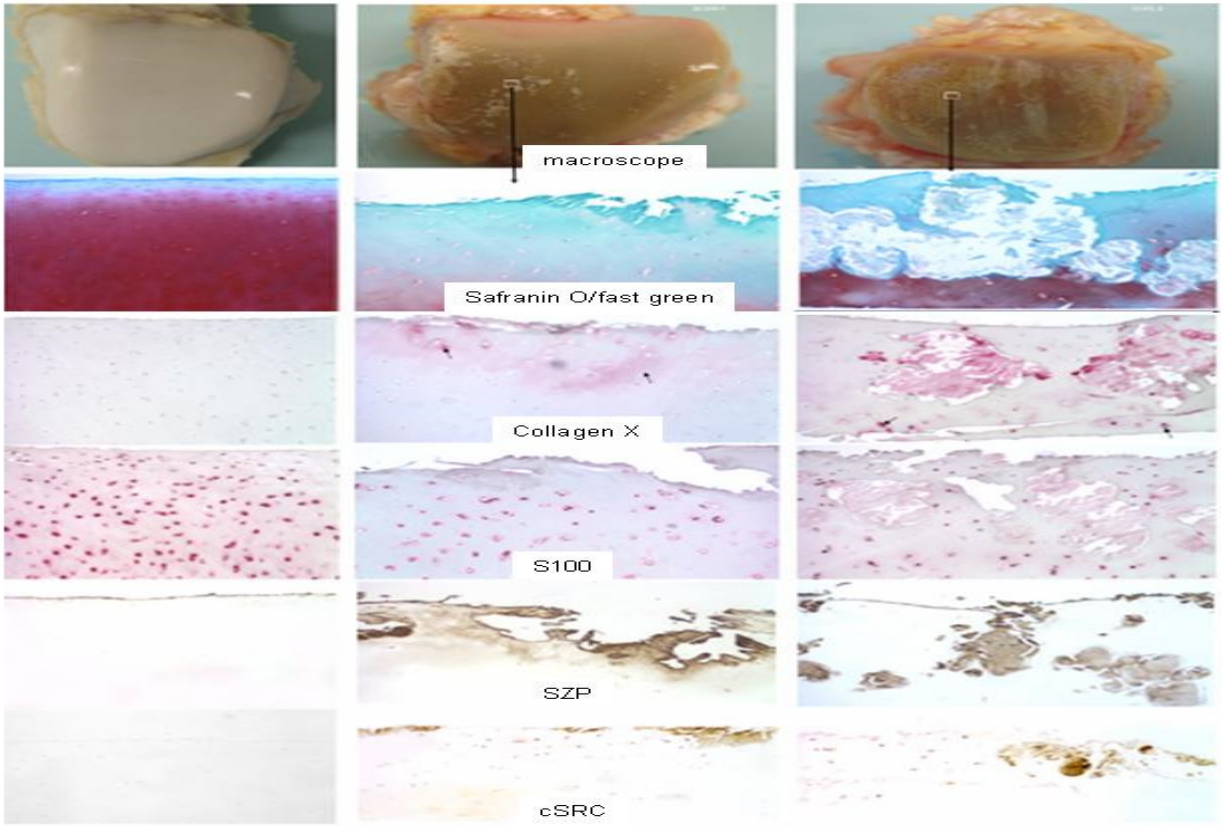
J Immunol. 2009 Feb 15; 182(4): 1912–1918.

Immunoglobulins play a role in gout crystal formation

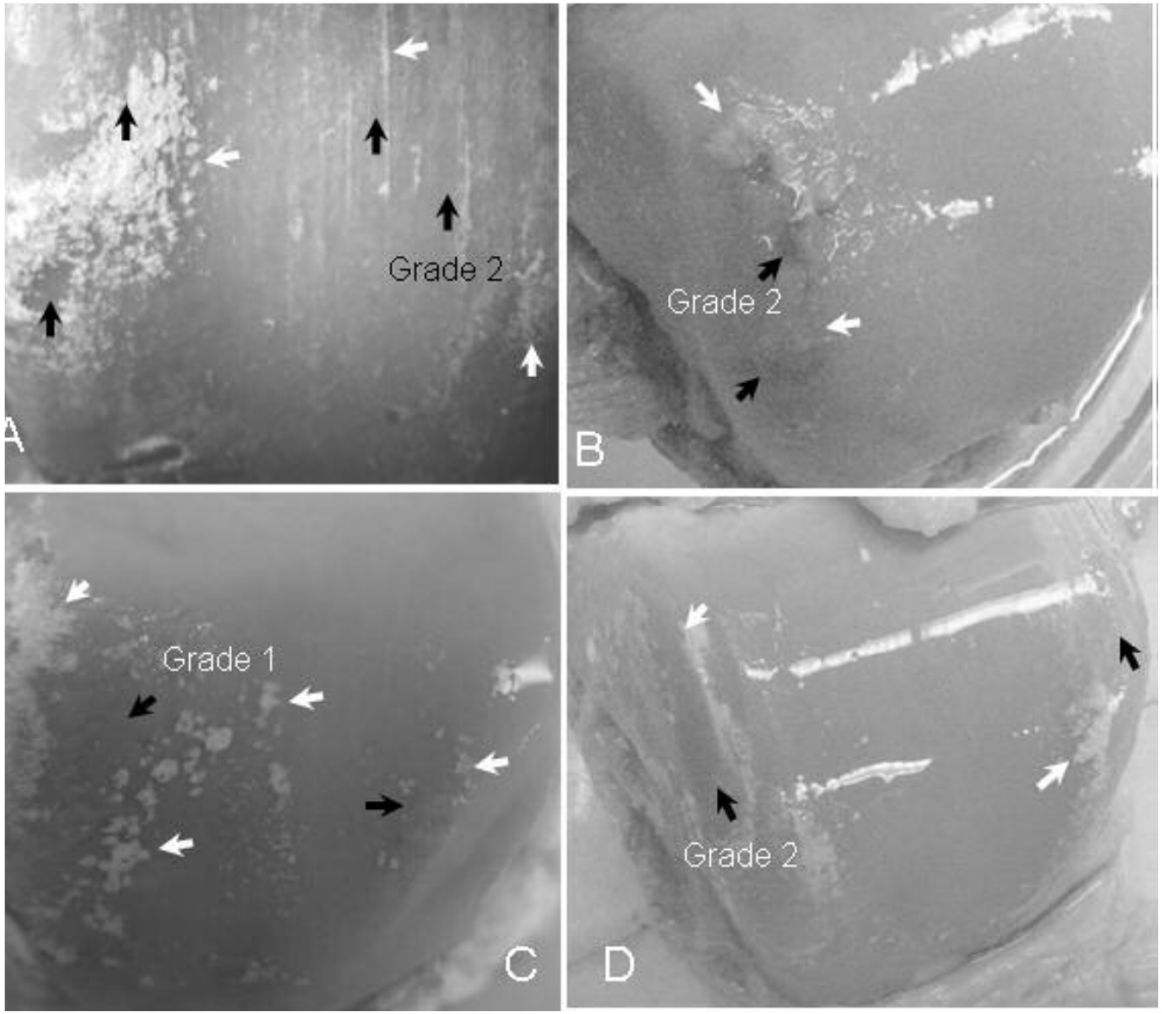


J Immunol. 2009 Feb 15; 182(4): 1912–1918.

Gout can deposit in or on cartilage



MSU crystals induce mechanical damage



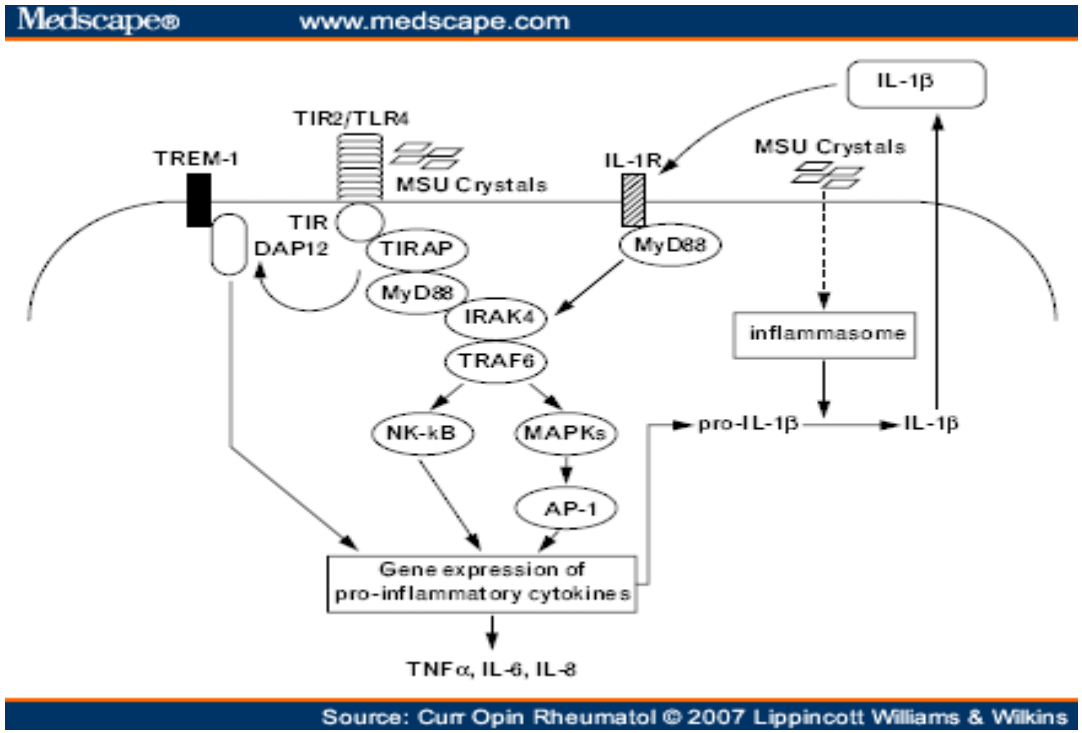
MSU crystals predict worse cartilage damage

	Total Sample	%	Crystal tali	%
# donors	4007		187	**4.7**
# individual tali	7855		344	**4.4**
Grade 0	2948	**38**	27	**7.8**
Grade 1	2856	**36**	129	**37.5**
Grade 2	1614	**20.5**	159	**46.3**
Grade 3	413	**5.2**	29	**8.4**
Grade 4	24	**0.3**	0	**0**
mean grade	0.83		1.57	

Table 2. Cartilage degeneration scores for the total pool of tali and for the subset displaying crystals.

For Peer Re

MSU crystals (sometimes) induce inflammatory responses



Factors in joints such as FFA modulate MSU's inflammatory response

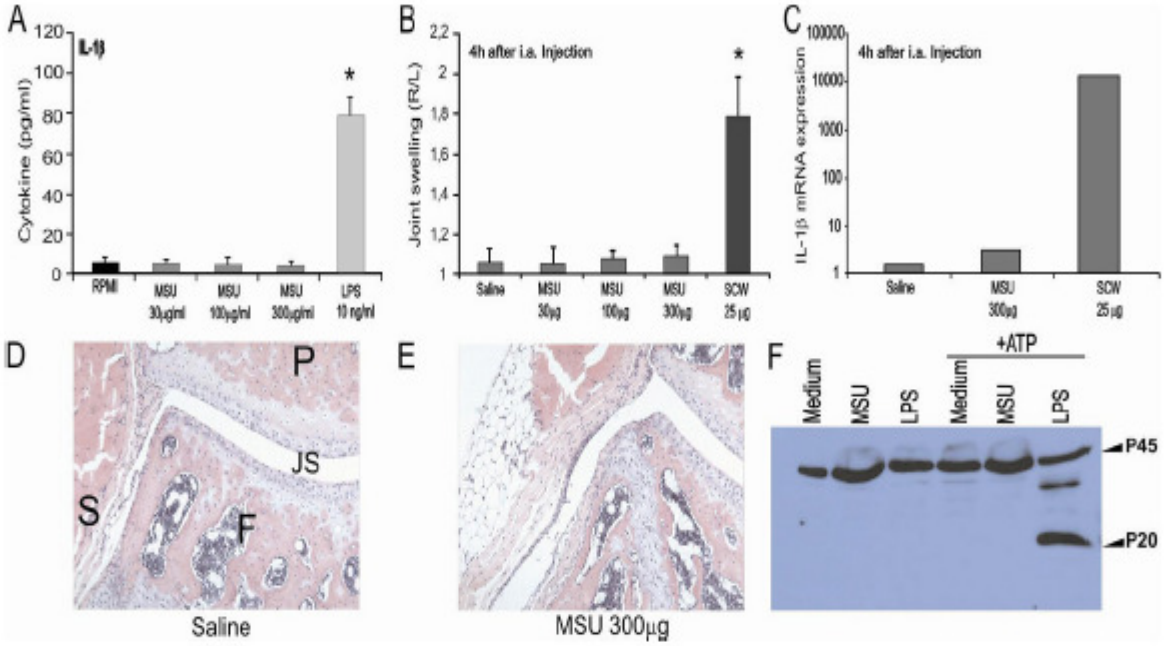


Figure 1. MSU crystals do not induce IL-1β production or joint inflammation

Joosten et al. *Arthritis Rheum.* 2010 November ; 62(11): 3237–3248

FFAs may be the second hit in MSU-induced inflammation

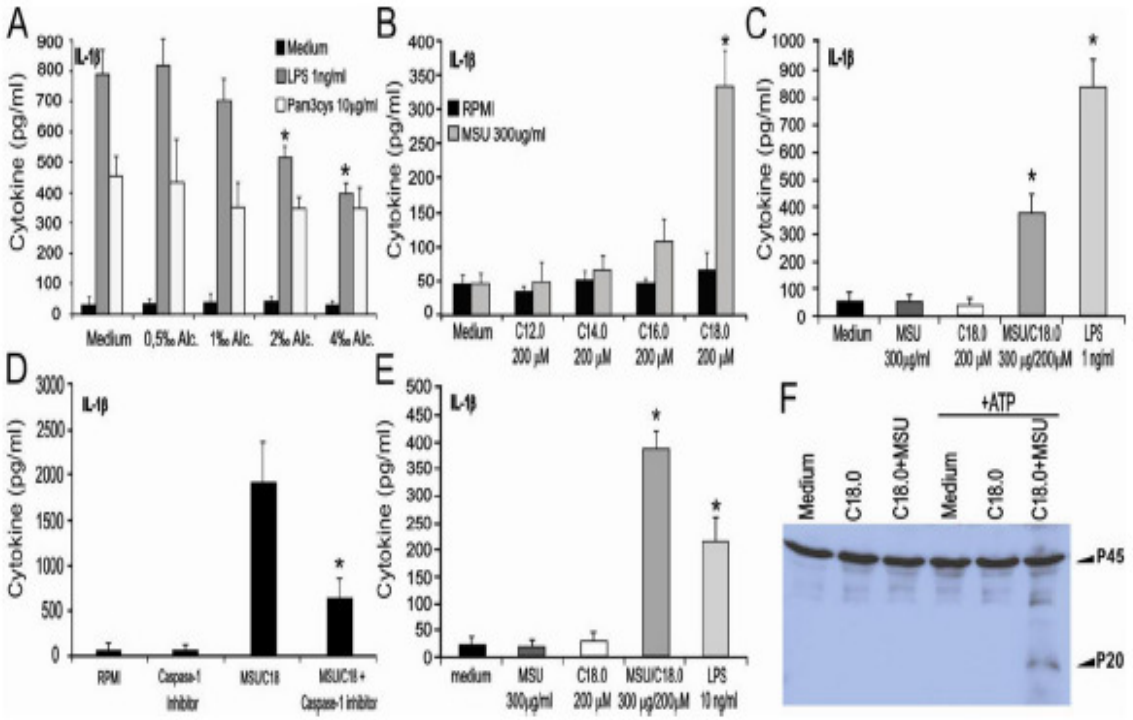
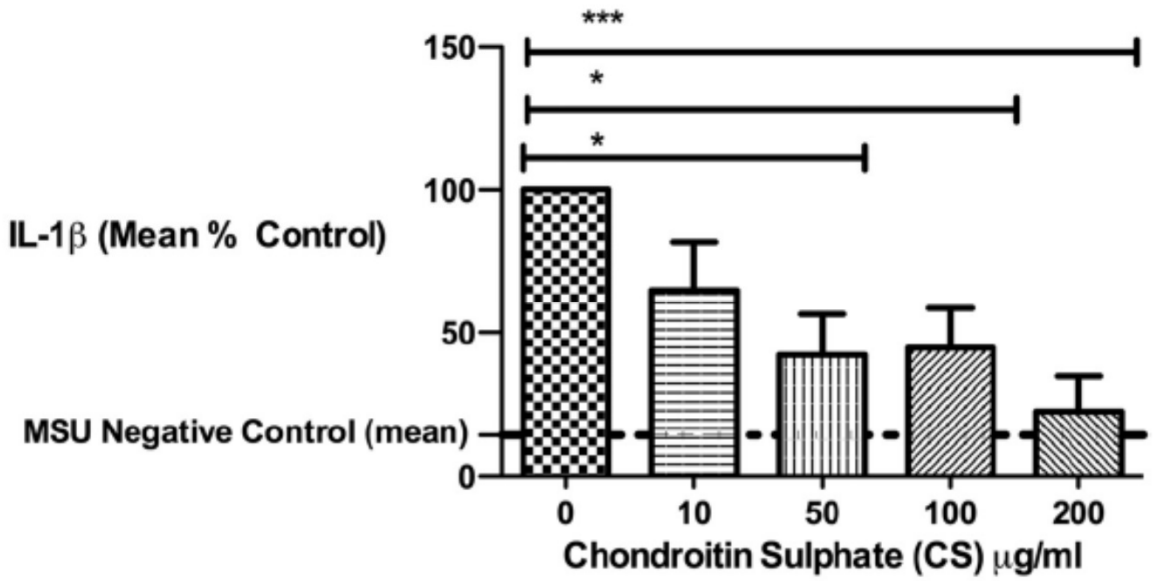


Figure 2. MSU synergizes with FFA for cytokine prodcution

Joosten et al *Arthritis Rheum.* 2010 November ; 62(11): 3237–3248

Chondroitin sulfate suppresses MSU induced IL-1β production by macrophages



Orlowsky *et al. BMC Musculoskeletal Disorders* 2014, **15**:318

Gout and OA

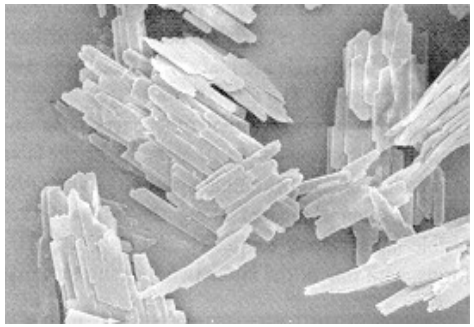
What we know

- MSU crystals damage cartilage
- OA predisposes to gout

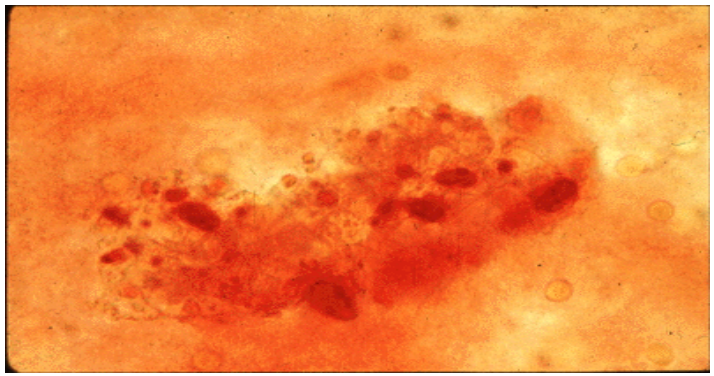
What we don't know

- Why urate deposits seem to become part of cartilage
- What initiates an acute inflammatory response
- Why crystals form
- One hit vs two hits

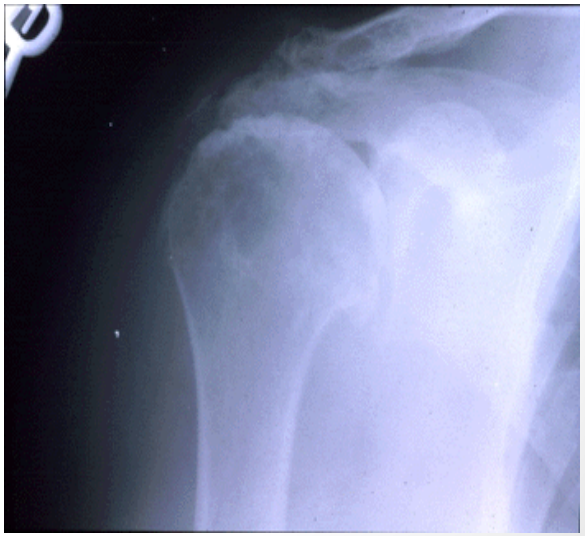
Calcium crystals



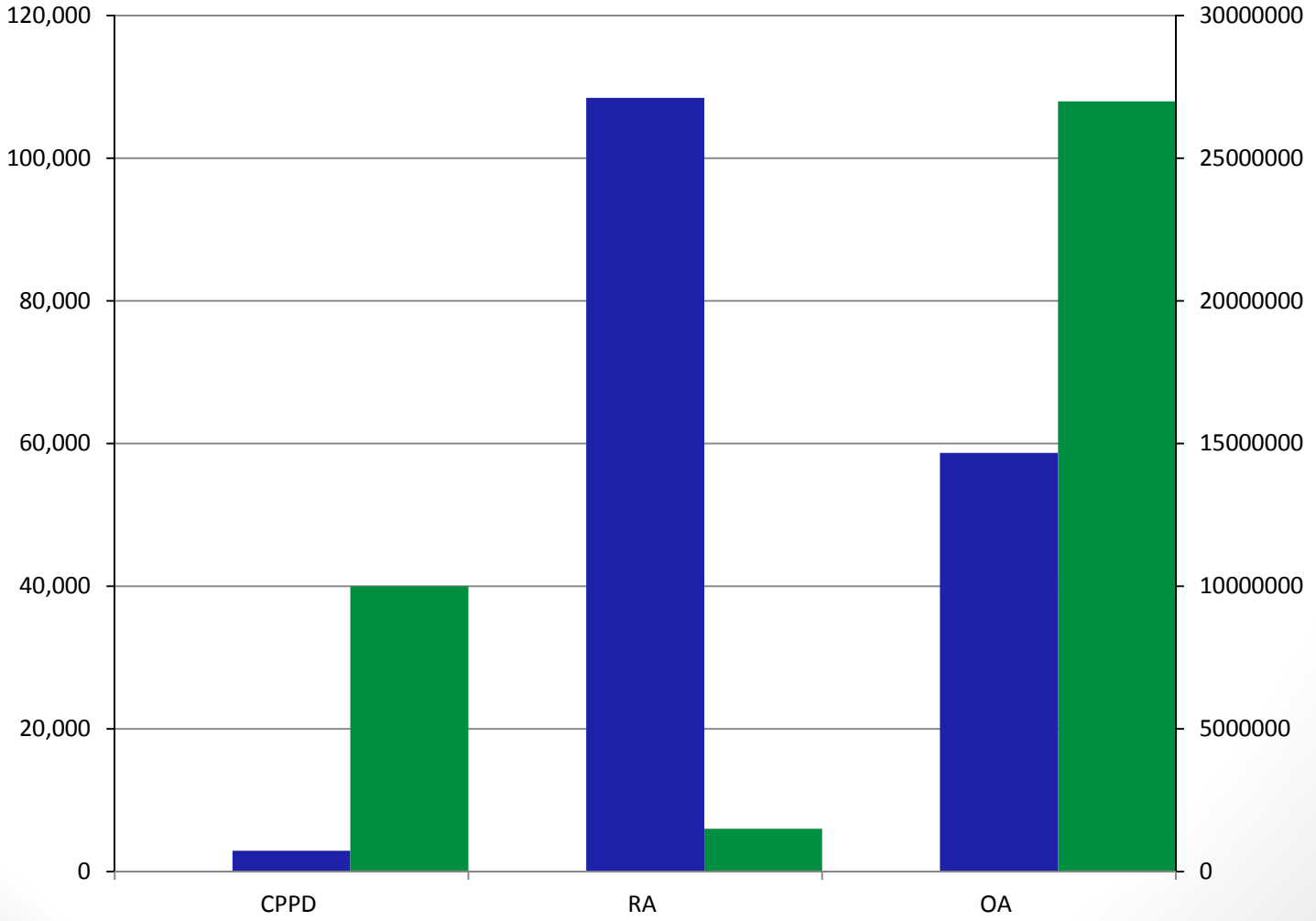
Calcium Pyrophosphate (CPP)



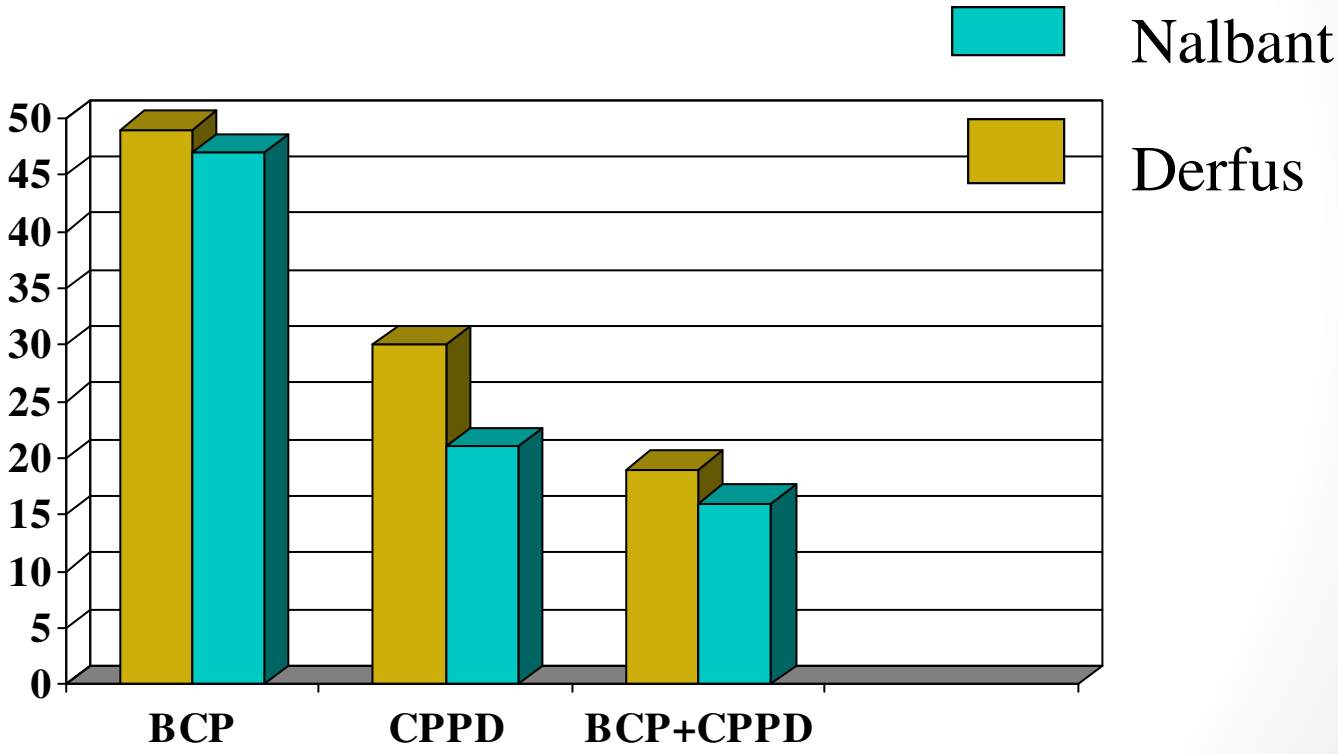
Basic calcium phosphate (BCP)



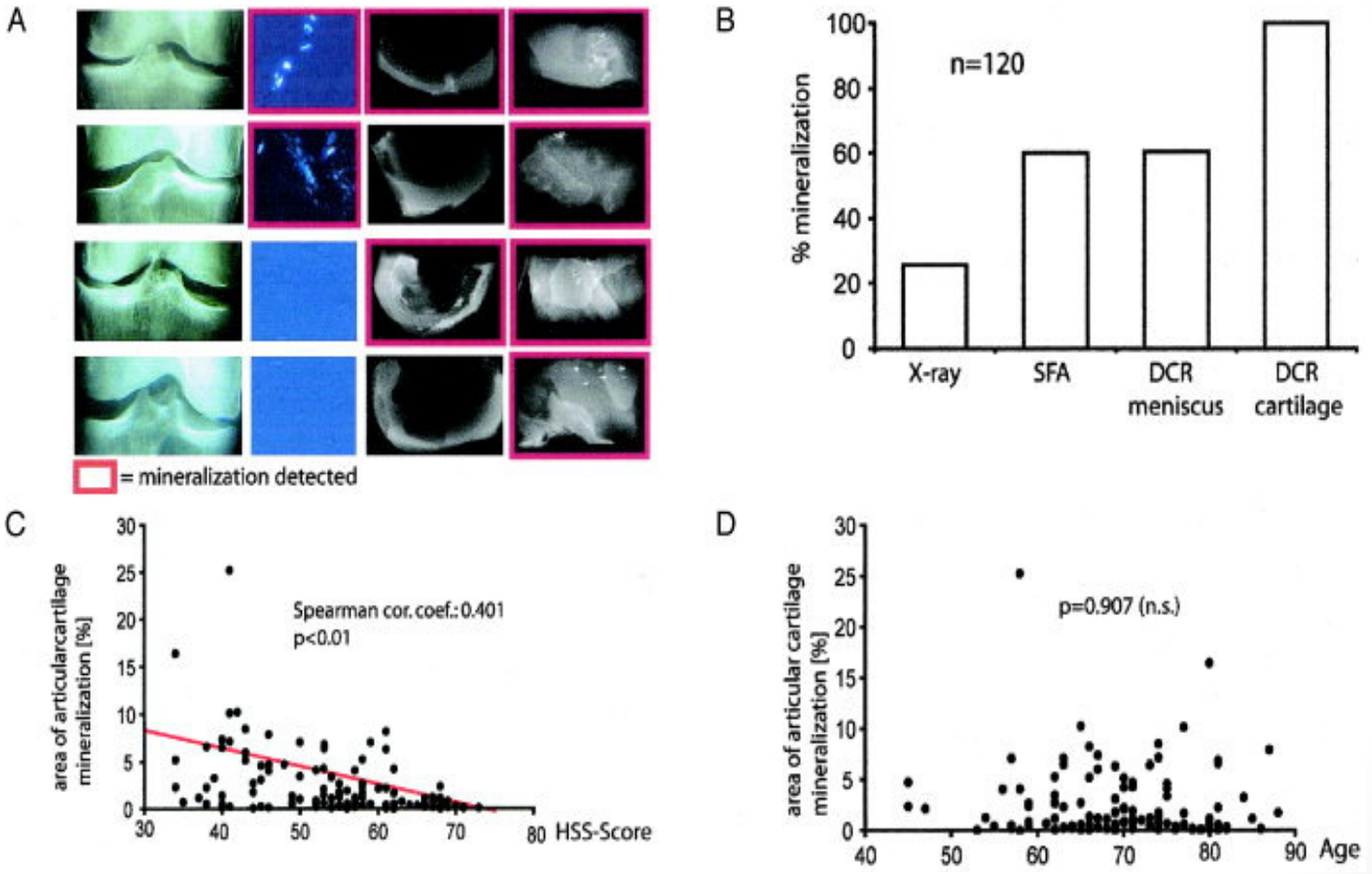
Calcium crystals are understudied



Calcium crystals are common in OA synovial fluids

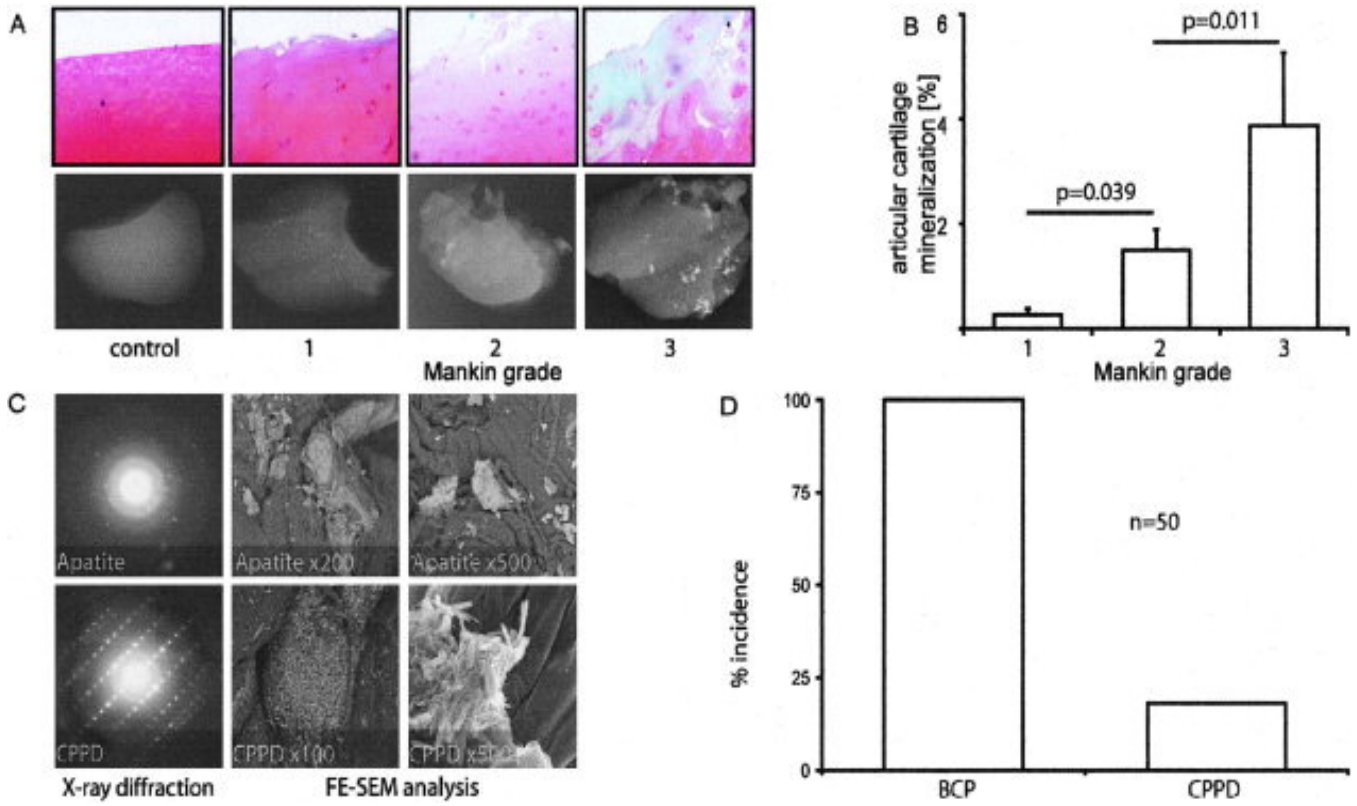


Calcium crystals are really common in OA joint tissues



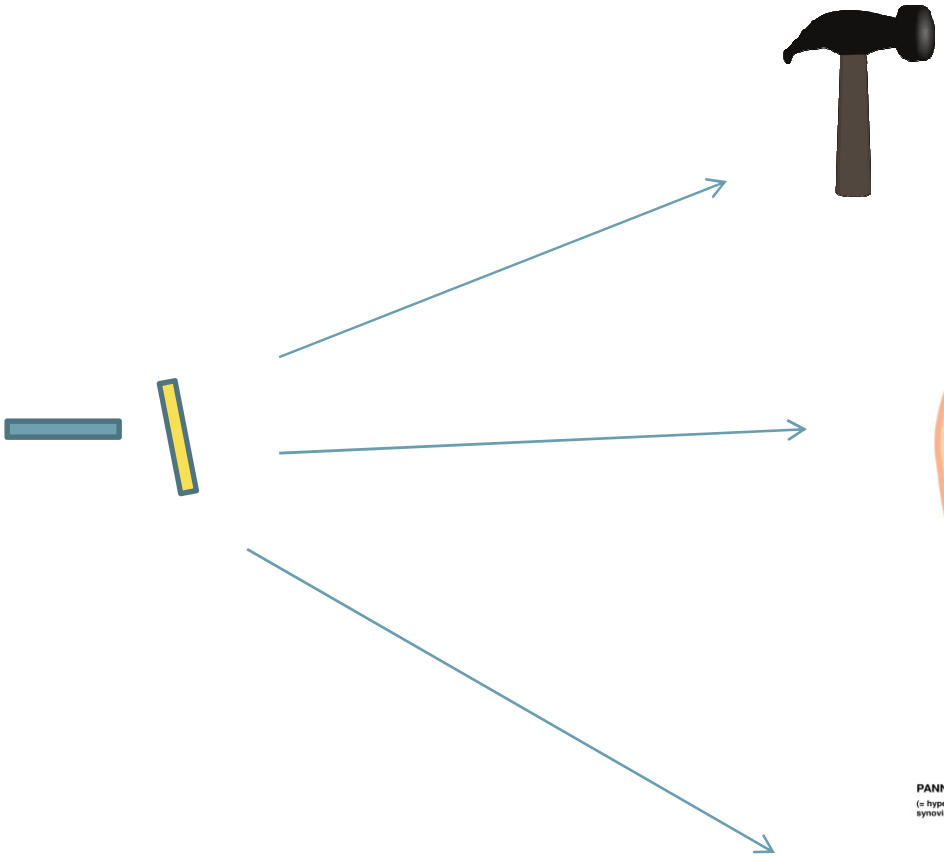
Fuerst et al. Arthritis Rheum 60:2694, 2009

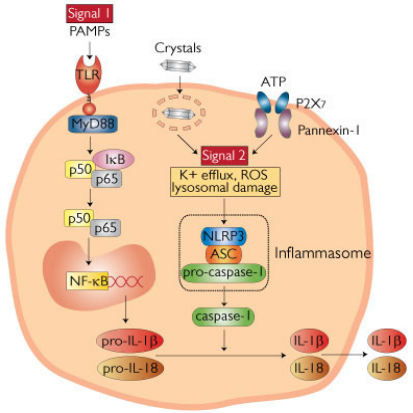
OA severity correlates with the presence and quantity of calcium crystals

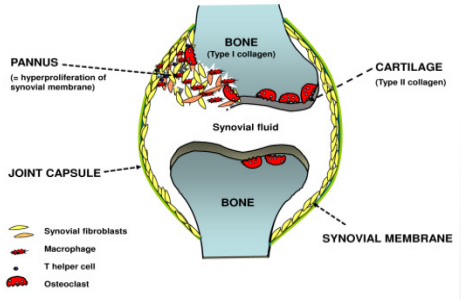


Fuerst et al. Arthritis Rheum 60:2694, 2009

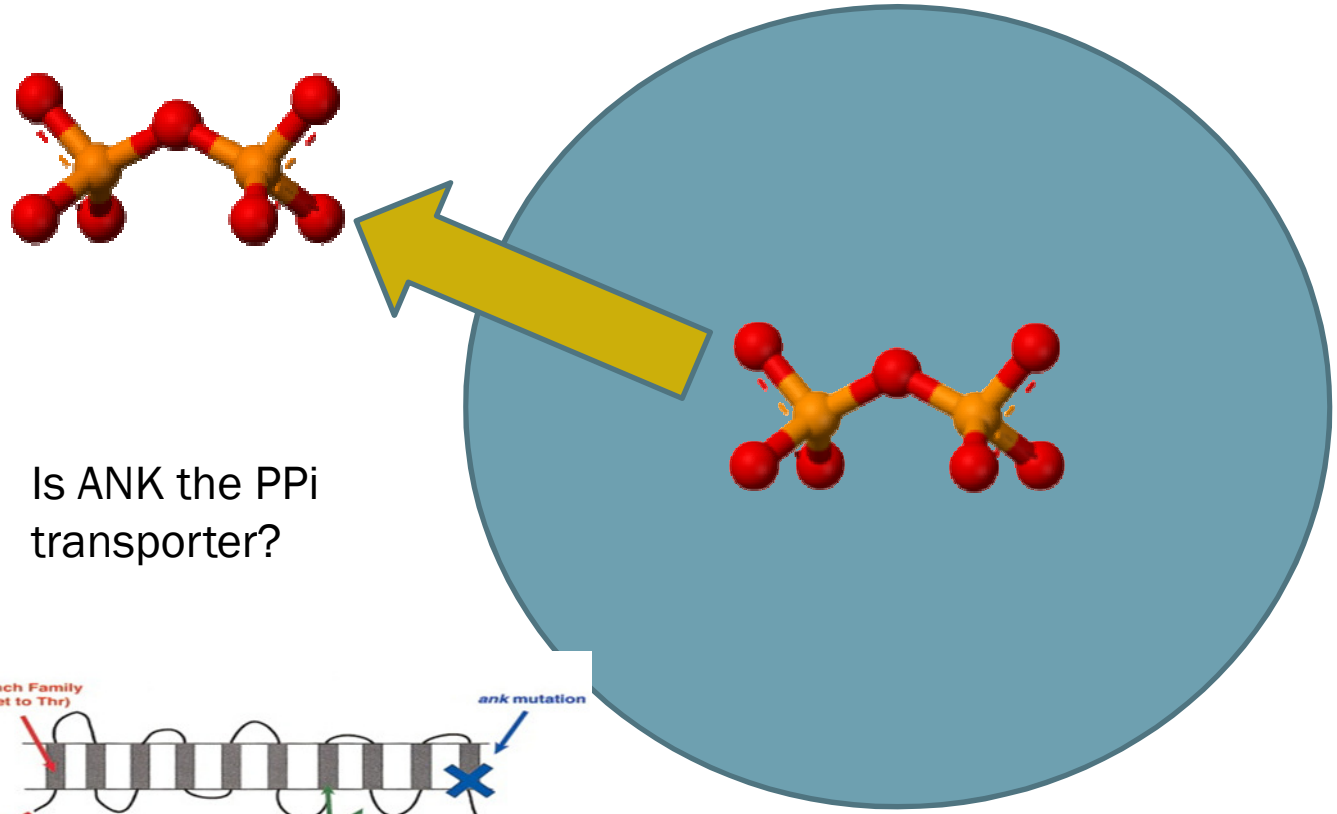
Calcium crystals contribute to cartilage damage through multiple mechanisms





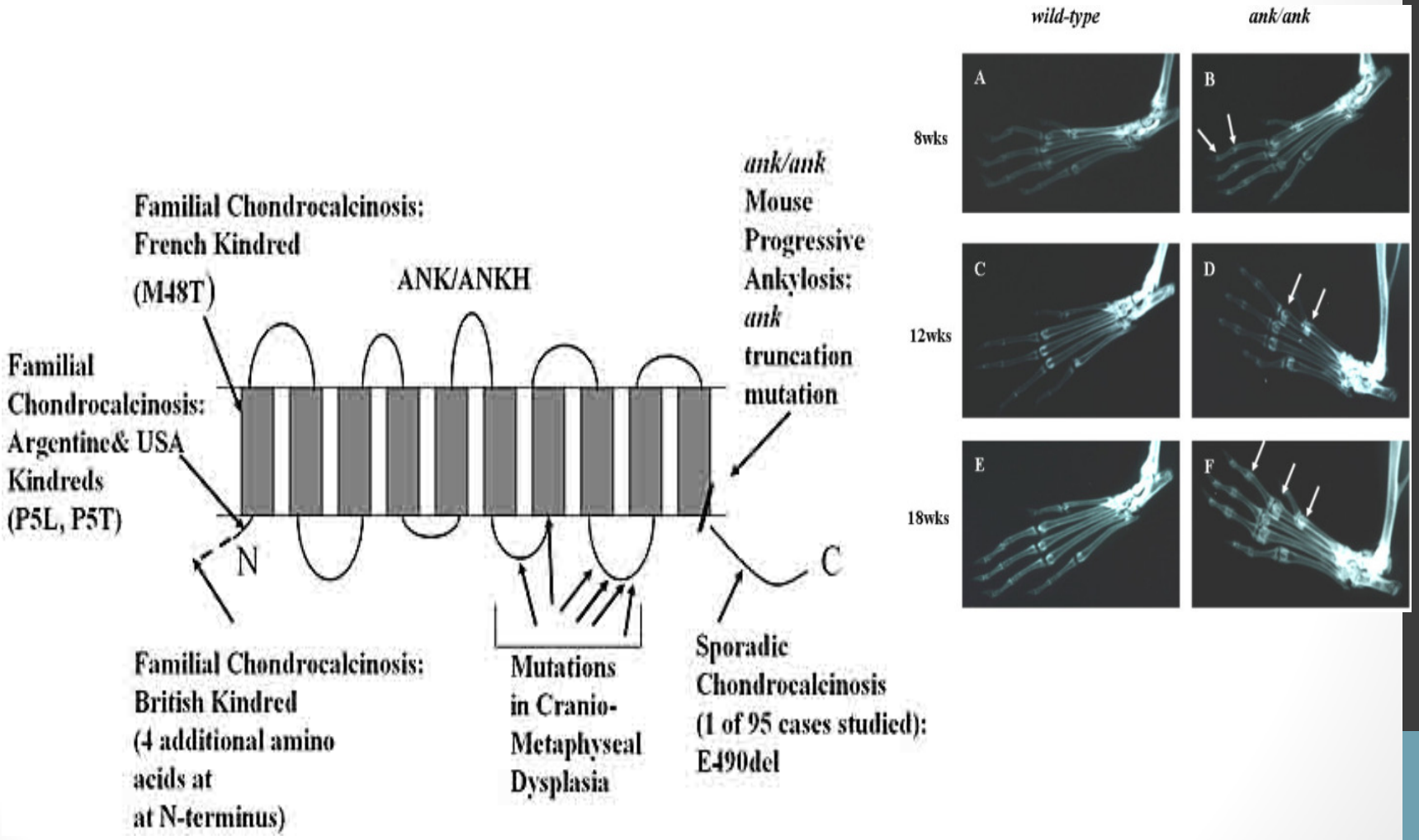


Excess extracellular pyrophosphate is necessary for CPP crystal formation



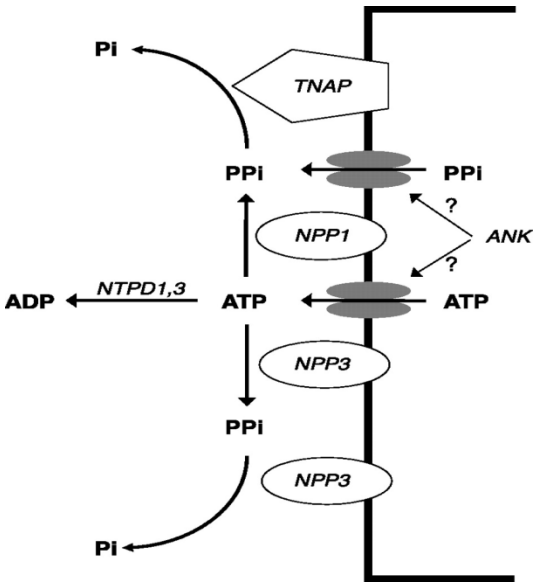
Is ANK the PPi transporter?

ANK mutations are linked to familial CPPD and excessive articular calcification



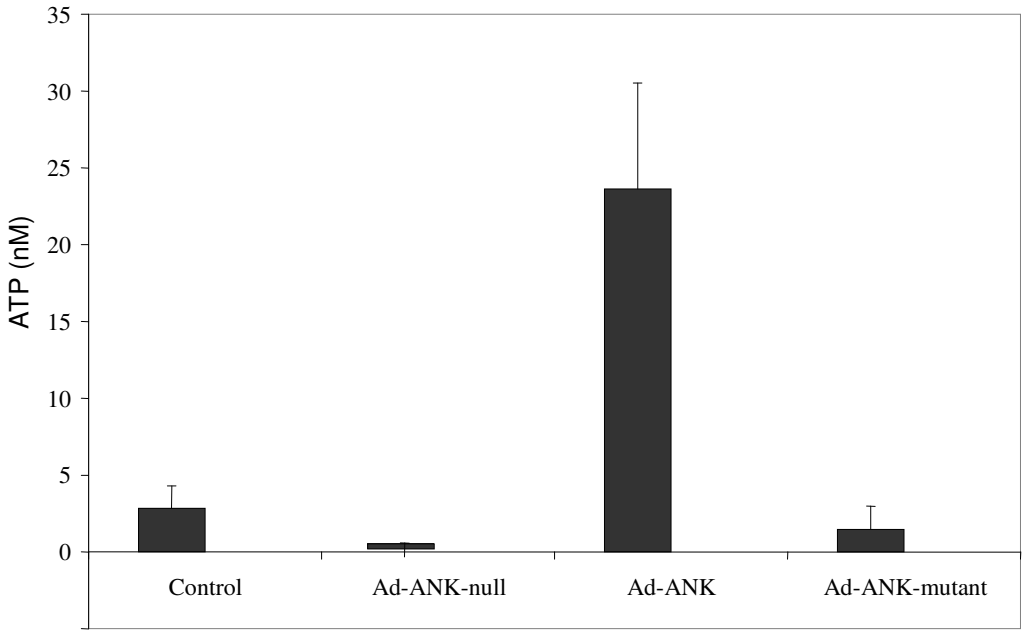
Johnson and Terkeltaub, Frontiers in Bioscience, 2005

Most PPi is generated by extracellular ATP

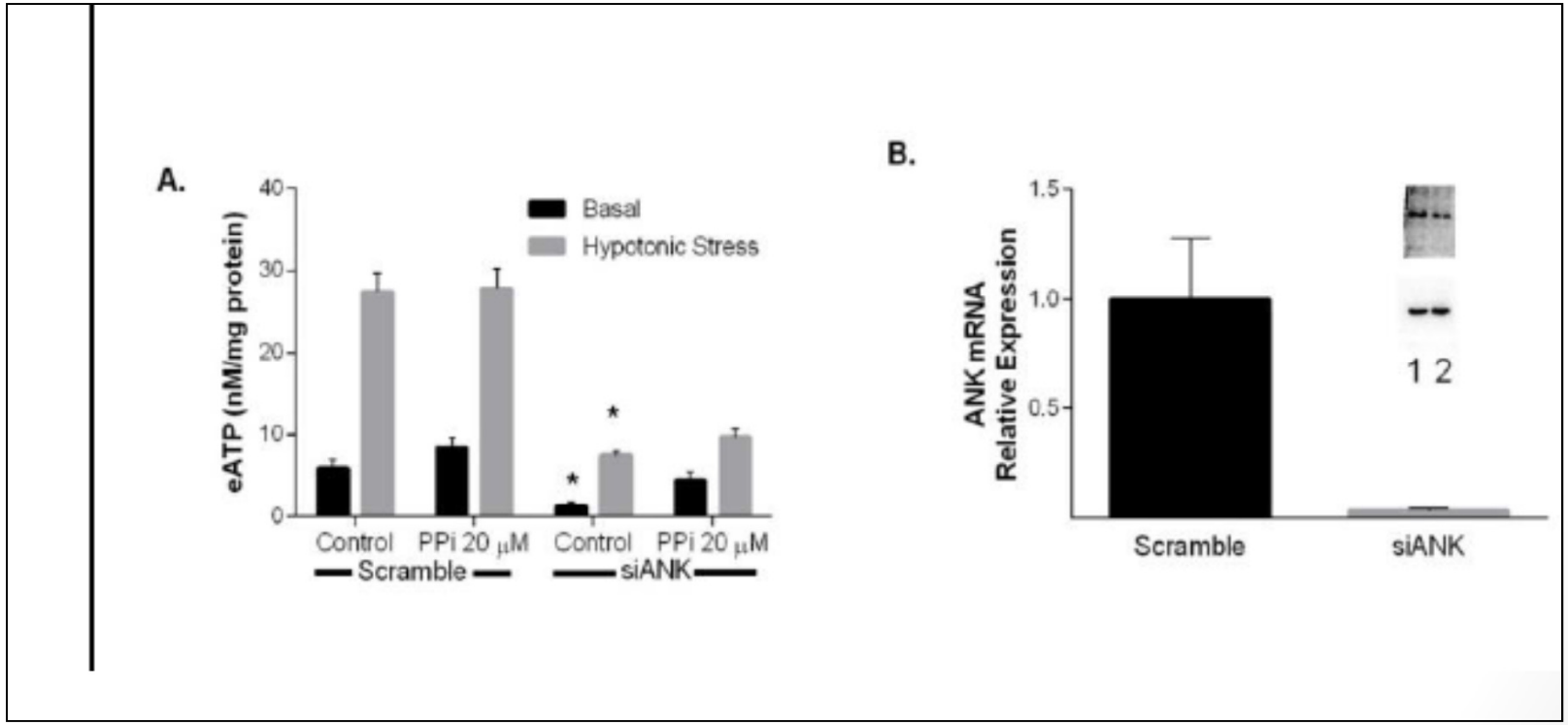


- Factors that increase levels of ePPi around chondrocytes also increase extracellular ATP.
- There is no known extracellular enzyme that regenerates ATP from PPi.

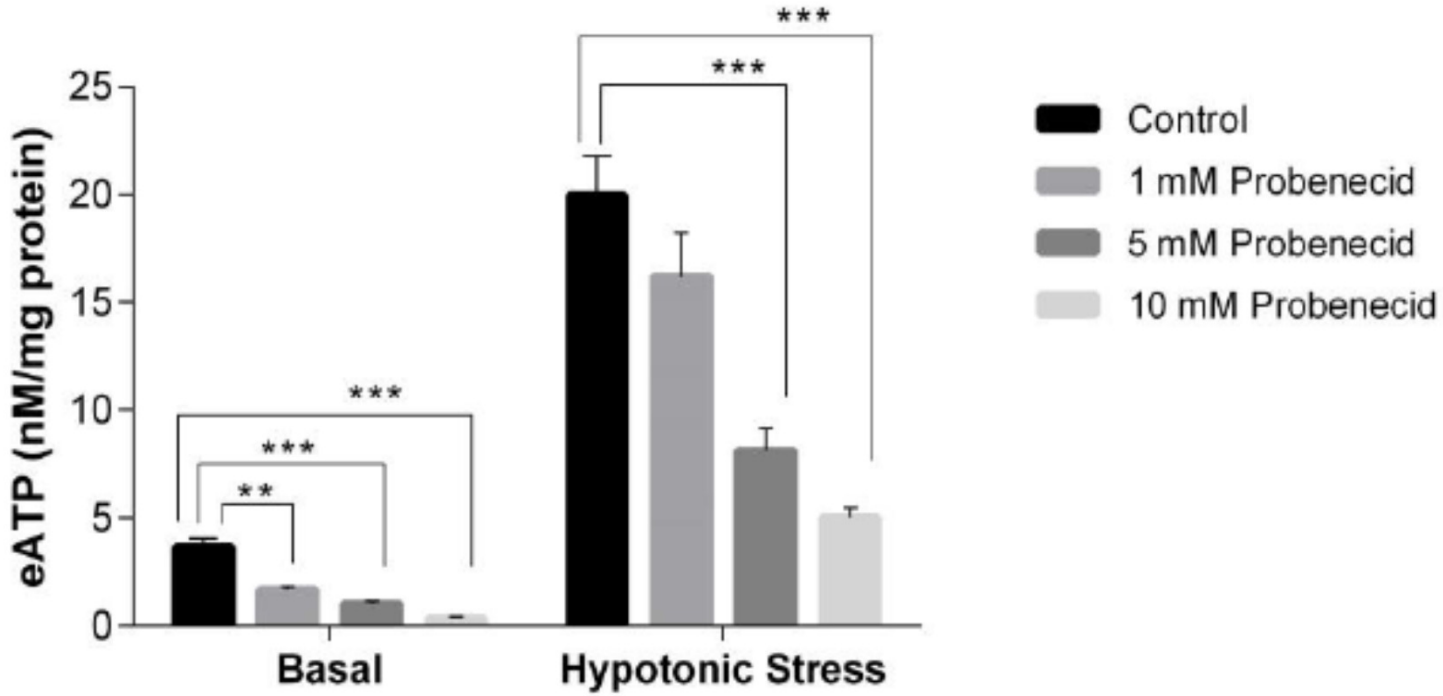
Over-expression of ANK increases extracellular ATP levels in chondrocytes



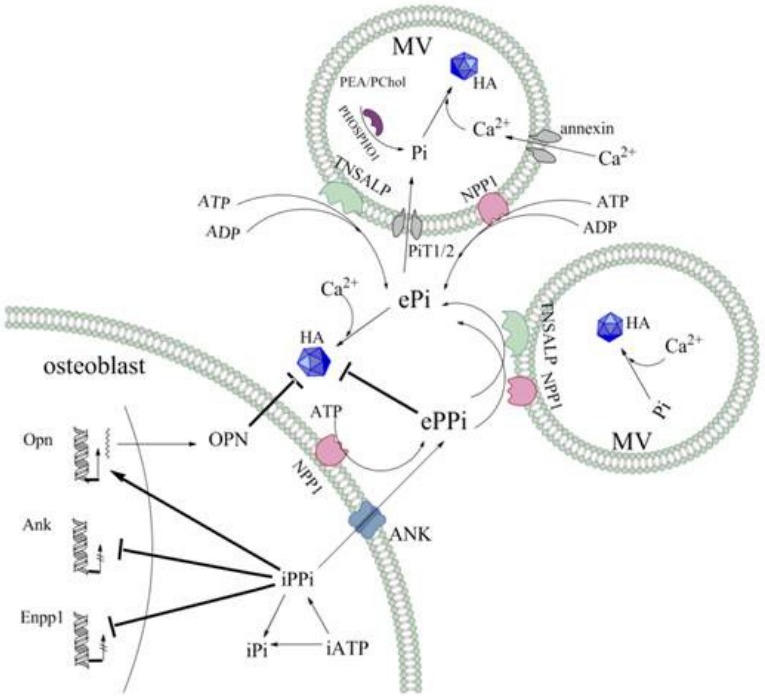
siANK reduces extracellular ATP levels in chondrocytes

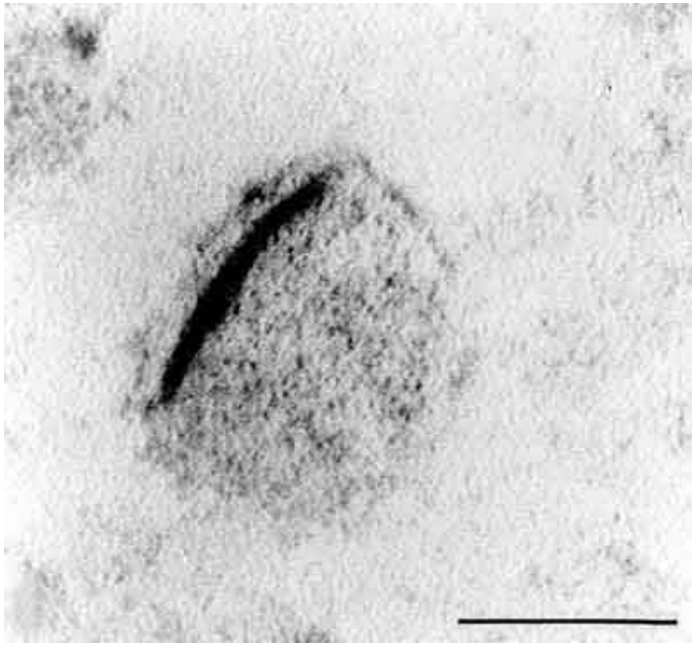


Probenecid, an ANK inhibitor, reduces eATP levels

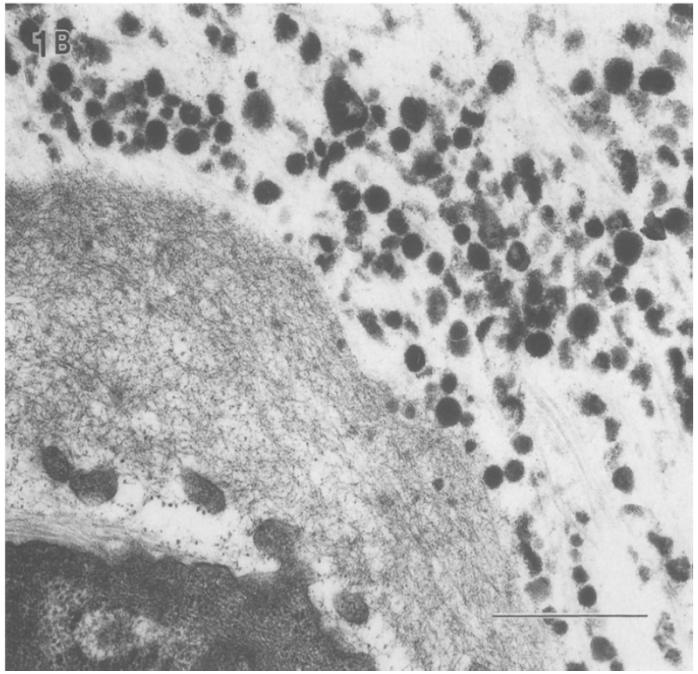


Matrix vesicles in growth plate cartilage mediate calcification

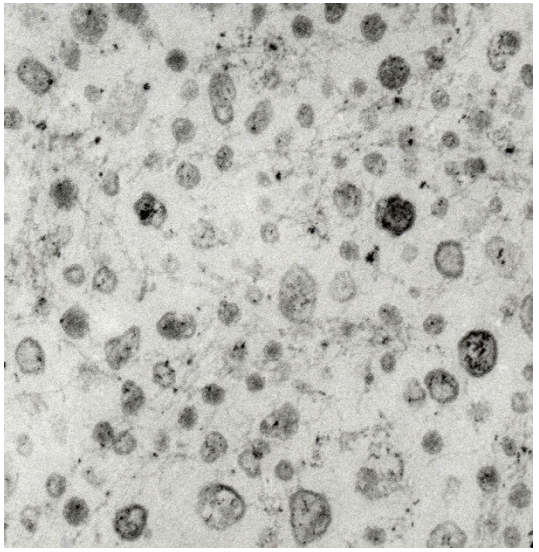




Analogous vesicles are present in articular cartilage



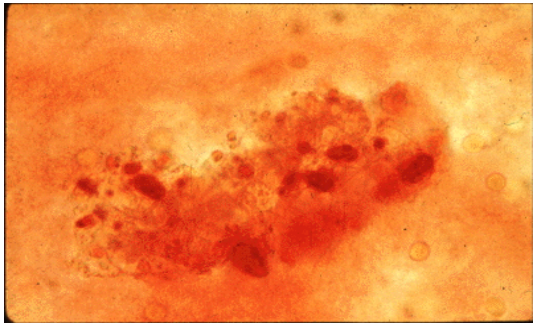
In situ EM

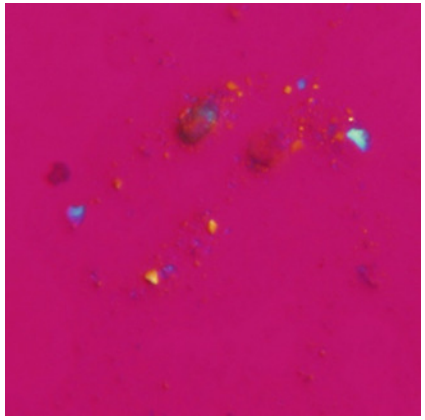


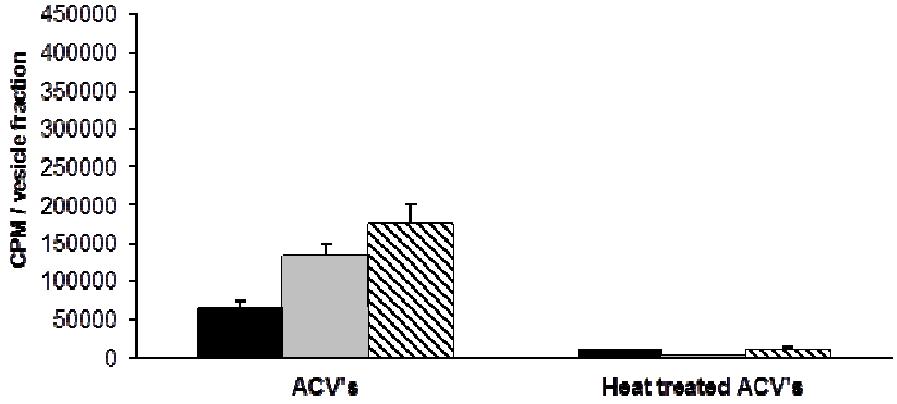
Isolated ACVs from cartilage

Sumii et al ,Med Electron Microsc 28(3-4), 156-62.

Articular cartilage vesicles generate both CPPD and BCP crystals in vitro

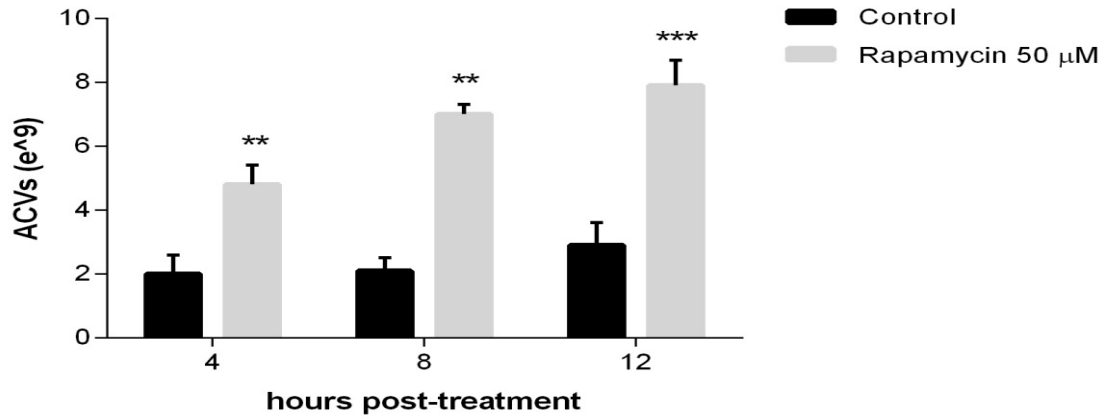






ACV number increases in conjunction with autophagy

A



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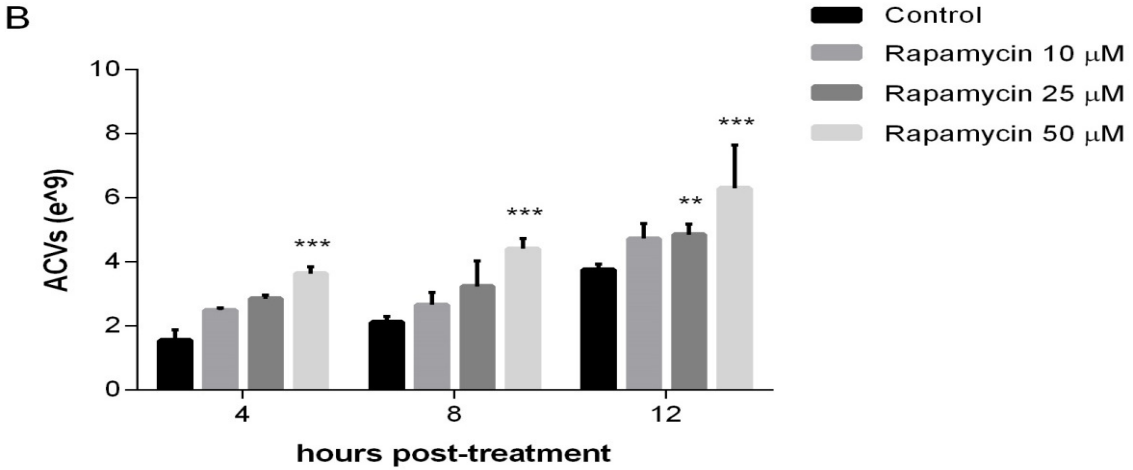
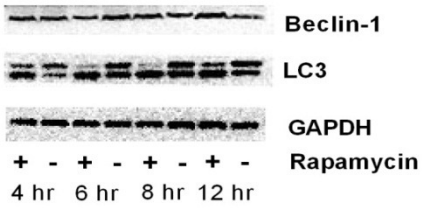


ACV number increases in conjunction with autophagy

A

	Rapamycin
LDH (% control)	115.1 ± 11.6
MTT (% control)	102.6 ± 20.3
caspase-3 activity (% control)	115.1 ± 3.94

B



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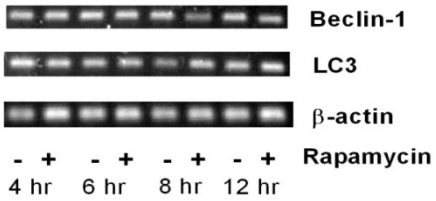
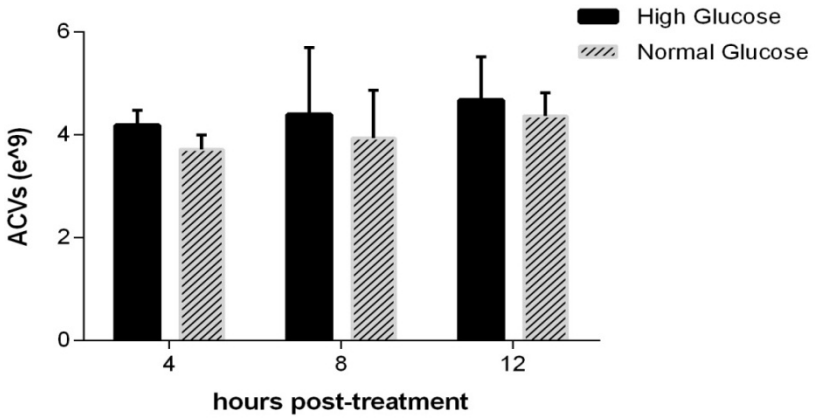
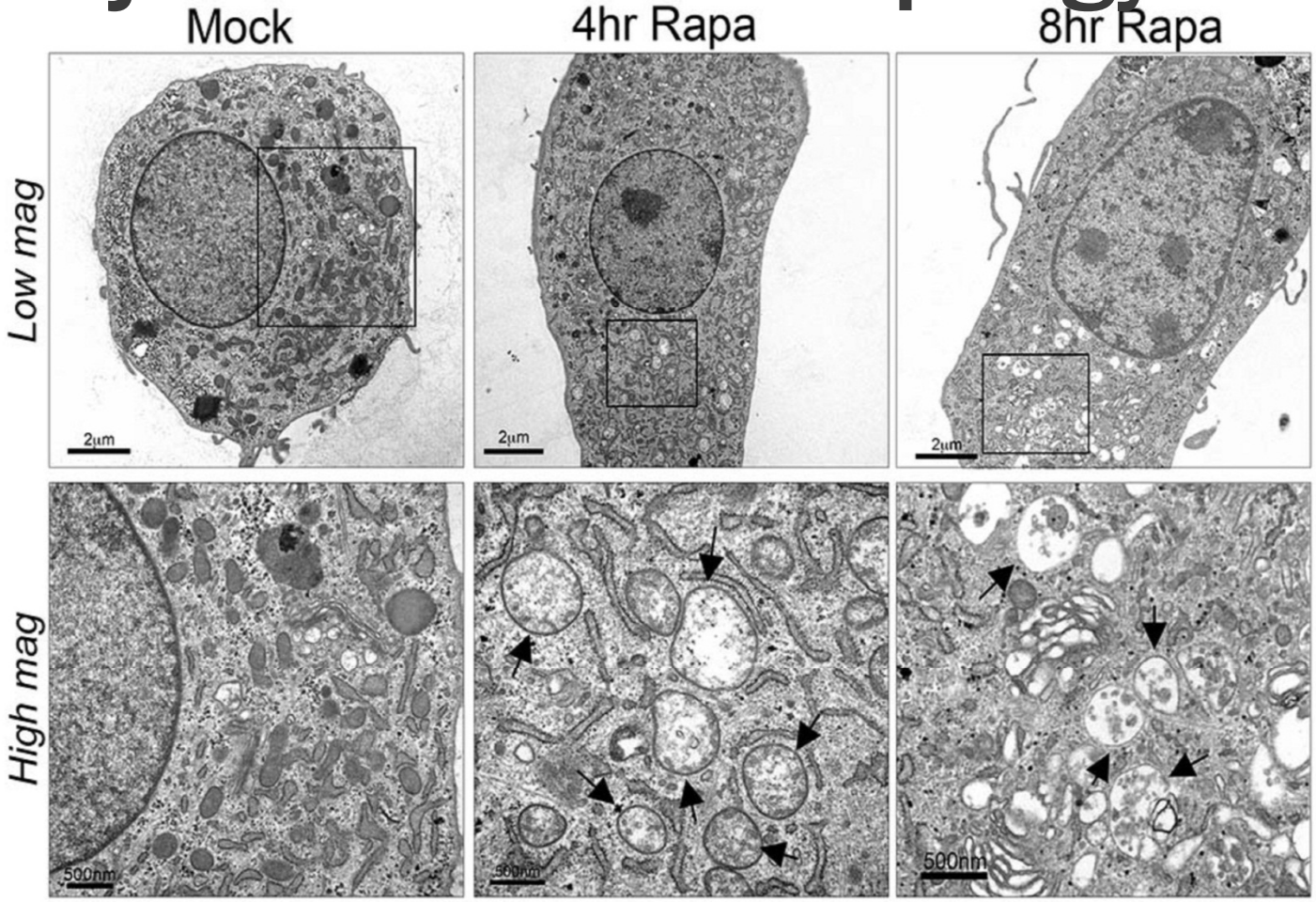


D



ACV number increases in conjunction with autophagy



ACVs contain LC3-II and usual ectoenzymes and RNA

A

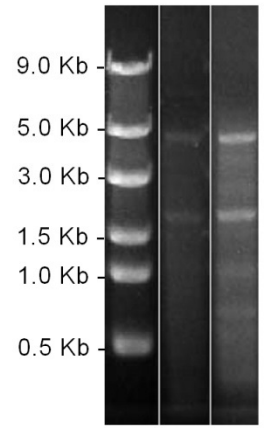
LC3

- + Rapamycin

B

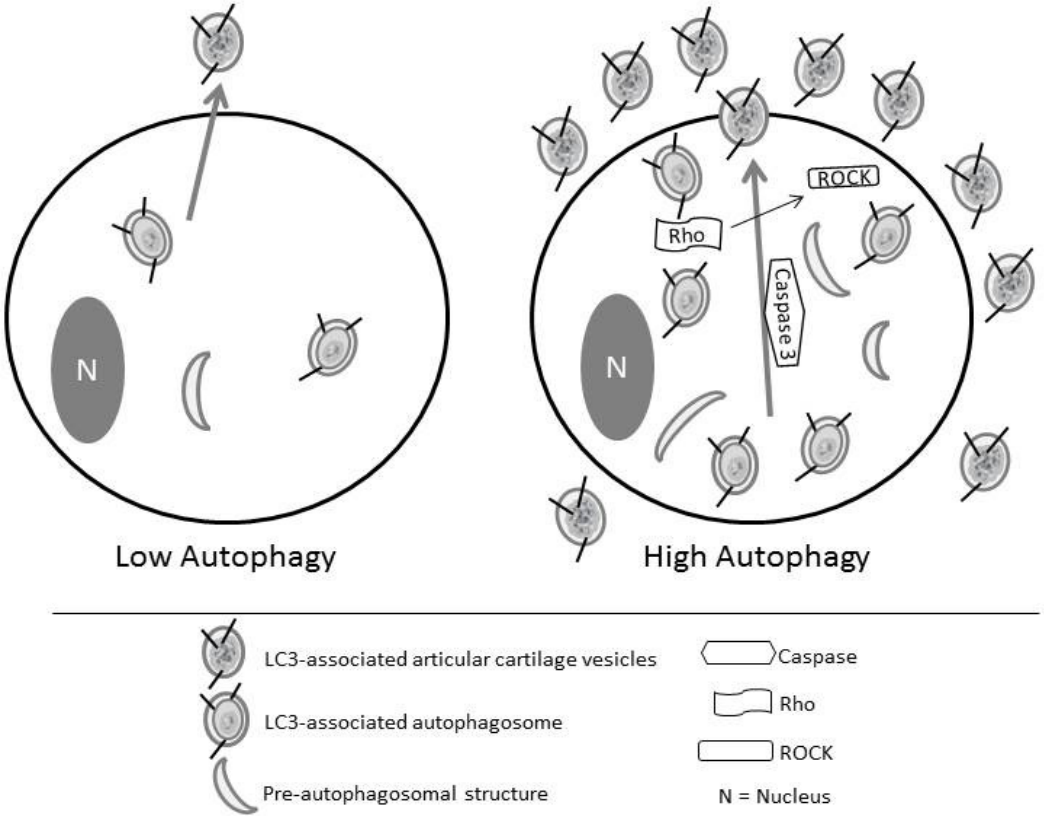
	Control	Rapamycin
Alk Phos	1.42 ± 0.1	1.23 ± 0.2
NTPPPH	339.1 ± 34.6	434.6 ± 54.4
5'NT	3.33 ± 0.1	4.27 ± 0.5

C

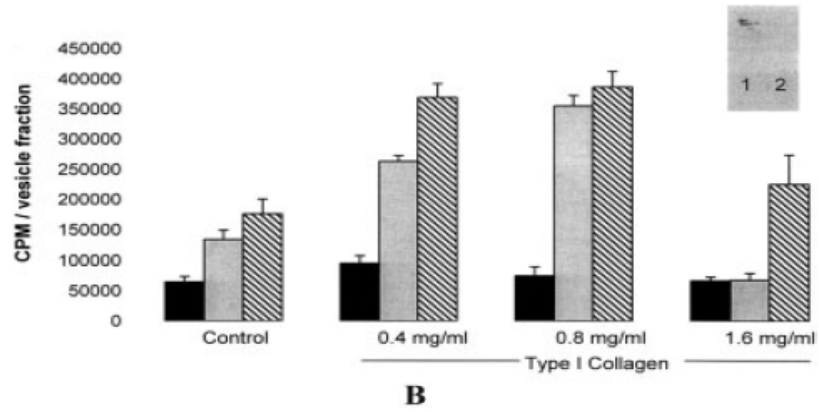


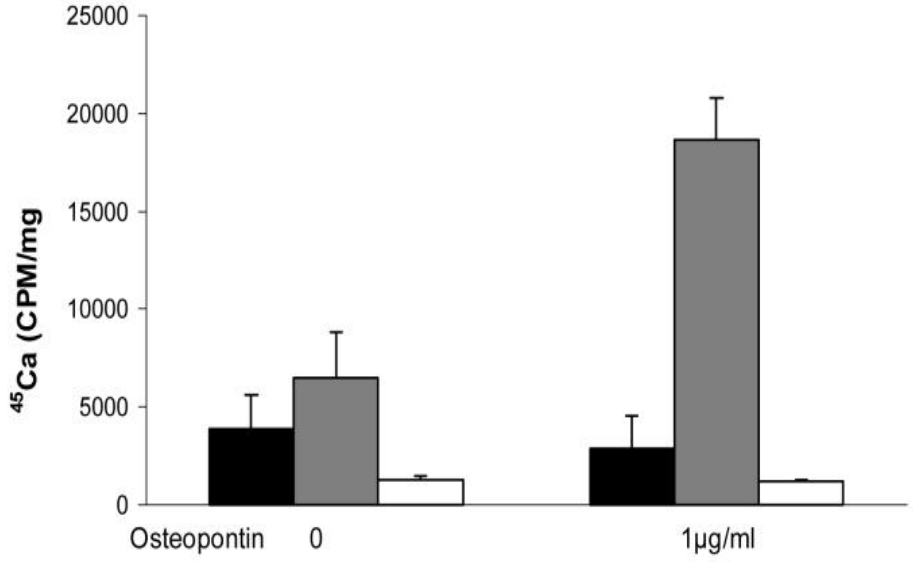
- + Rapamycin

Autophagy increases ACV formation and release in chondrocytes



Matrix matters !!

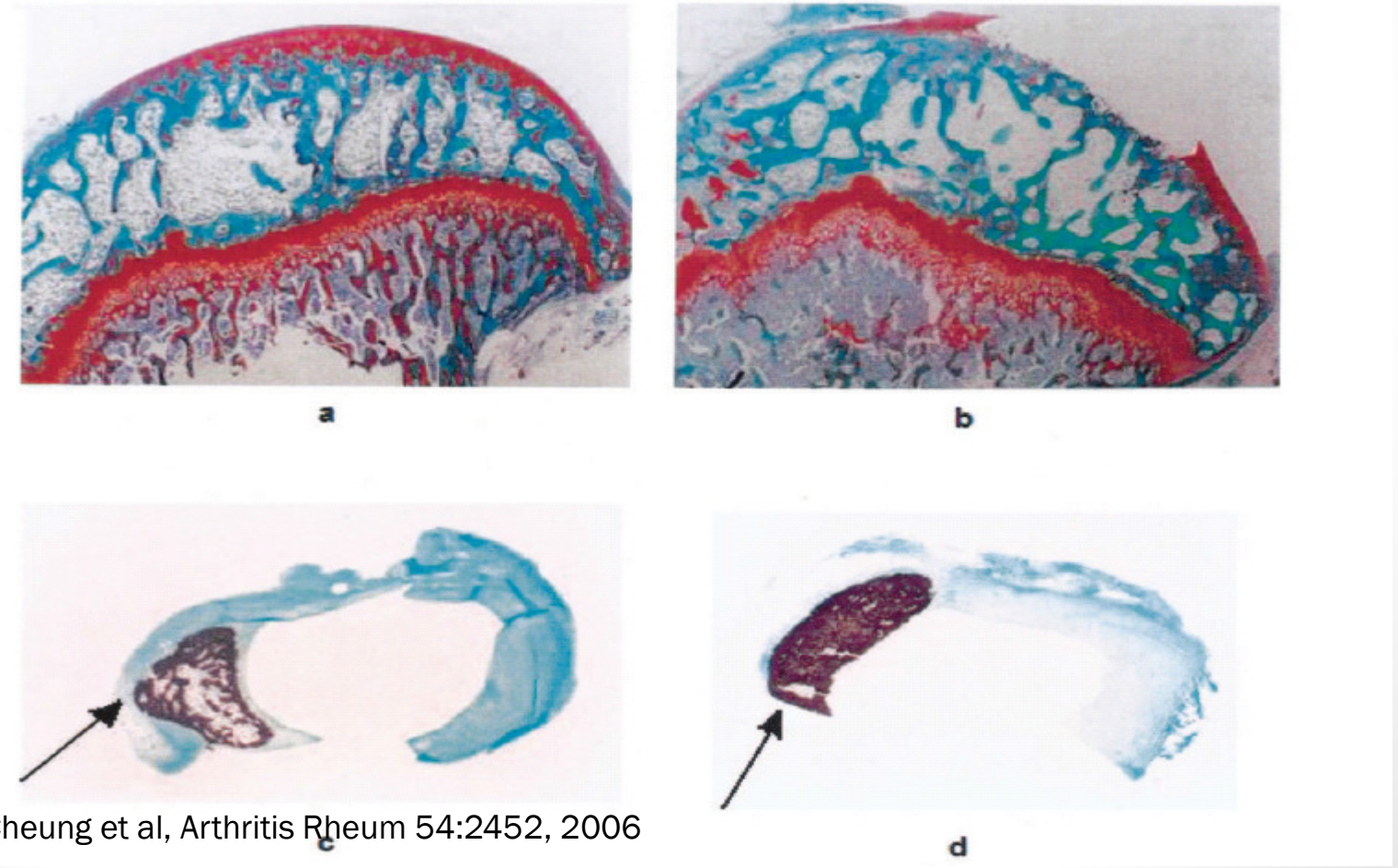




BCP crystal formation

- BCP crystals coexist with CPP crystals
- PPi/Pi ratio critically regulates which type of crystal forms.
  - Pi/PPi < 6 → CPPD
  - Pi/PPi > 140 → BCP

Meniscal calcification accelerates OA



From: Cheung et al, Arthritis Rheum 54:2452, 2006

Clinical association of vascular and cartilage calcification in CPPD suggests a systemic process

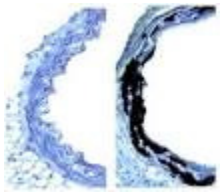


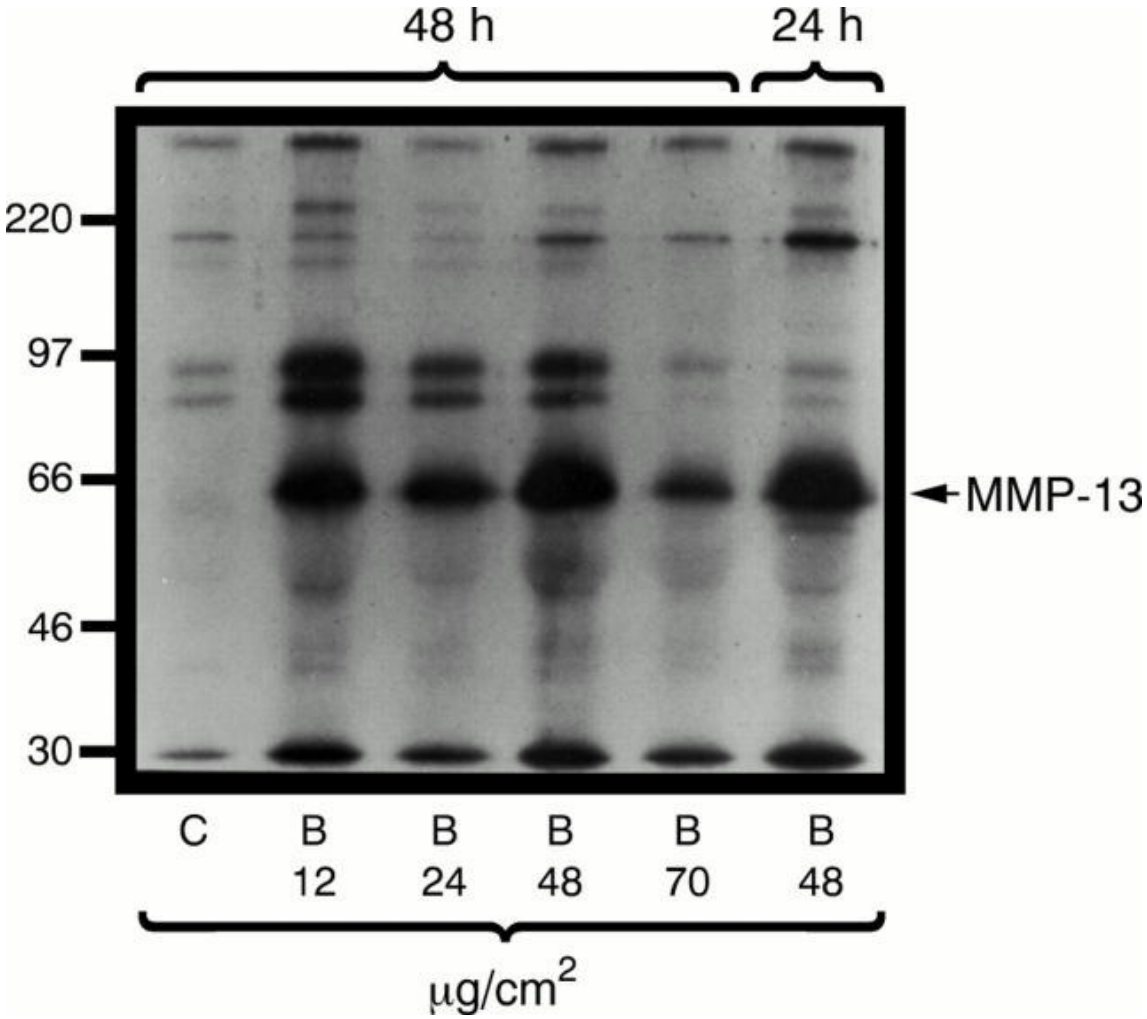
Table 2 Association between extra-articular sites of calcification and CC at any joint, and at more than one joint

Extra-articular sites with calcification	CC				Number of joints with CC			
	–	+	OR (95% CI)	aOR (95% CI)	1	>1	OR (95% CI)	aOR (95% CI)
None	2372	324	1.00	1.00	193	131	1.00	1.00
Either vascular or soft-tissue calcification	306	88	2.11 (1.62 to 2.74)	1.85 (1.40 to 2.44)	48	40	1.23 (0.76 to 1.97)	1.12 (0.67 to 1.87)
Vascular and soft-tissue calcification	23	13	4.14 (2.08 to 8.25)	3.08 (1.50 to 6.31)	9	4	0.66 (0.20 to 2.17)	0.48 (0.13 to 1.75)

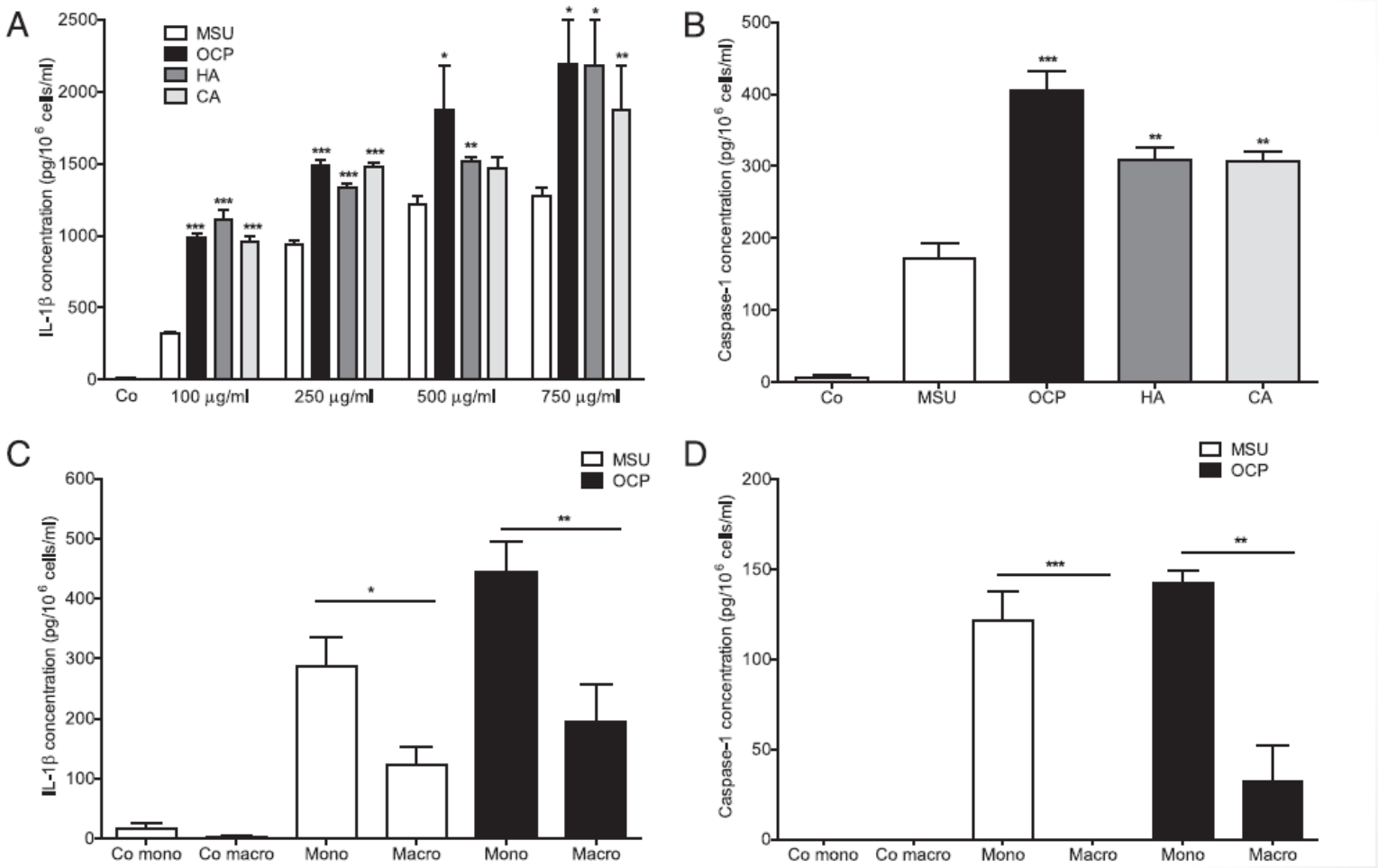
CC, chondrocalcinosis.

Abhishek A, *et al. Ann Rheum Dis* 2013;**0**:1–6. doi:10.1136/annrheumdis-2013-203400

Calcium crystals directly interact with synovial fibroblasts and chondrocytes



Calcium crystals (sometimes) induce an inflammatory response



Animal models are problematic in crystal diseases

Summary

- Crystals may cause and certainly worsen OA
- Calcium crystal- associated arthritis is under-studied and under-recognized.
- Animal models present unique challenges in crystal-induced arthritis.
- Crystals are interesting and important !!

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