RENCONTRES EN IMMUNOLOGIE & IMMUNOTHERAPIE PRATIQUES

Calcinoses sous cutanés: quels mécanismes? Quel espoir thérapeutique?

Hang Korng EA

Paris

29 et 30 SEPTEMBRE 2022
UIC-P - Espaces Congrès
16, rue Jean Rey - 75015 Paris

Sous l'égide de :

Conflits d'intérêts

Subventions recherches : pfizer, Abbvie, MSD, Janssen, Medac

Subventions congrès : pfizer, Abbvie, MSD, Janssen, Lilly, Novartis, Sandoz, Medac, Grunenthal

Interventions ponctuelles : pfizer, sandoz, Ipsen

Calcinoses

- Les 2 différents types de calcifications calciques
- Quelques exemples dont DM
- Le rôle des ions Ca2+, Pi, PPi
- Les pistes des traitements de réduction calcique
    - Le PPi
    - Le thiosulfate de sodium
- Points clés

Calcifications ectopiques

Cristaux de phosphate de calcium (PC)

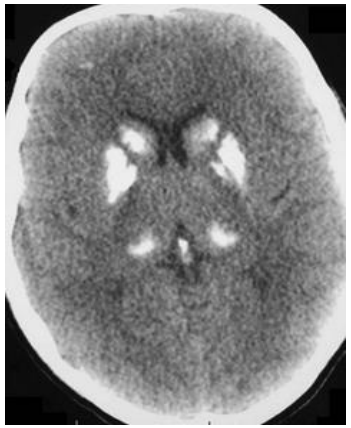
- Distrophique
- Métastatique
- Idiopathique

Cristaux de pyrophosphate de calcium (PPC)

- Age
- Hypophosphatasie, hypomagnésémie (Gitelman), hémochromatose, familial, hyperparathyroïdie

Cristaux de phosphate de calcium (PC)

- **Différents types de cristaux de PC**
  - Hydroxyapatite
  - Apatite carbonatée
  - Octacalcium phosphate (OCP)
  - Tricalcium de phosphate
  - Whitlockite

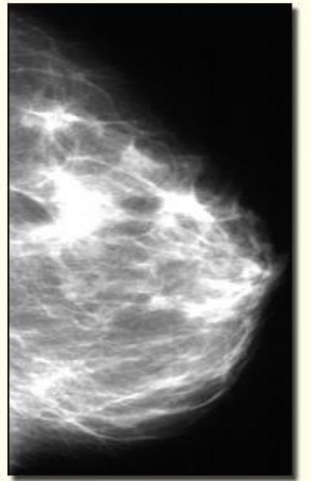


- **Maladies génétiques**

  IPPSD, CTFH, GACI, PXE…

- **Maladies inflammatoires**

  Dermatomyosite, sclérodermie



Calcinose et dermatomyosite

Fréquence

30 à 70 % dans la forme juvénile, plus rare dans la forme adulte

Localisation

Ubiquitaire, zones de frottement

Surviennent à tout moment de la maladie, en moyenne entre 1 et 3 ans après le début de la maladie

FdR associés

Retard dg, inflammation persistante, faible dose initiale CT, CPK élevé, anti-NXP2

Calcifications, hypothèses de formation

Vieillissement

Génétique

F. environnementaux

Altérations ɛ

Vieillissement

Génétique

F. environnementaux

Déséquilibre facteurs pro- et anti-calcifiants

Calcification

Altération homéostasie Ca2+, Pi et PPi

PPi, fétuin A, MGP, Ostéopontine, protéoglycanes…

Intestin, os, rein

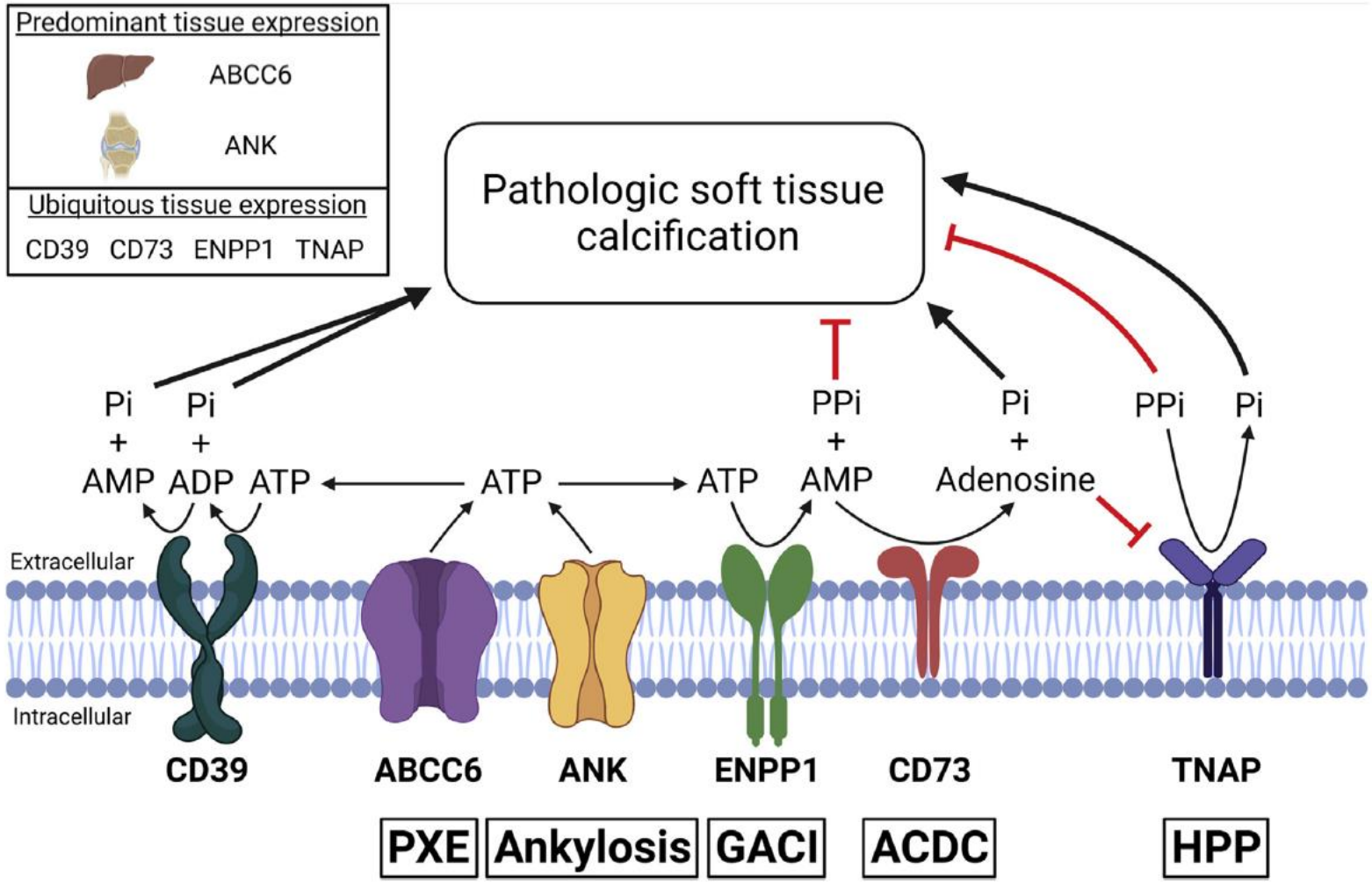
Altération de la MEɛ

Vieillissement

Génétique

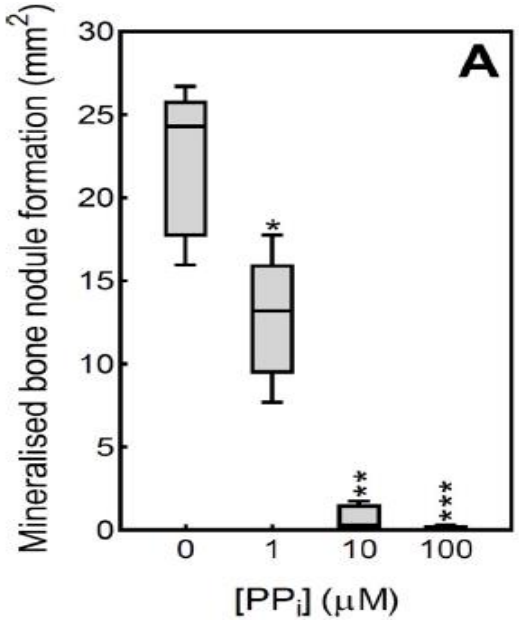
F. environnementaux

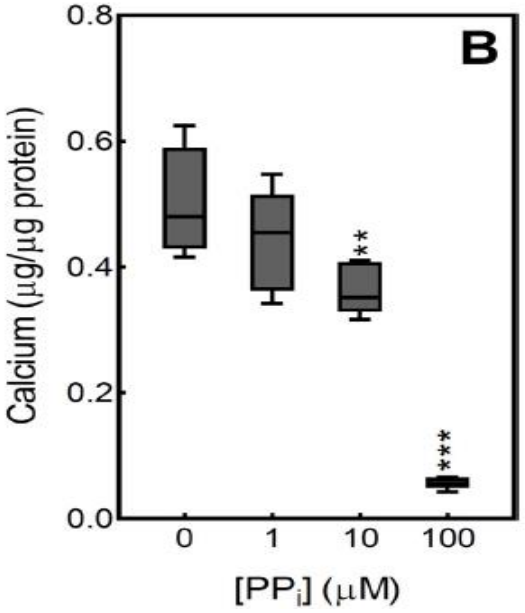
Equilibre PPi/Pi et calcification

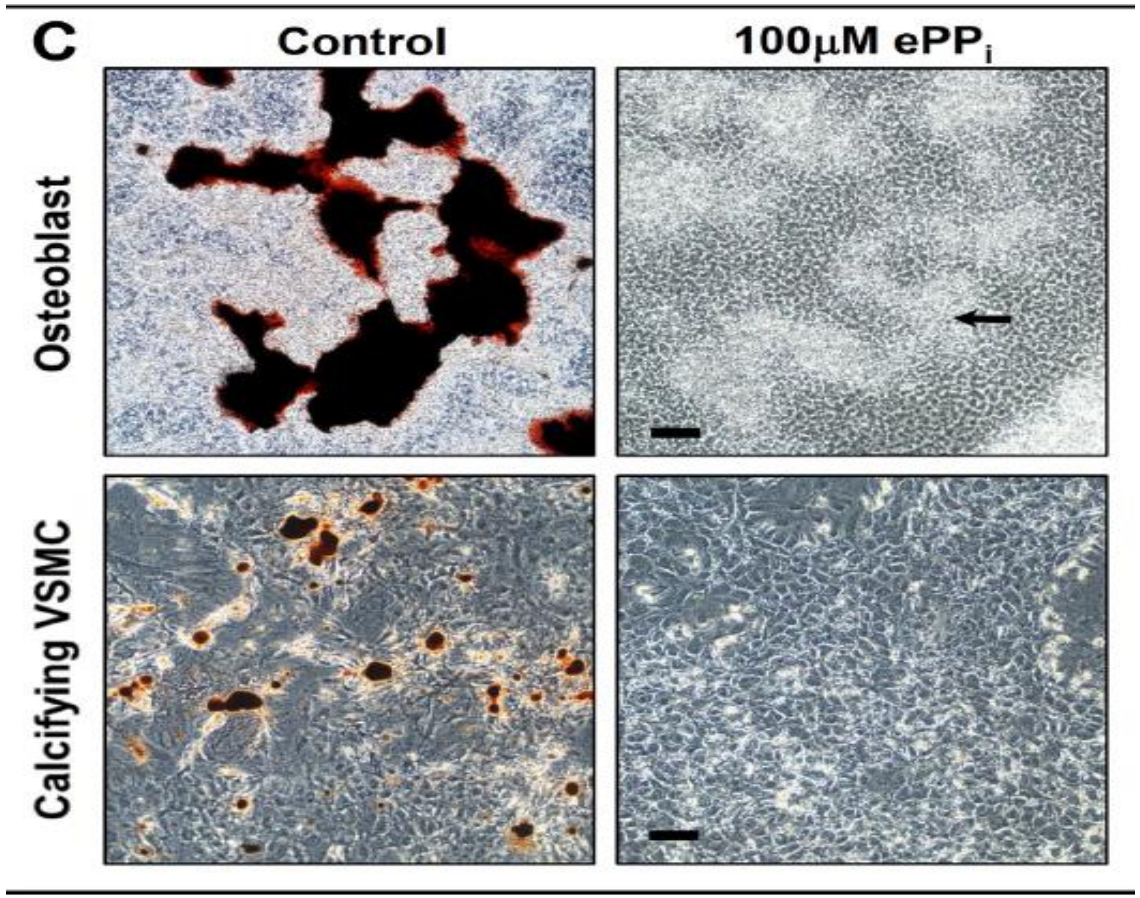


Ralph D 2022 Am J Pathol

Réduction des calcifications: le PPi ?







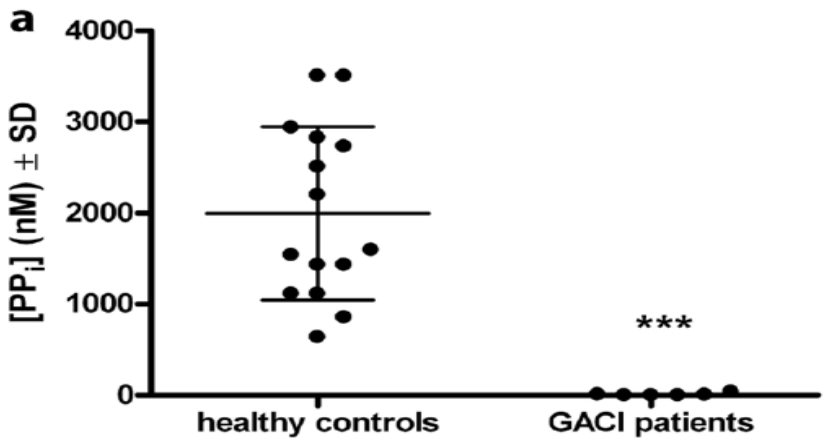
Orriss 2020 Bone

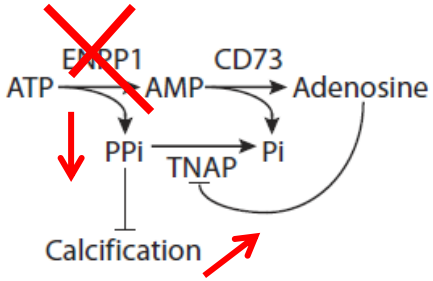
Diminution des PPi et calcifications

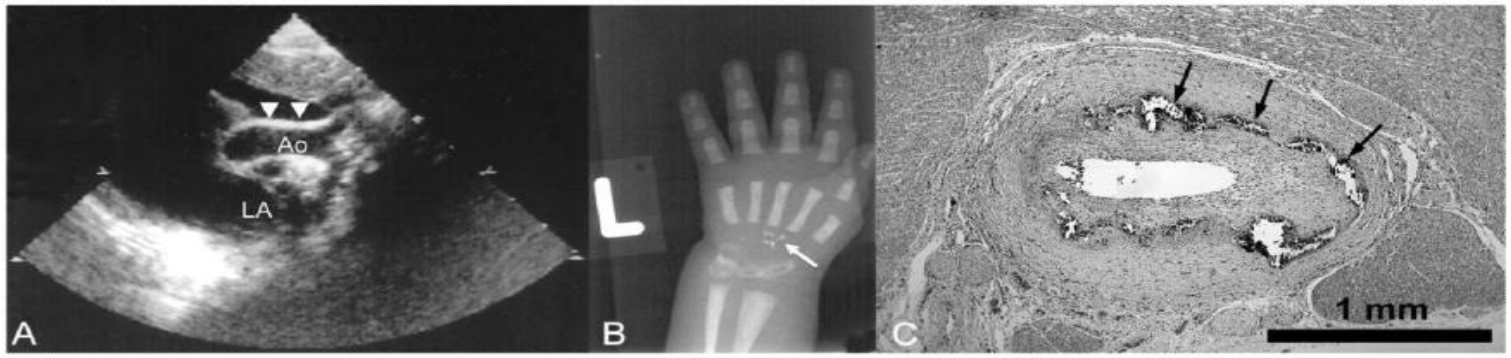
Mutations in *ENPP1* are associated with 'idiopathic' infantile arterial calcification

Rutsch F et al.

2003 NATURE GENETICS

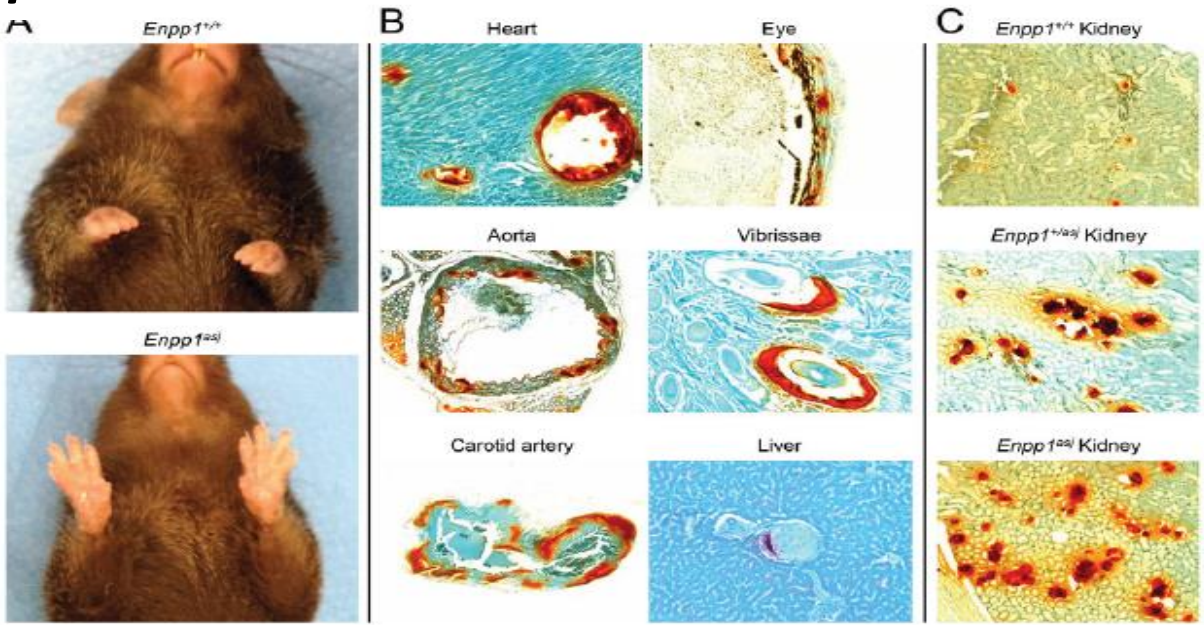


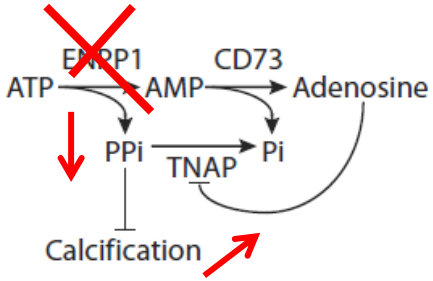




Diminution des PPi et calcifications

Mouse GACI model *Enpp1^{asj}*





Parameter	Concentration (mean ± s.e.m.)		
	Enpp1$^{+/+}$ (*n*=9)	*Enpp1$^{+/asj}$* (*n*=9)	*Enpp1^{asj}* (*n*=6)
Calcium (mg/dl)	10.81±0.17	10.27±0.21	10.87±0.27
Phosphorus (mg/dl)	6.82±0.31	7.10±0.58	9.83±2.00
Ca:P_i ratio	1.61±0.06	1.52±0.13	1.29±0.20
PP_i (mg/dl)	0.73±0.13	0.33±0.03*	0.13±0.02*
PP_i:P_i ratio (×100)	9.70±1.90	4.67±0.50**	1.80±0.40*

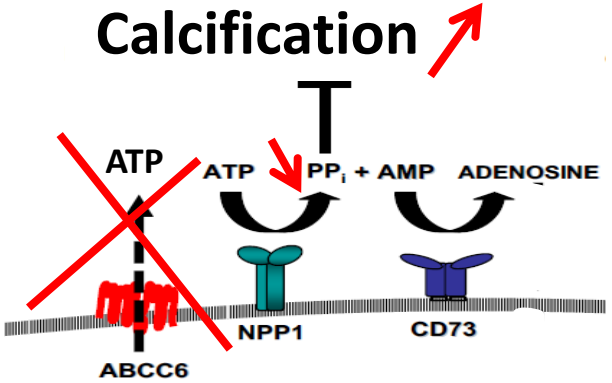
Li 2013 Dis Mod Mechan

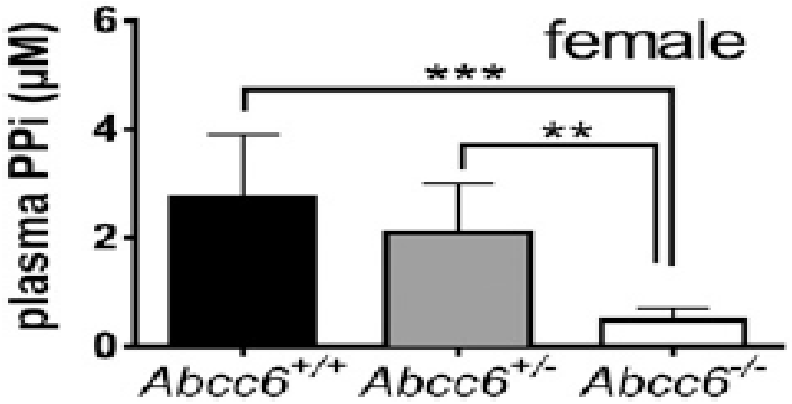
Diminution des PPi et calcifications

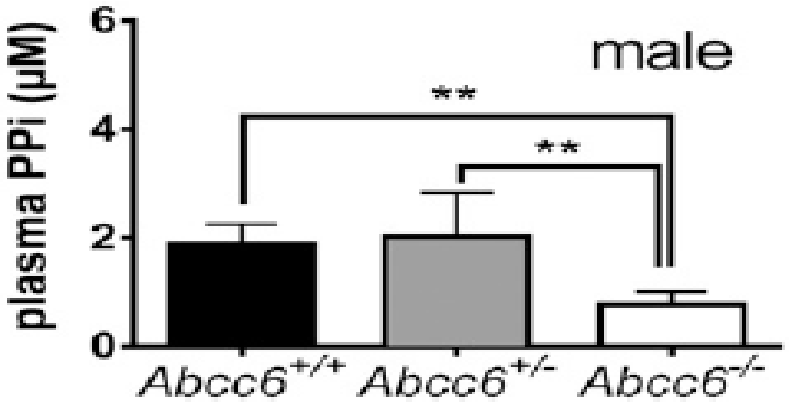
European Journal of Human Genetics (2003) 11, 215–224
© 2003 Nature Publishing Group All rights reserved 1018-4813/03 $25.00
www.nature.com/ejhg

ARTICLE

ABCC6/MRP6 mutations: further insight into the molecular pathology of pseudoxanthoma elasticum







Original article

Inorganic pyrophosphate is reduced in patients with systemic sclerosis

Vivien M. Hsu[1], Eszter Kozák[2,*], Qiaoli Li[3,*], Márta Bocskai[4], Naomi Schlesinger[1], Ann Rosenthal[5], Scott T. McClure[6,7], László Kovács[4],

Rheumatology key messages

- Circulating inorganic pyrophosphate binds directly to hydroxyapatite crystal to inhibit its growth.
- We found reduced circulating inorganic pyrophosphate levels in scleroderma patients with or without calcinosis.
- This may contribute to pathophysiology of calcinosis and administering inorganic pyrophosphate may be a therapeutic strategy.

	No SSc	SSc – diffuse cutaneous	SSc – limited cutaneous	Total	*P*-Anova
US cohorts					
n (%)	15 (15.6)	40 (41.7)	41 (42.7)	96 (100.0)	
Female, *n* (%)	12 (80.0)	33 (82.5)	34 (82.9)	79 (82.3)	0.967
Age, mean (S.D.), years	57.2 (17.3)	54.1 (12.4)	56.5 (13.1)	55.6 (13.5)	0.636
Calcinosis, *n* (%)		16 (40.0)	17 (41.5)	33 (40.7)	0.893[b]
Disease duration,[a] mean (S.D.), years		8.9 (8.4)	12.8 (8.0)	10.9 (8.4)	**0.036**[b]
PPi ATPS assay, mean (S.D.)	1.2 (0.3)[A]	1.0 (0.2)[B]	1.1 (0.2)[A]	1.1 (0.2)	**0.003**
Hungarian cohort					
n (%)	26 (36.6)	19 (26.8)	26 (36.6)	71 (100.0)	
Female, *n* (%)	23 (88.5)	15 (78.9)	25 (96.2)	63 (88.7)	0.197
Age, mean (S.D.), years	61.9 (10.8)	58.3 (12.5)	61.5 (10.2)	60.8 (11.0)	0.515
Calcinosis, *n* (%)		10 (52.6)	11 (42.3)	21 (46.7)	0.493[b]
Disease duration,[a] mean (S.D.), years		8.1 (6.0)	13.5 (8.4)	11.2 (7.9)	**0.022**[b]
PPi ATPS assay, mean (S.D.)	1.7 (0.3)[A]	1.4 (0.3)[B]	1.4 (0.4)[B]	1.5 (0.3)	**<0.001**

Bold indicates statistically significant at the $P < 0.05$ level. Different superscript upper-case letters indicate groups are statically significantly different by Tukey's HSD at the $P < 0.05$ level. PPi: inorganic pyrophosphate. [a]Years from onset of non-Raynaud's symptoms. [b]*P*-value from *t* test.

Calcinose, quels traitements médicaux ?

Réduction de l'inflammation

Anti-IL-1

Anti-IL-6R ?

AINS, colchicine, corticoïdes

Réduction des cristaux

Pyrophosphate ?

Sodium Thiosulfate ?

Bisphosphonate, inhibiteurs canaux calciques, probénécide, minocycline, cyclosporine, colchicine, NSAID, carbon dioxide laser, corticosteroide, anti-TNF, anti-CD20…

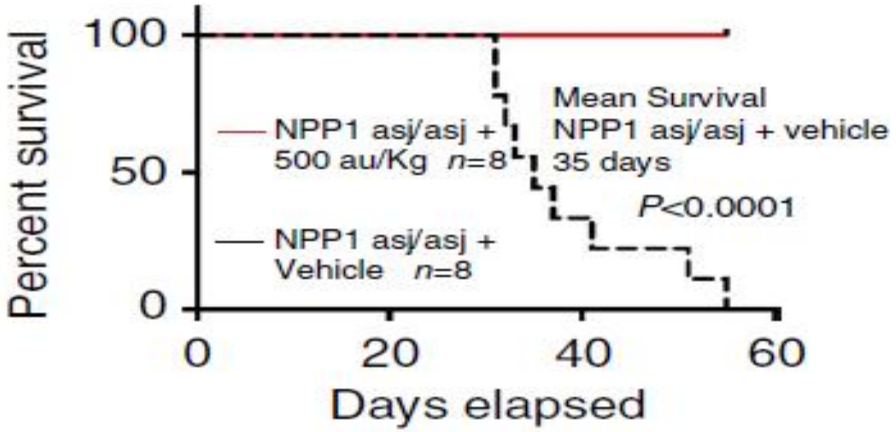
Réduction des calcifications: le PPi ?

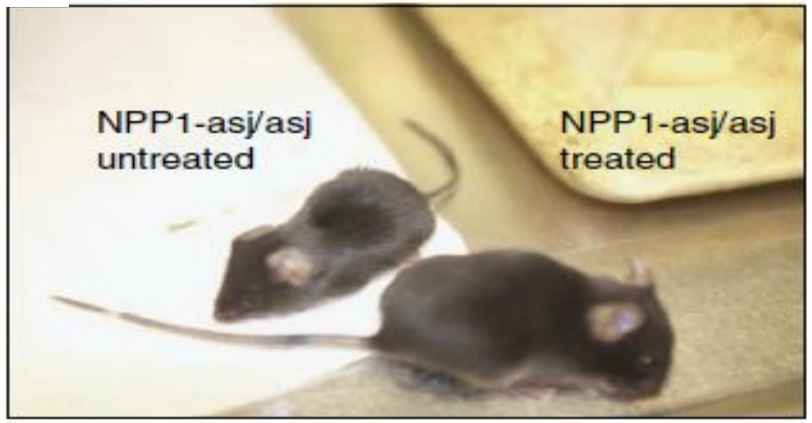
ARTICLE
Received 11 May 2015 | Accepted 23 Oct 2015 | Published 1 Dec 2015
DOI: 10.1038/ncomms10006 OPEN

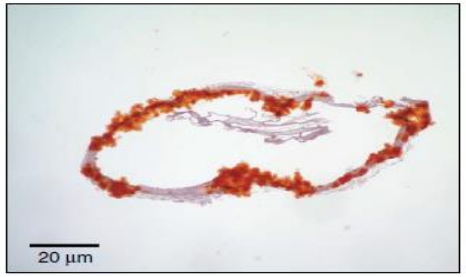
ENPP1-Fc prevents mortality and vascular calcifications in rodent model of generalized arterial calcification of infancy

nature COMMUNICATIONS

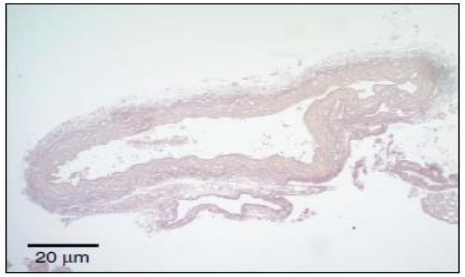
Albright R et al. 2015



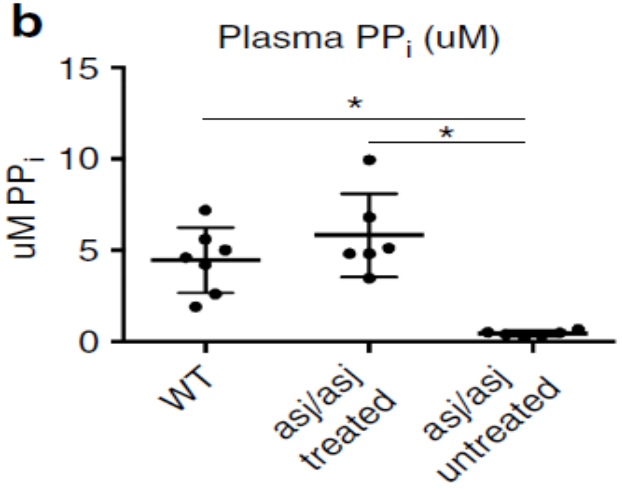




b



b



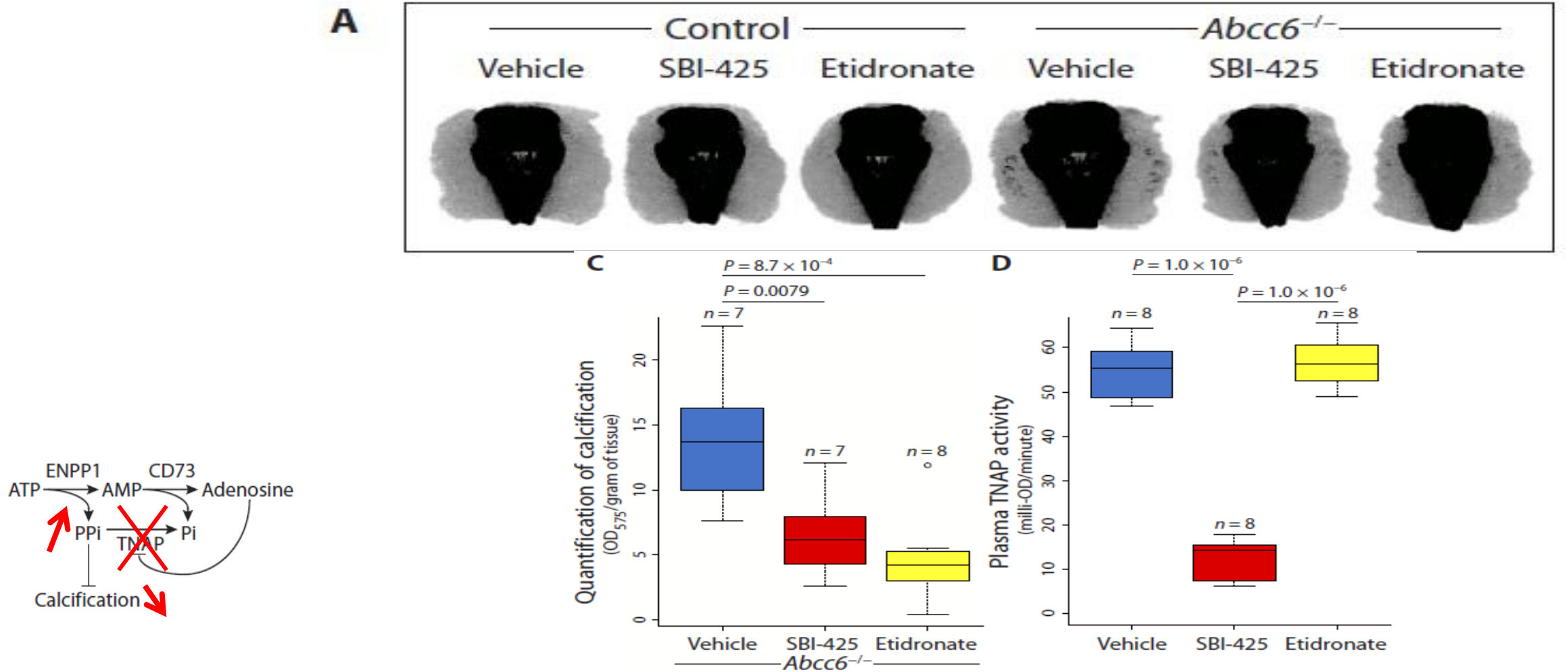
Réduction des calcifications: le PPi ?

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

GENETIC DISORDERS

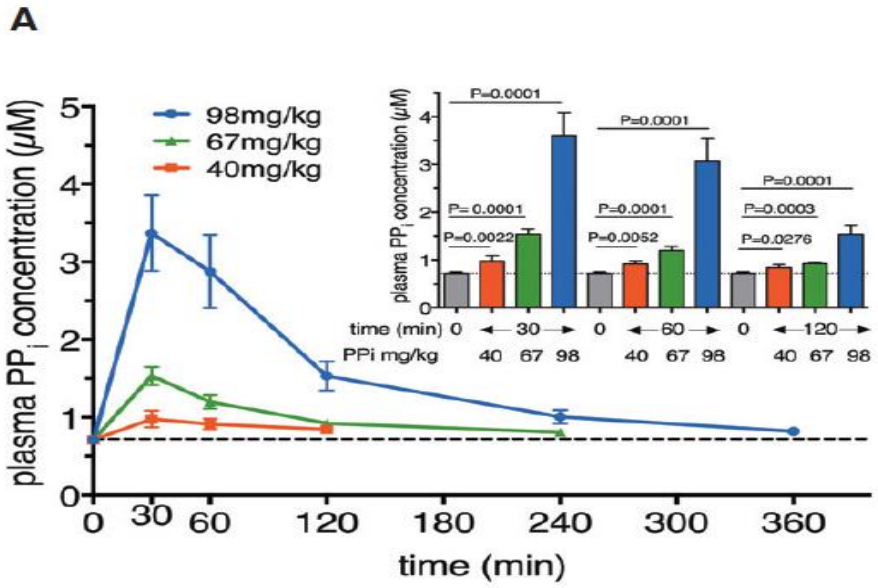
Ectopic calcification in pseudoxanthoma elasticum responds to inhibition of tissue-nonspecific alkaline phosphatase

Ziegler et al. 2017

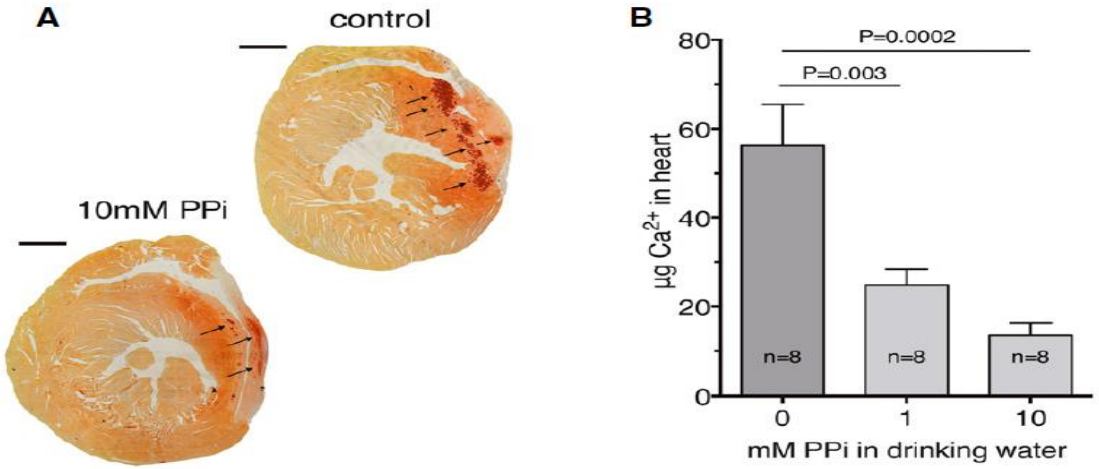


Réduction des calcifications: le PPi ?

Augmentation PPi plasmatique après administration orale chez volontaires sains



Eau enrichie en PPi diminue les calcifications des souris *Abcc6-/-*



Dedinszki 2017 Embo Mol Med

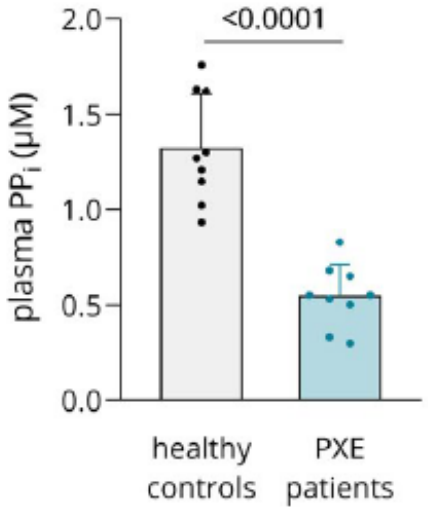
RESEARCH ARTICLE

Experimental Dermatology WILEY

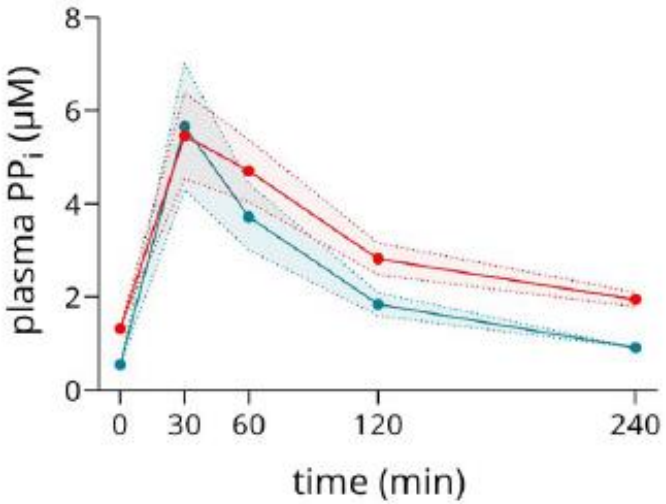
Oral supplementation of inorganic pyrophosphate in pseudoxanthoma elasticum

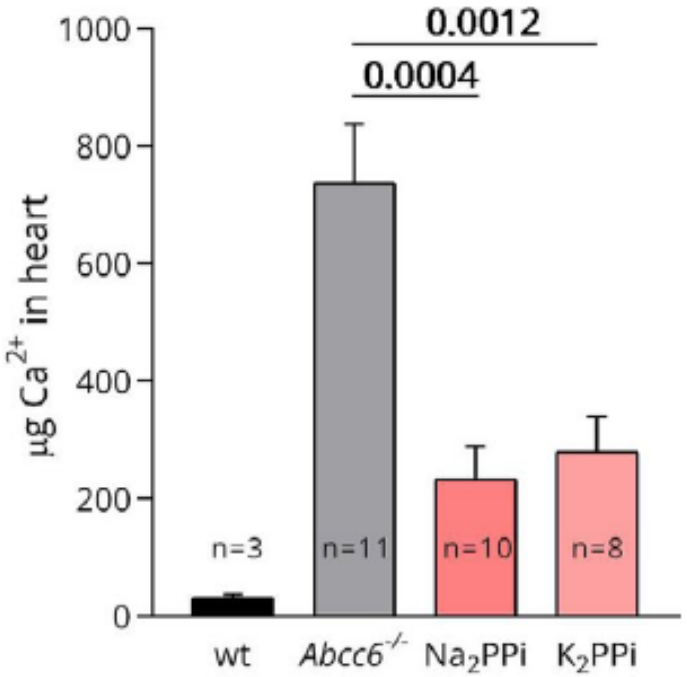
Kozak E 2022 Exp Dermatol

Etat basal



PPi encapsulé, 40 mg/kg





Réduction des calcifications cardiaques chez souris traitées par gavage de PPi

Calcinose, quels traitements médicaux ?

Réduction de l'inflammation

Anti-IL-1

Anti-IL-6R ?

AINS, colchicine, corticoïdes

Réduction des cristaux

Pyrophosphate ?

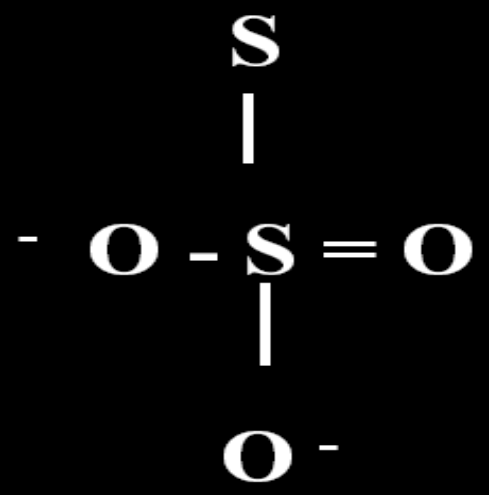
Sodium Thiosulfate ?

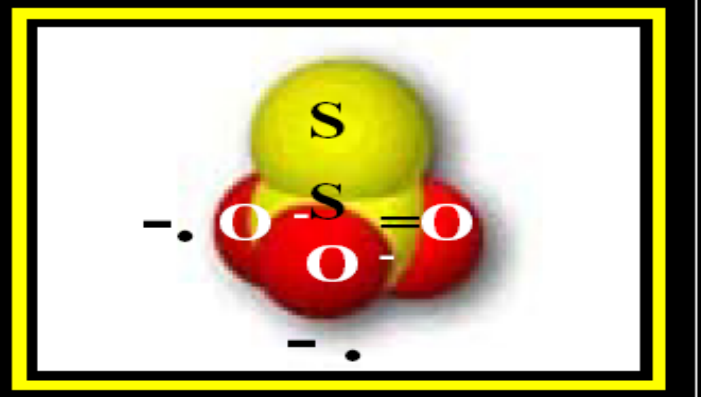
Bisphosphonate, inhibiteurs canaux calciques, probénécide, minocycline, cyclosporine, colchicine, NSAID, carbon dioxide laser, corticosteroide, anti-TNF, anti-CD20…

Sodium Thiosulfate

2 Na+

Ca^{++}





(5 H2O2) peroxide

(O2 - .) superoxide

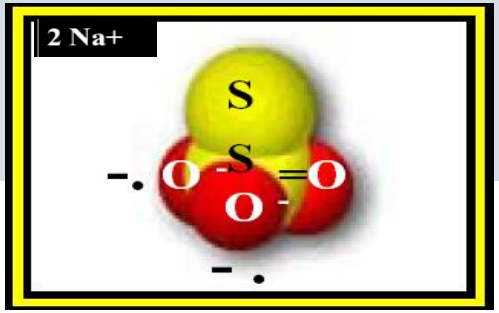
1 GSSG + 2 Na2S2O3 ----------→ 4 NaHSO4 + 2 GSH + 2 H2O

Oxidized glutathione *Glutathione reductase* *glutathione*

Ca^{++} $S\text{-}SO_3{}^{2-}$: Calcium Thiosulfate

Hayden 2005 Cardiovascular Diabetology

Sodium thiosulfate



Antidote des empoisonnements au cyanure

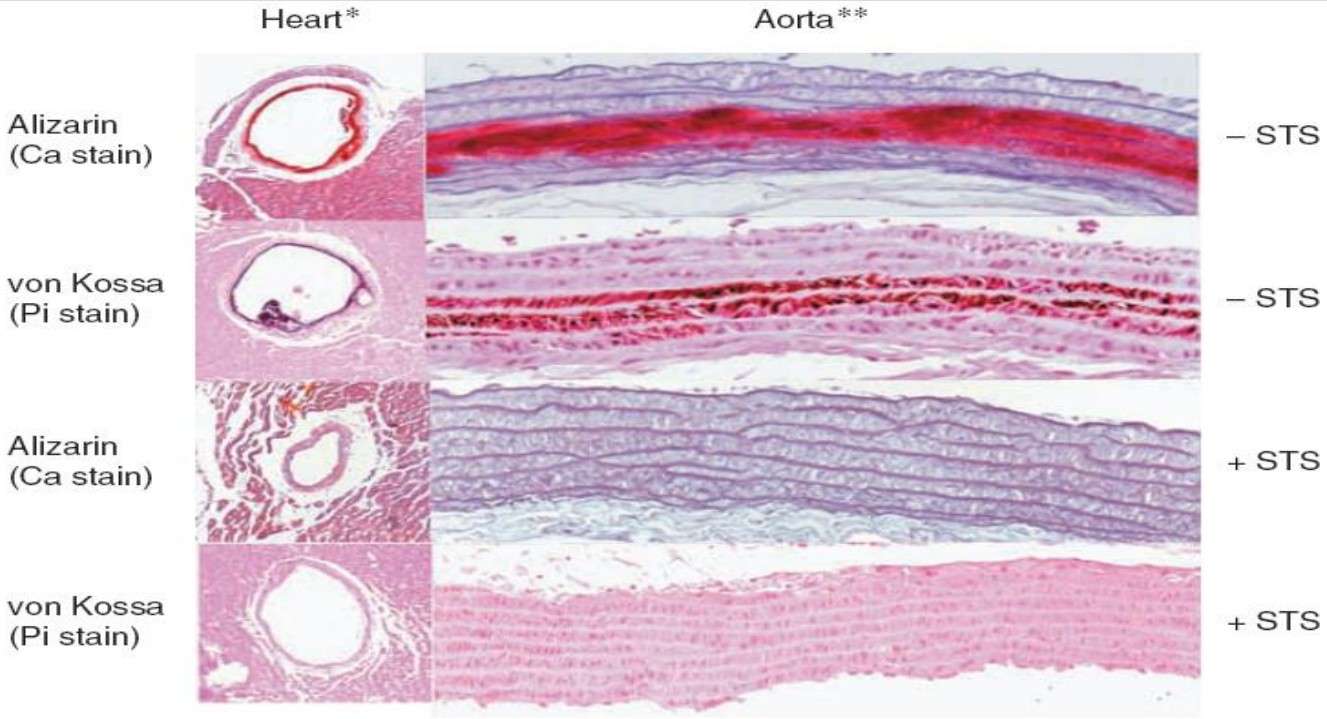
Application locale pour acné et pityriasis versicolor

Prévention des toxicités des carboplatines et cisplatines

Proposé dans :

- Calcification vasculaire au cours de MRC
- Artériolopathie urémique calcifiante (CUA)
- Calcinose tumorale urémique
- CTFH
- Sclérodermie systémique et DM

TSS prévient les calcification de l'aorte chez les rats urémiques



	Nonuremic controls (n=12)	Uremic controls*** (n=11)	Early treatment*** (n=10)	Late treatment*** (n=8)
Uremia	–	+	+	+
STS treatment	+	–	+	+
Aortic wall				
Presence of histologic calcifications (n)	2	8	0	0
Severity of calcification	++ (n=1) +++ (n=1)	+++ (n=8)		

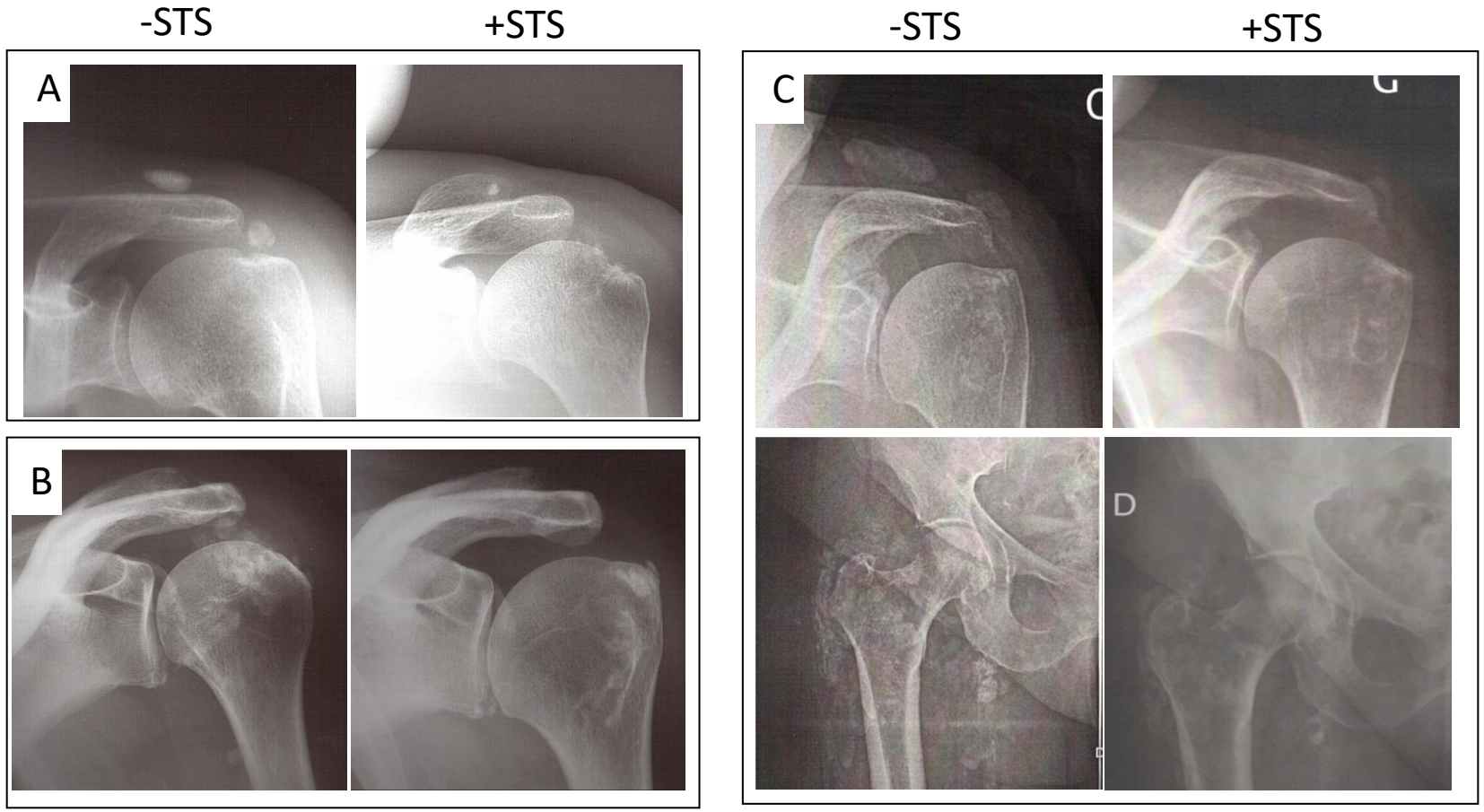
STS, sodium thiosulfate.
Number of animals (n) with aortic calcifications assessed by histology in each treatment group and severity of calcifications (none, +, ++, +++).
***Fisher's exact test $P<0.001$ for the comparison of STS-treated versus untreated uremic animals (0 of 18 versus 8 of 11).

Pasch 2008 Kidney International

TSS dans les calcinoses tumorales urémiques

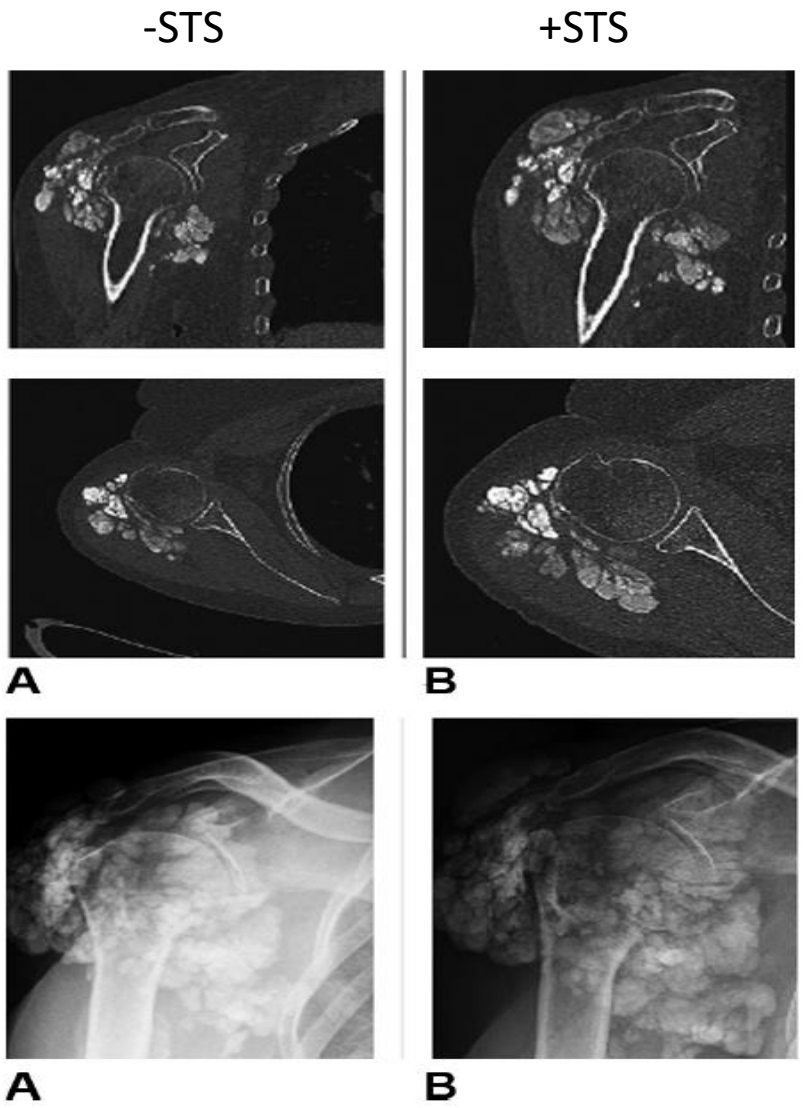
4 patients, calcinoses tumorales symptomatiques

STS 10-20g/session de dialyse



Malbos 2013 Rheumatology

TSS dans sclérodermie systémique et DM



Quel schéma proposé aux patients non dialysés?

Schéma thérapeutique

17 à 20 g TSS IV/j
5j/mois
6 cycles

4 pts (1 SS, 2 DM, 1 Lupus), 3 adultes and 1 enfant (11y)
TSS diminue les douleurs chez 3 pts

Mais…les calcinoses restent inchangées…

Margeau 2016 Joint Bone Spine

TSS dans sclérodermie systémique et DM

Femme 27 ans

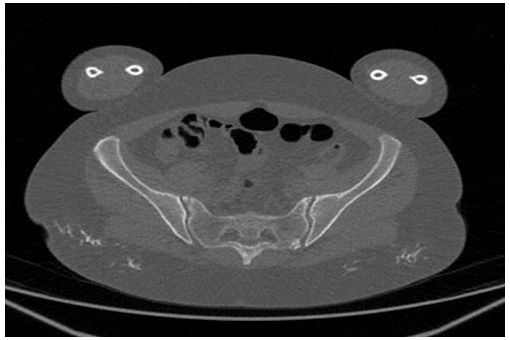
2017: DM, anti-NXP2 +

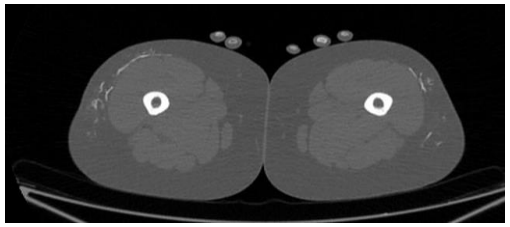
CT 1 mg/kg 2018
IgIV 9 Cures 2018
Ritux 1000 mg 2019

2017 : calcinoses avec douleur inflammatoire

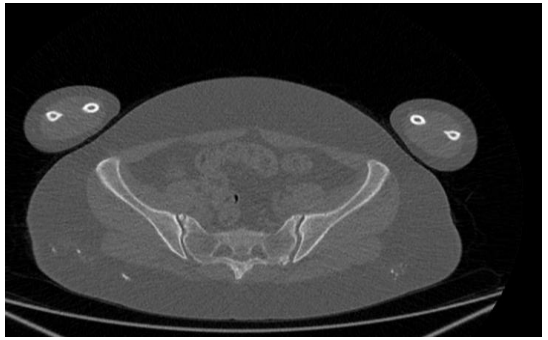
TSS 20 g/semaine : T0 10/2019

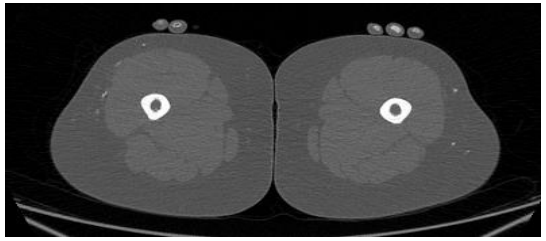
4/10/19





23/04/21

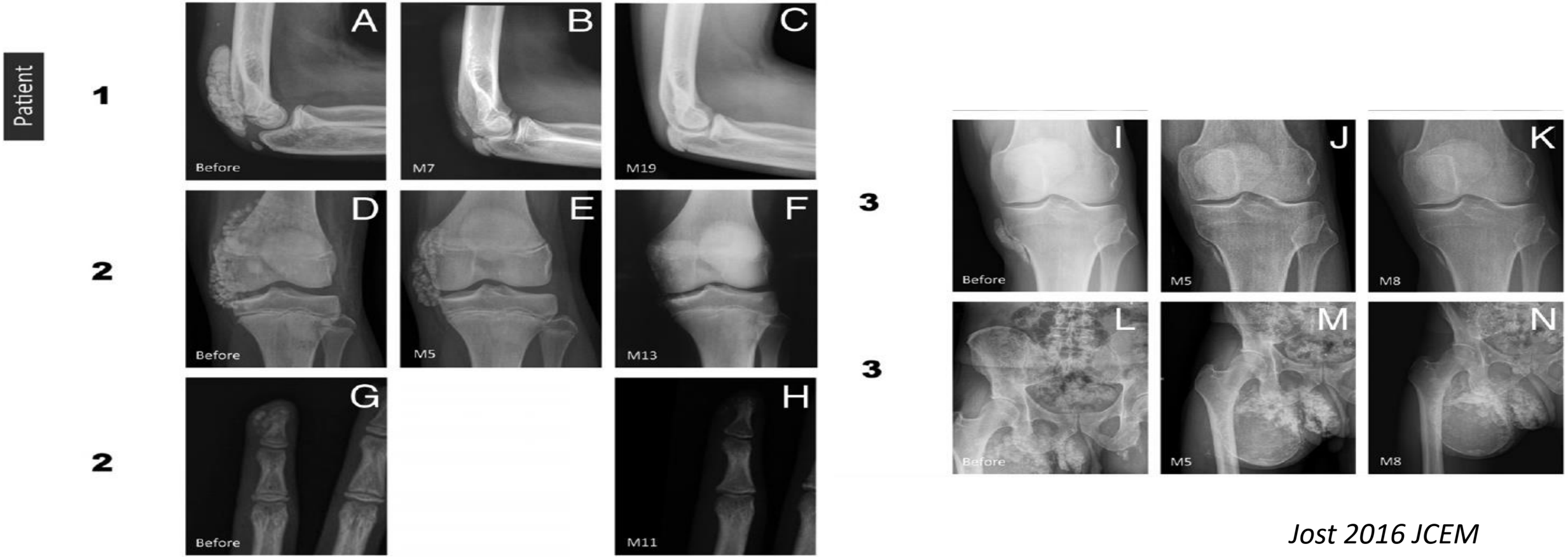




TSS en topique dans les CTFH

Table 1. biochemical presentation of patients at diagnosis

Serum levels	Calcium (mmol/liter)	Phosphate (mmol/liter)	Parathormone (pg/ml)	25 OH Vit D (ng/ml)	Alcaline Phosphatases (UI/liter)
Patient 1	2.66	2.42	10.7	31.6	155
Patient 2	2.57	1.78	36	50	307
Patient 3	2.43	1.79	15	33	ND



Jost 2016 JCEM

2021

Concise report

CED
Clinical and Experimental Dermatology

Topical sodium thiosulfate for calcinosis cutis associated with autoimmune connective tissue diseases: the Mayo Clinic experience, 2012–2017

J. E. Ma,[1] F. C. Ernste,[2] M. D. P. Davis[3] and D. A. Wetter[3]

[1]Mayo Clinic School of Medicine, Mayo Clinic College of Medicine and Science, Rochester, MN, USA and [2]Division of Rheumatology and [3]Department of Dermatology, Mayo Clinic, Rochester, MN, USA

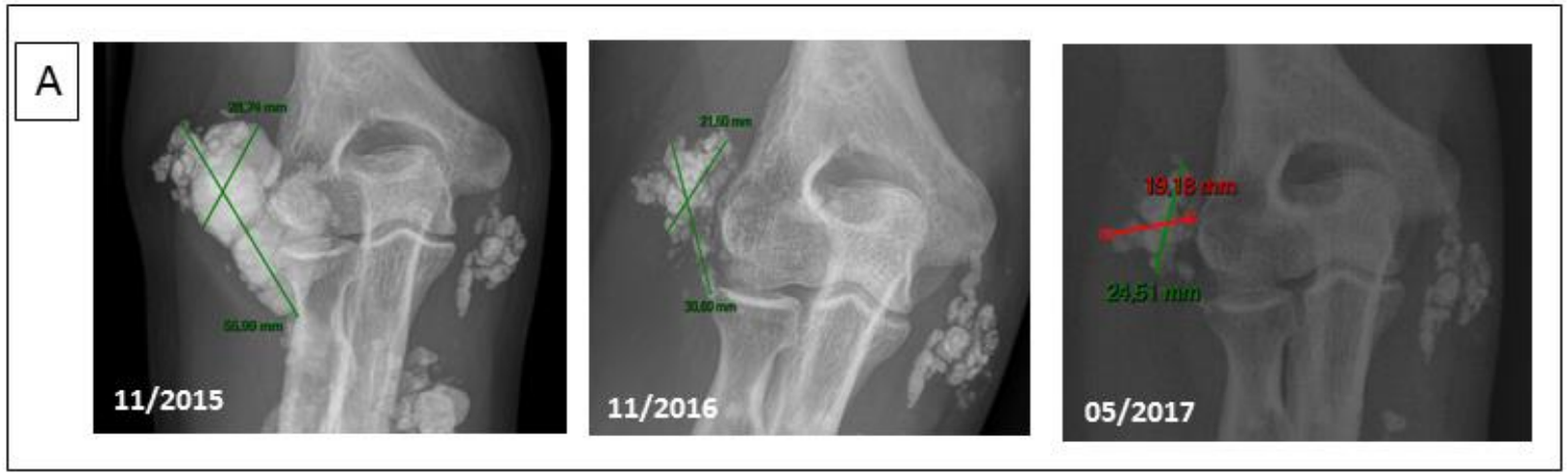
Parameter	CR, *n*	PR, *n*	NR, *n*	UR, *n*	Total, *n* (%)
Overall[a]	2	17	7	2	28[b]
Frequency of application					
Twice daily	1	14	6	2	23 (82)
Three times daily	1	3	1	0	5 (18)
Anatomical sites of involvement					
Hands/feet	0	7	3	1	11 (39)
Extremity	1	8	3[c]	1	13 (46)
Trunk	1	0	0	0	1 (4)
Multiple sites[d]	0	2	1	0	3 (11)
Ulceration of CC					
Yes	2	10	4	1	17 (61)
No	0	7	3	1	11 (39)
Concurrent use of other treatments during TST treatment[i]					
Medication(s) reported to improve CC	0	5[j]	2	2	9 (32)
Wound care dressings	0	6	2	0	8 (29)
None	2	9	2	0	13 (46)

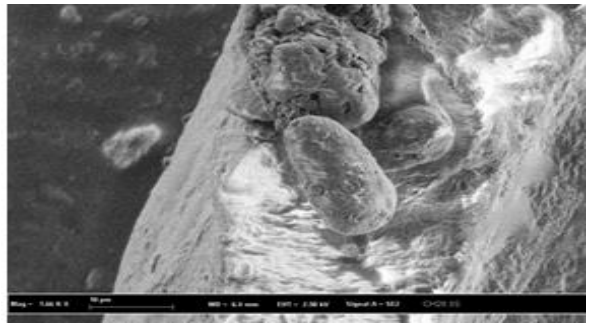
ACTD	*n* (%)
Dermatomyositis, juvenile	1 (4)
SS with cutaneous scleroderma	15 (54)
Diffuse	3 (11)
Limited	12 (43)
Overlap CTD	4 (14)*
Undifferentiated CTD	4 (14)†
Lupus erythematosus	2 (7)
Systemic	1 (4)
Cutaneous	1 (4)‡
Rheumatoid arthritis	2 (7)
Classic	1 (4)
Juvenile	1 (4)

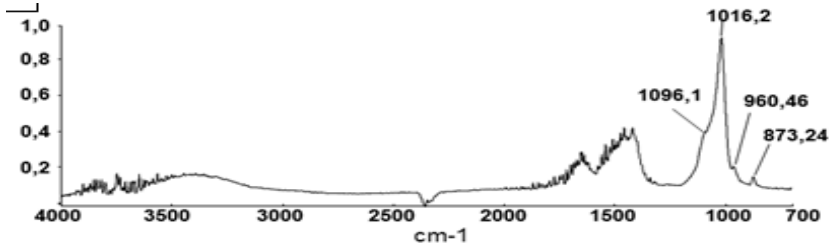
TSS injection intralésionnelle

- DM, 44 ans, calcinoses diffuses, handicapantes, résistantes à multiples traitements

- **TSS injectable** → Régression majeure des calcinoses en 18 mois







Goossens J 2018 Sem Arthritis Rheum

Comment le TSS diminue les calcifications ?

Hypothèses

Anti-oxydant *Hayden 2010 Cardiovascular Diabetology*

Chélation du calcium *Pasch 2008 Kidney International*

Production H2S *Marutani 2015 J Am Heart Assoc*

Stimulation eNOS *Hayden 2010 Cardiovascular Diabetology*

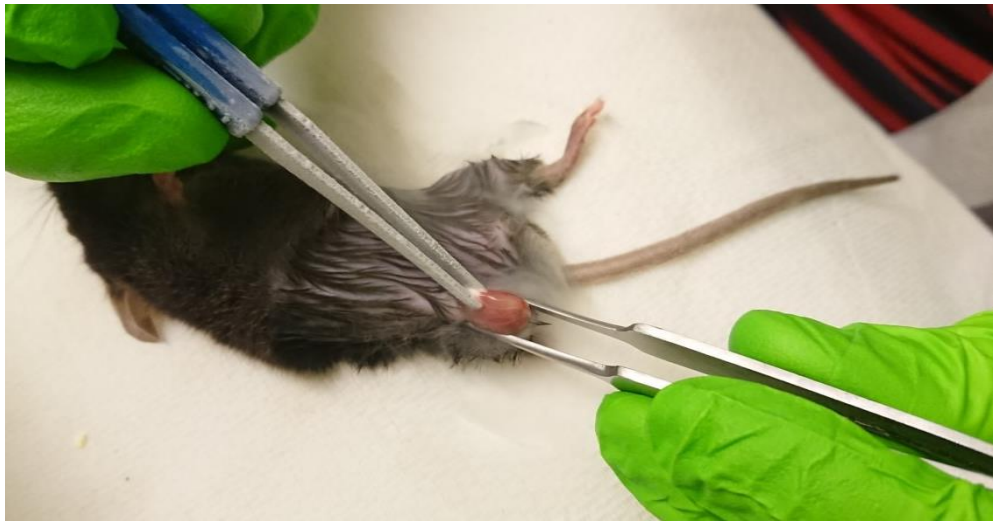
Induction d'inhibiteur de la minéralisation *Pasch 2008 Kidney International*

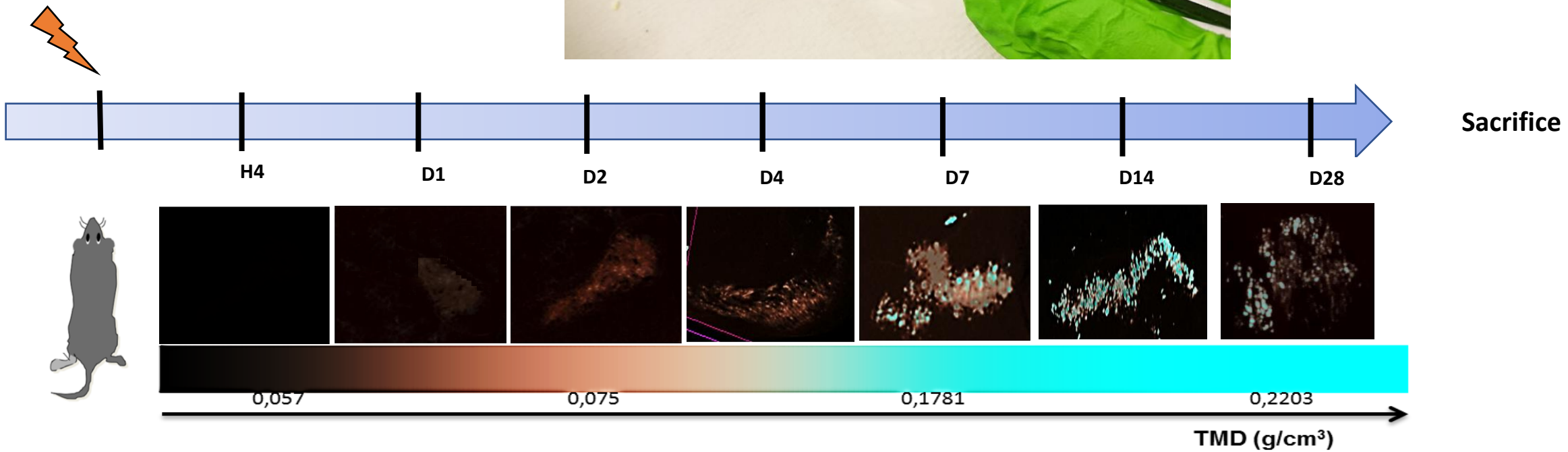
Inhibition de la transdifférenciation *Chen 2014 BBRC*

Inhibition de l'inflammation *Nasi 2016 PlosOne*

Modèle de calcifications dystrophiques

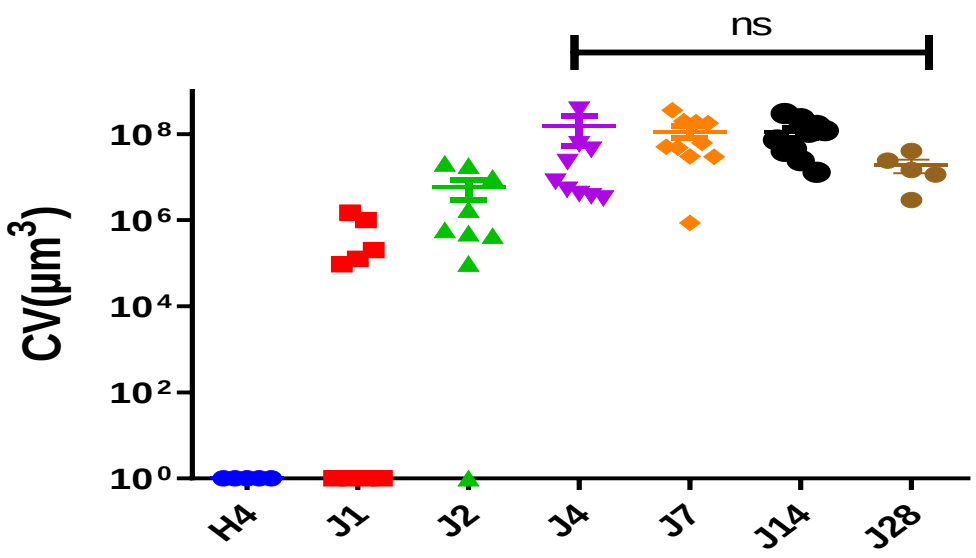
Cryo-brûlure (T_0)

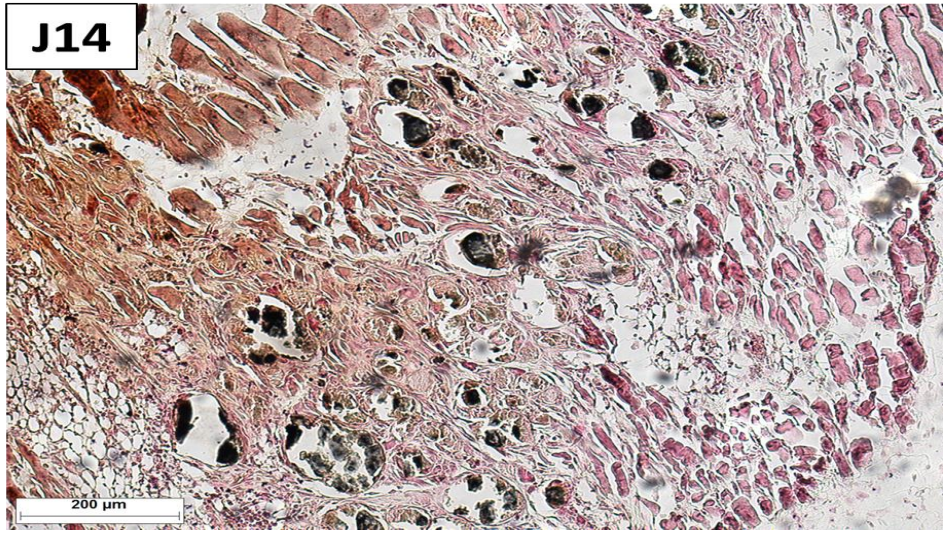


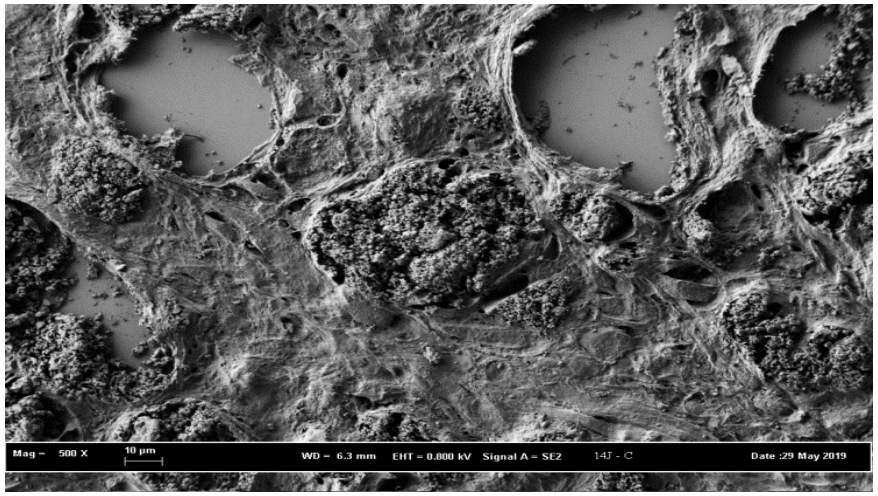


Gauffénic et al, données non publiées

Modèle de calcifications dystrophiques



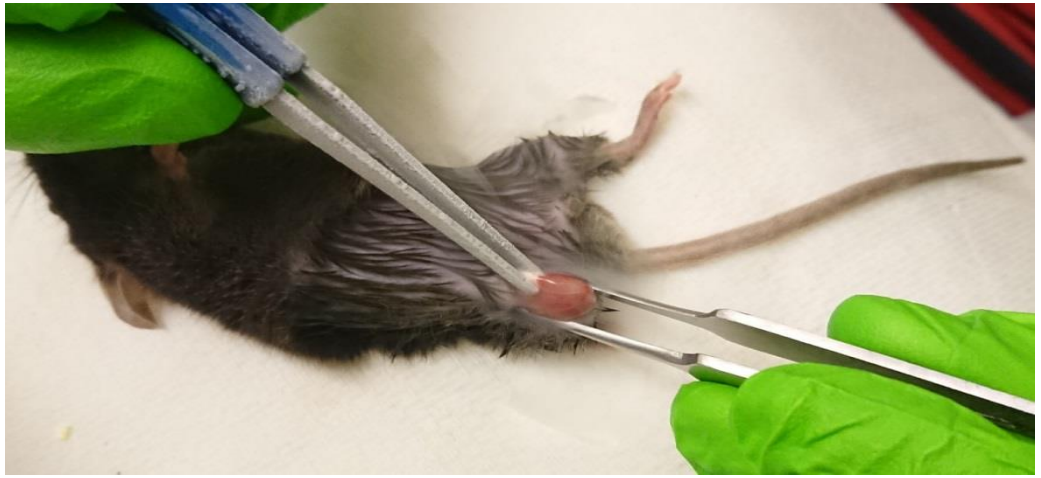




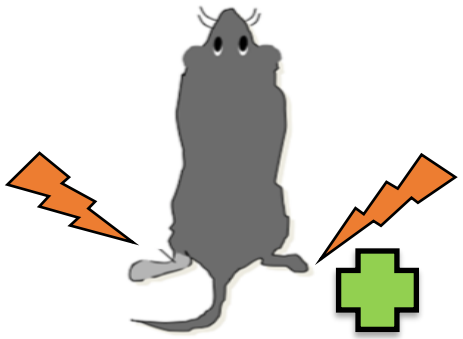
Gauffénic et al, données non publiées

Modèle de calcifications dystrophiques

Cryo-brûlure bilatérale

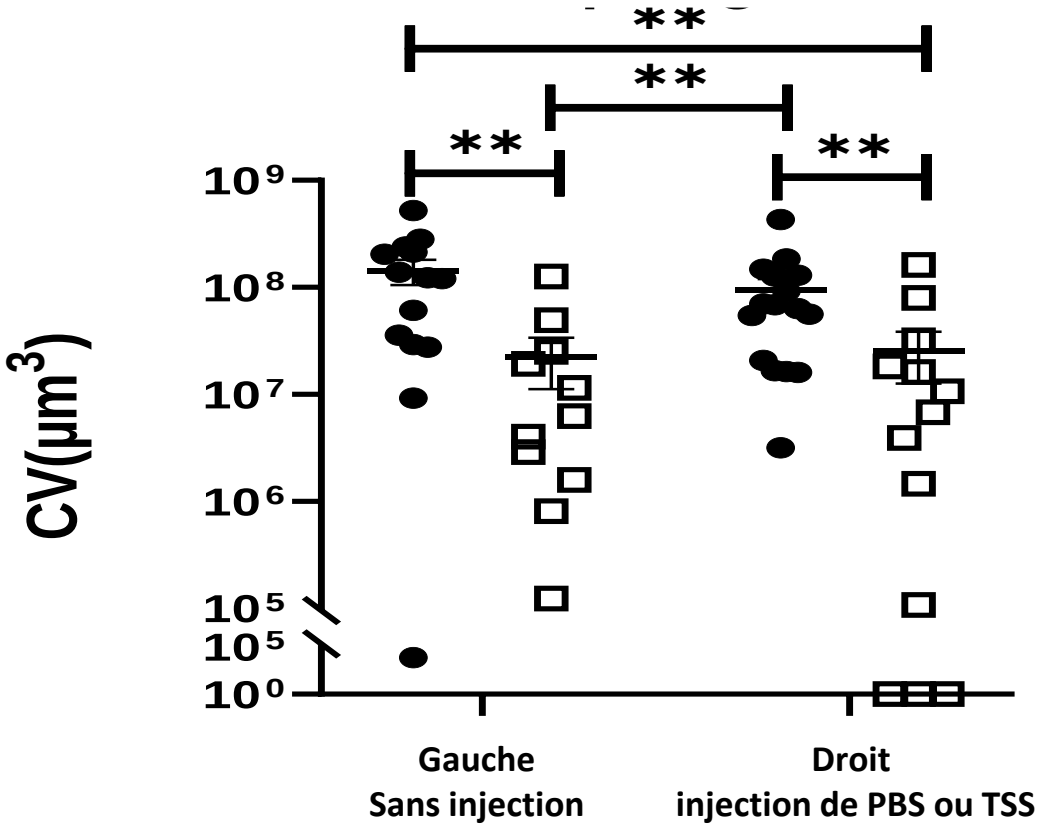


Injection de TSS à droite



Gauffénic et al, données non publiées

Modèle de calcifications dystrophiques



PBS à droite

TSS à droite

Réduction des calcifications par injection locale de TSS avec un effet systémique controlatéral

Mécanismes ??

Gauffénic et al, données non publiées

Conclusion

Calcinoses : mécanismes de formation complexes

Rôle majeur du PPi

Difficile à traiter médicalement

Réduction calcique : pistes potentiels

- **PPi**
- **TSS**

PHRCN 2017, ITS pilot : étude pilote nationale évaluant efficacité du TSS en injection locale dans les calcifications IPPDS, DM et sclérodermie (Pr. GUIGONIS Vincent, Limoges)

Merci de votre attention