SFTH
SOCIÉTÉ FRANÇAISE DE THROMBOSE ET D'HÉMOSTASE
CONGRÈS DE LA SOCIÉTÉ FRANÇAISE DE THROMBOSE ET D'HÉMOSTASE
1ER–3 OCTOBRE 2025

Laboratory for Vascular Translational Science
LVTS UMRS 1148
Inserm
Université Paris Cité
Sorbonne Paris Nord

Role of PN-1 in hemophilic arthropathy, a major complication of hemophilia

Pierre GRÈS

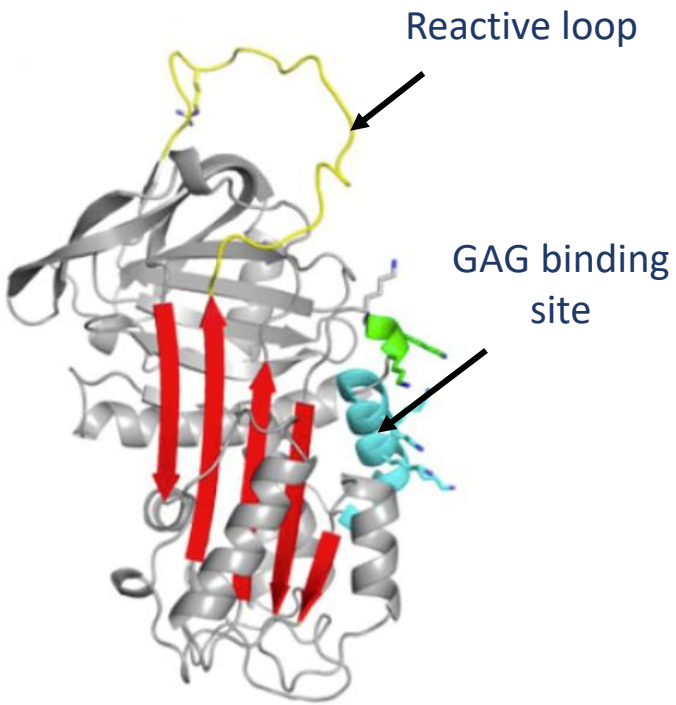
ECOLE DOCTORALE
Hématologie · Oncogenèse · Biothérapies

SFHT Congress (Lyon)
October 2nd, 2025

Inserm U1148

Protease nexin-1 (PN-1)

Protease nexin-1 (PN-1)

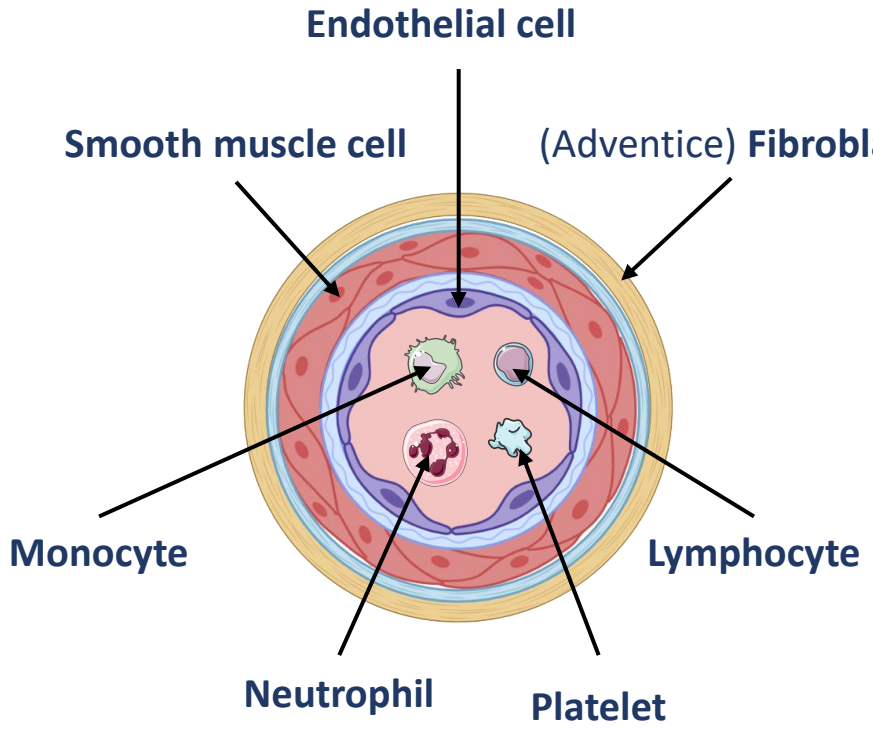


Li and Huntington, *Blood,* 2012

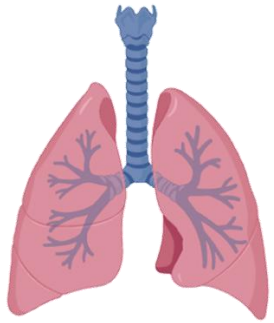
- ***Antiprotease***
- ***Serpin super family***
- ***Tissue localisation***

Ubiquitous expression of PN-1

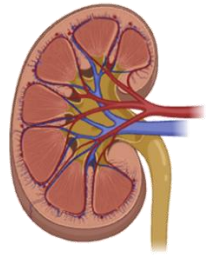
Vessel Wall and circulating cells



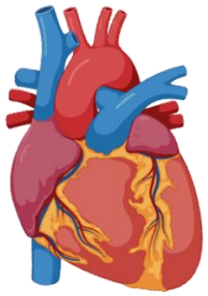
Other organs

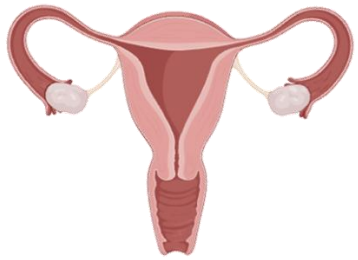

Lungs


Brain

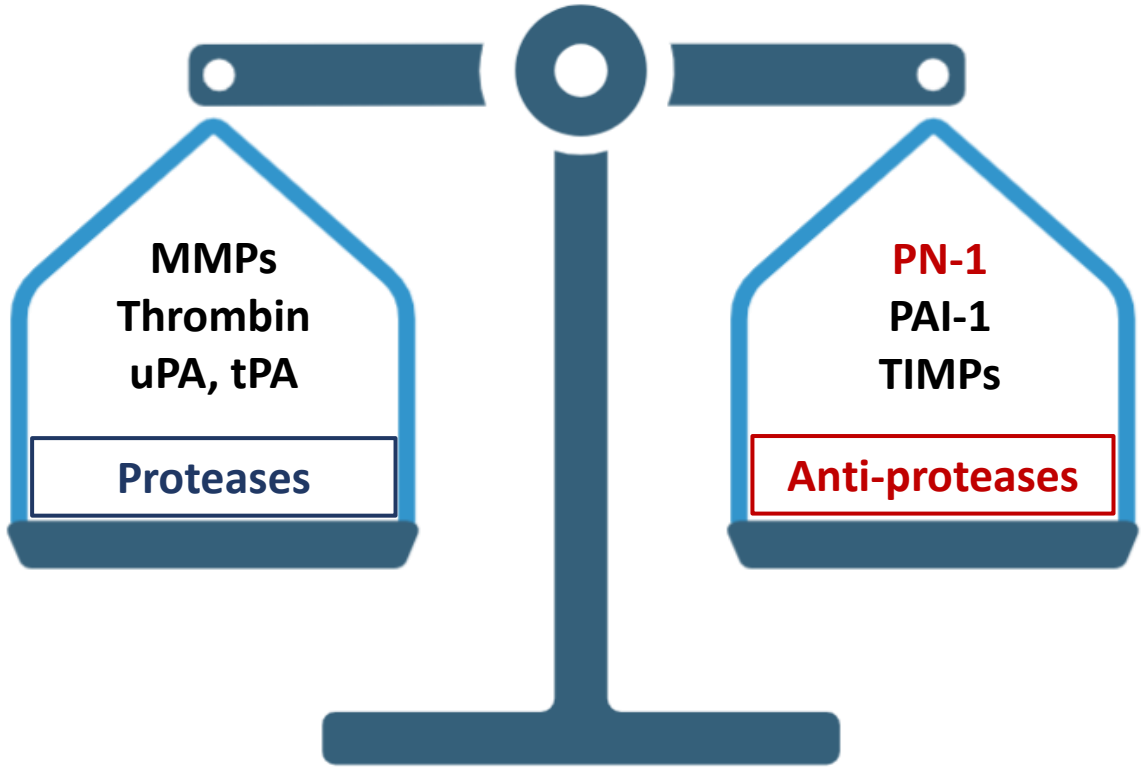

Kidneys

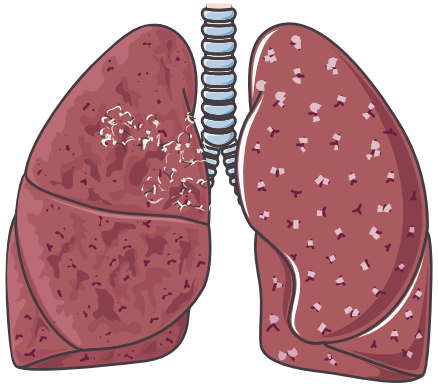

Joints


Heart


Genitalia

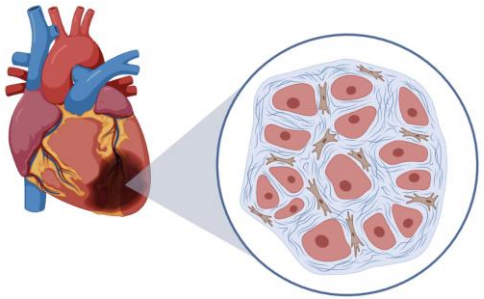
Protease/anti-protease balance and pathologies





Pulmonary fibrosis

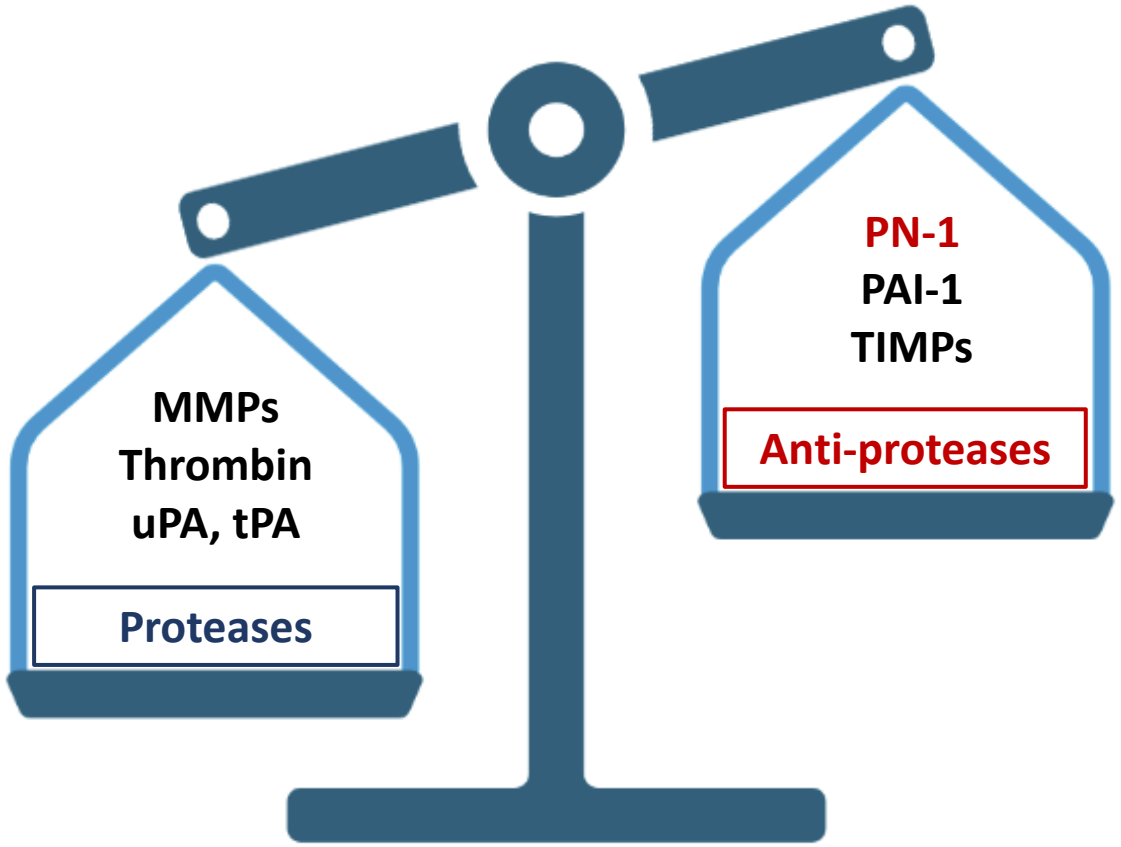
François D. and *al, Blood adv,* 2018



Cardiac fibrosis

Li and *al, Sci Rep*, 2016

Protease/anti-protease balance and pathologies

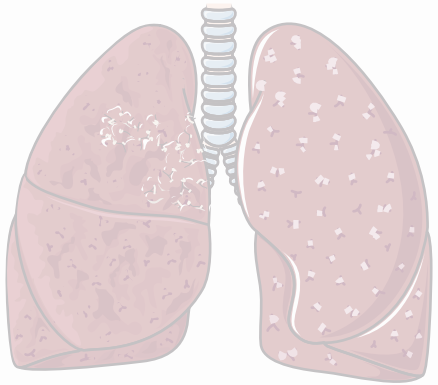


Imbalance → Pathologies

Atherosclerosis

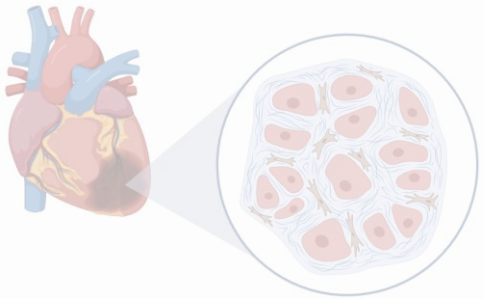
Boukais K. and *al, Front. Physiol*, 2016

SFTH SOCIÉTÉ FRANÇAISE DE THROMBOSE ET D'HÉMOSTASE



Pulmonary fibrosis

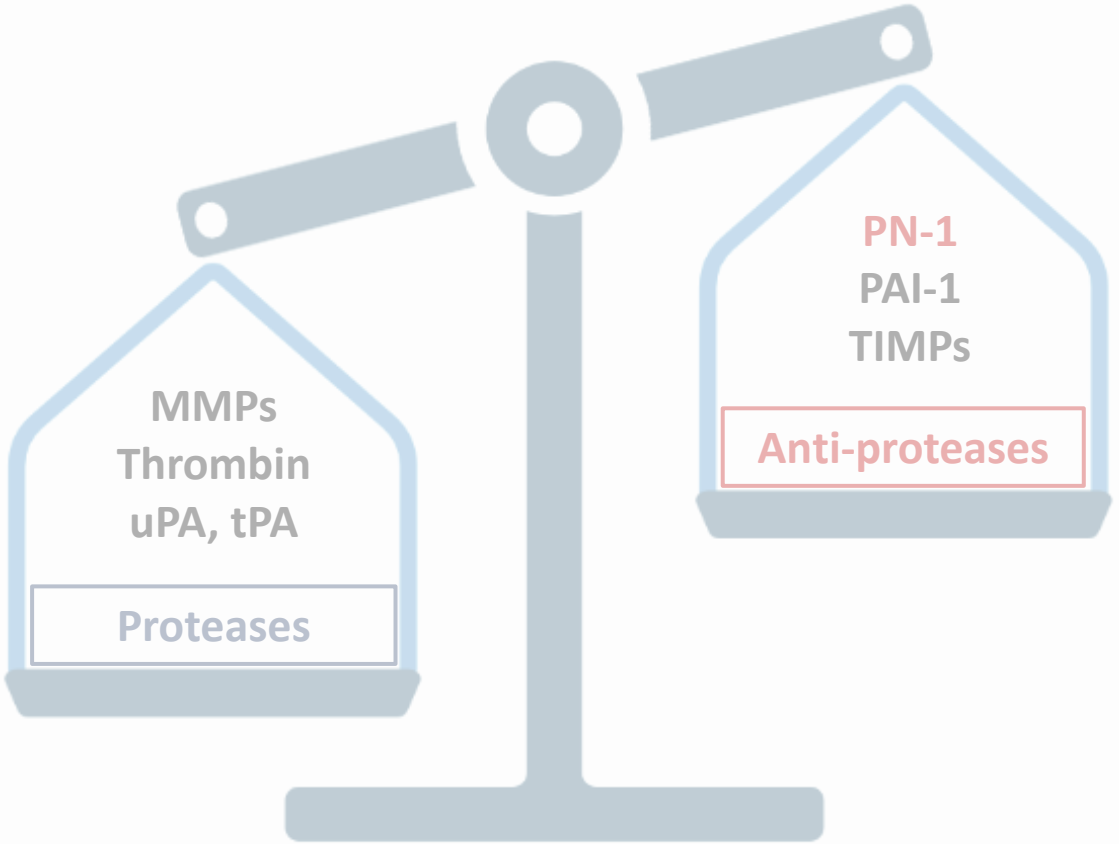
François D. and *al, Blood adv*, 2018



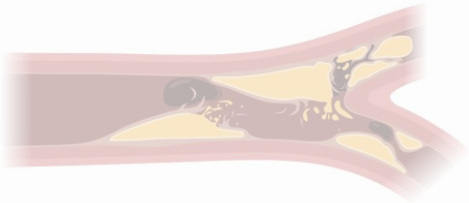
Cardiac fibrosis

Li and *al, Sci Rep*, 2016

Protease/anti-protease balance and pathologies

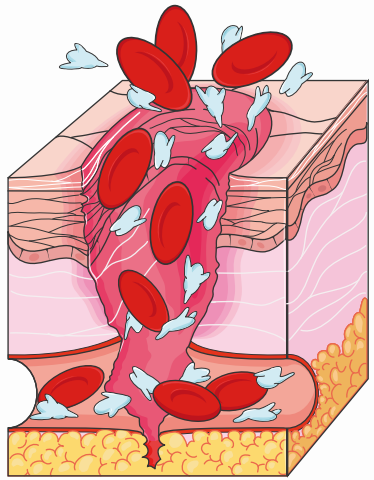


Imbalance → Pathologies



Atherosclerosis

Boukais K. and *al, Front. Physiol*, 2016



Hemophilia

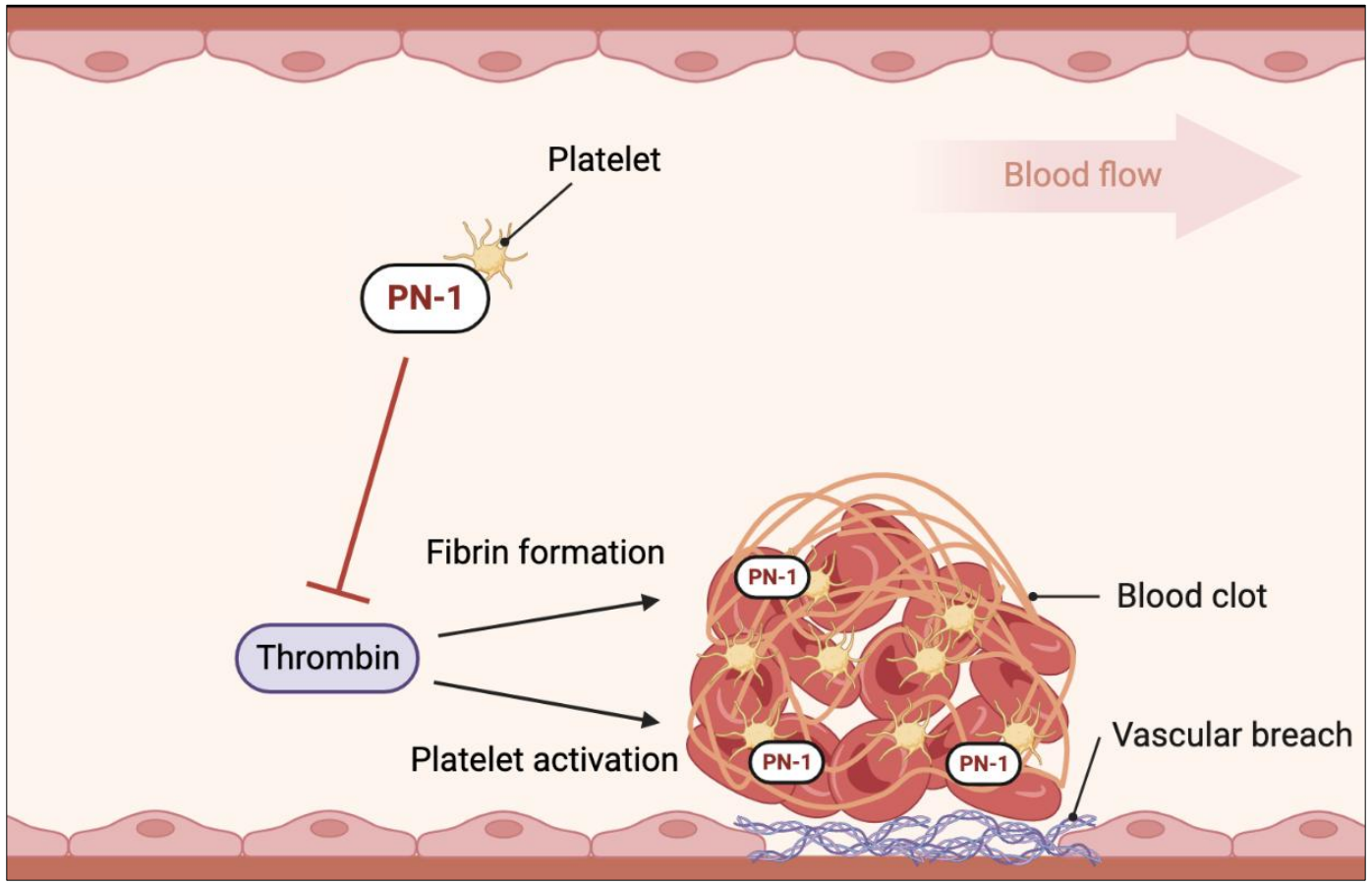
Aymonnier K. and *al, Blood*, 2019

SFTH SOCIÉTÉ FRANÇAISE DE THROMBOSE ET D'HÉMOSTASE

BioRender.com and Servier Medical Art

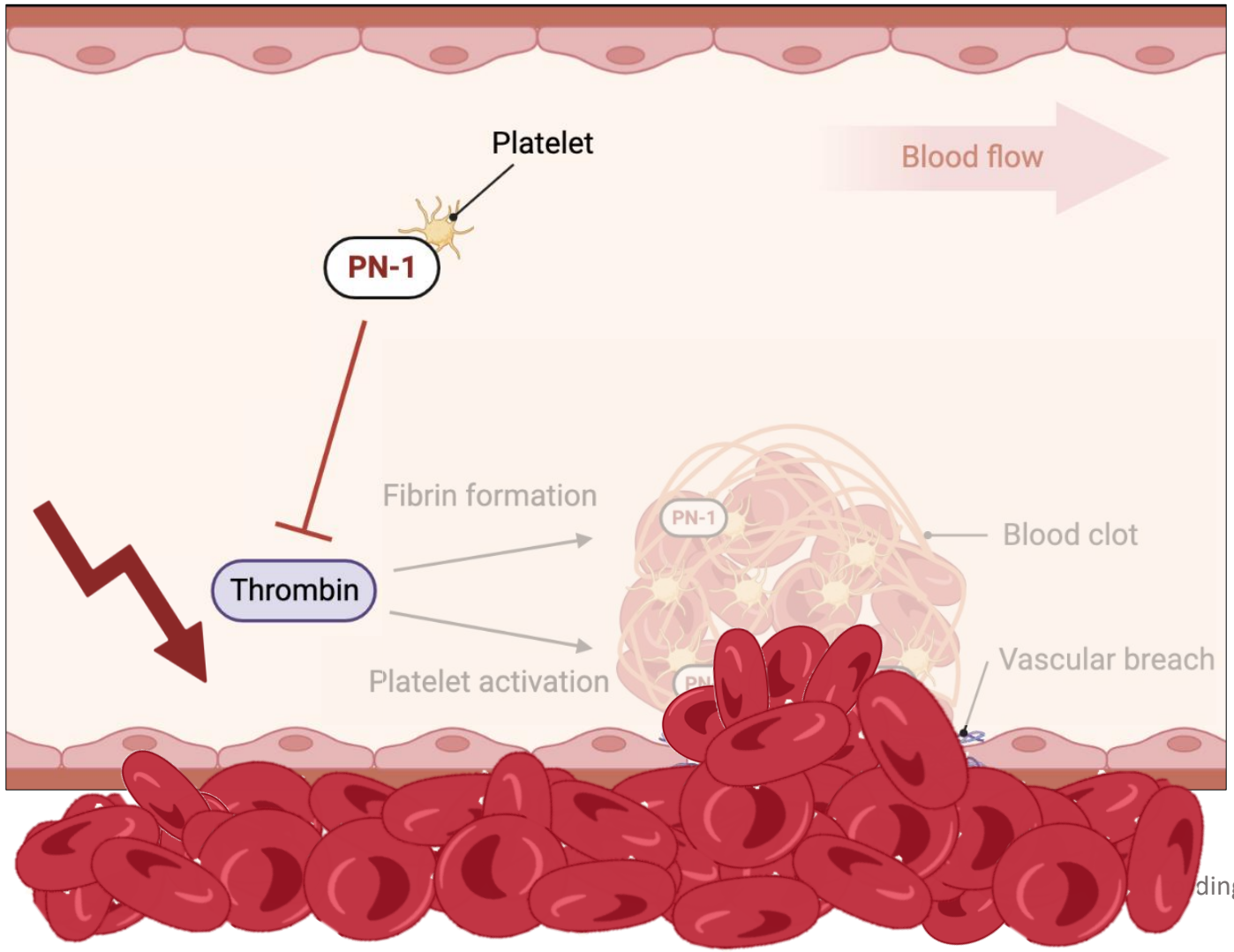
Role of platelet PN-1 on human hemostasis

Anti-thrombotic activity



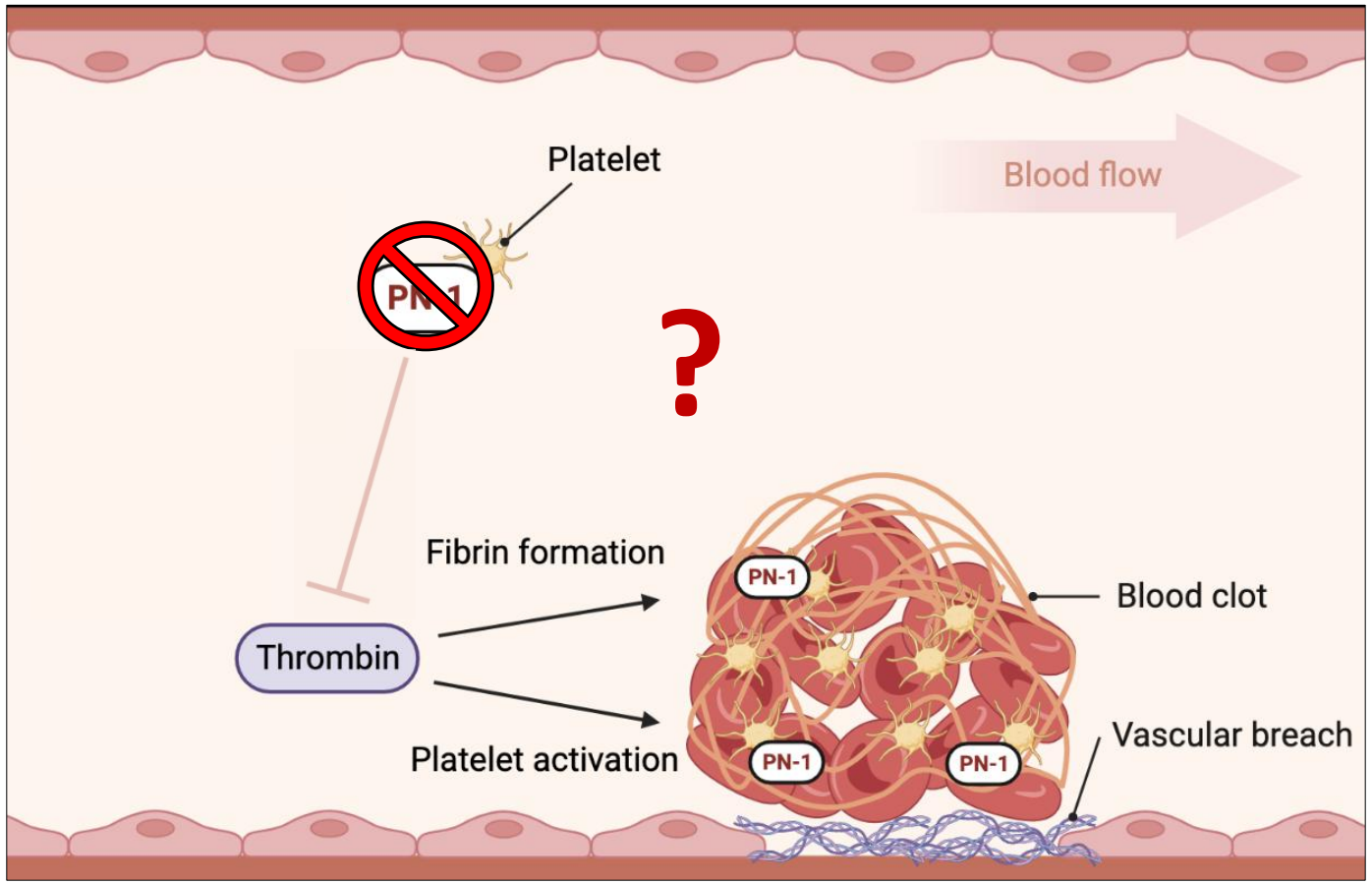
According to Bouton M.C. and *al, Blood,* 2012
BioRender.com

In hemophilia …



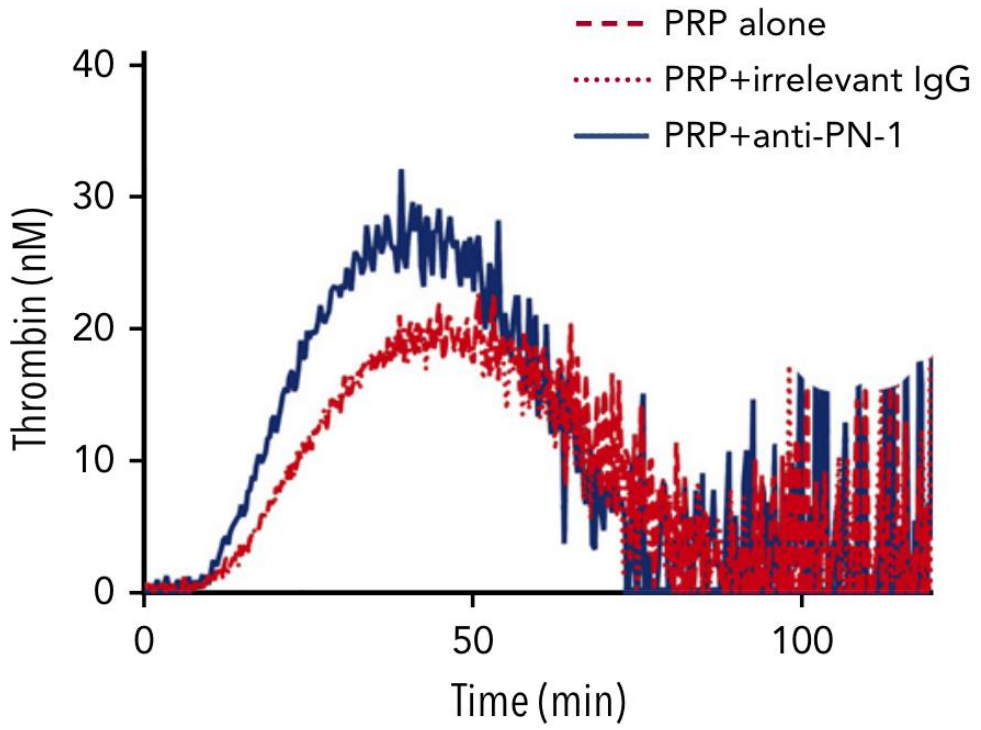
ding to Bouton M.C. and *al, Blood,* 2012
BioRender.com

In hemophilia …



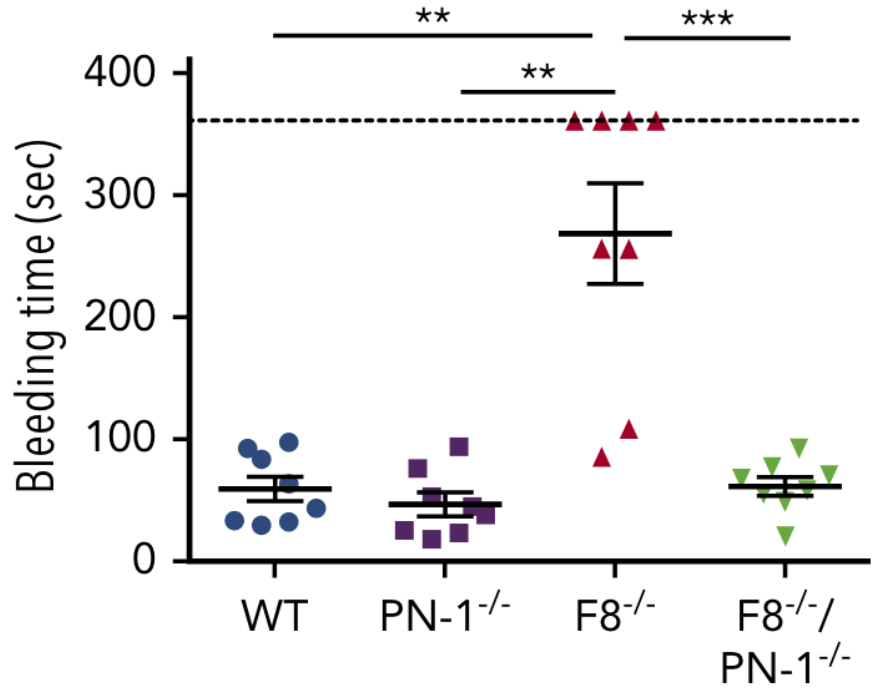
According to Bouton M.C. and *al, Blood,* 2012
BioRender.com

Proof of concept: Platelet PN-1 & Hemophilia



Inhibition of PN-1 increases thrombin generation in PRP from patients with hemophilia A & B

PRP : Platelet-rich plasma



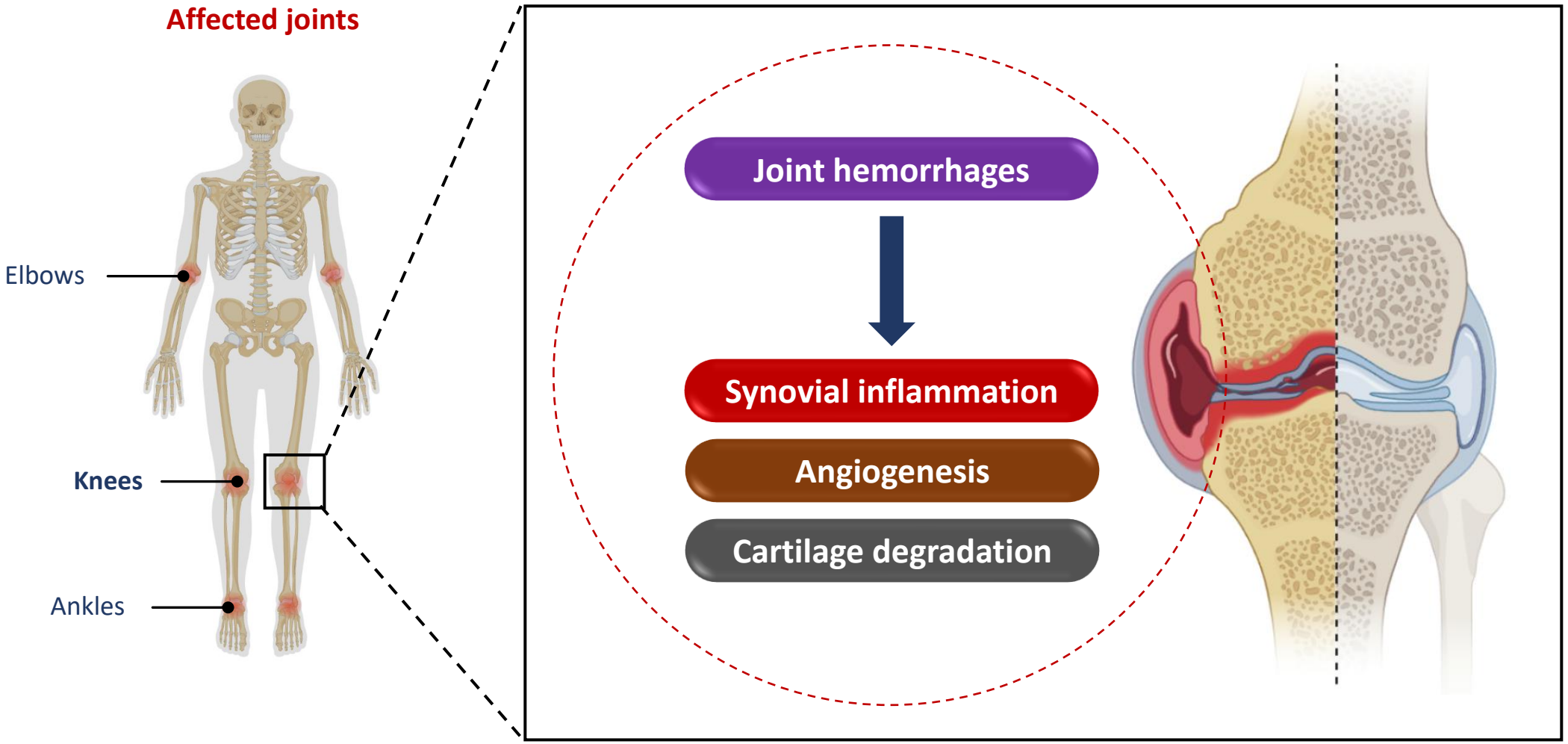
PN-1 deficiency limits tail bleeding in hemophilic mice (F8-/-)

→ **Targeting PN-1 may improve hemostasis in hemophilia**

SFTH SOCIÉTÉ FRANÇAISE DE THROMBOSE ET D'HÉMOSTASE

Aymonnier K. and *al, Blood*, 2019

Hemophilic arthropathy: a major complication of hemophilia A & B



BioRender.com
Adapted from Berntorp and *al, Nature Reviews*, 2021

Hemophilic arthropathy: a major complication of hemophilia A & B

Arthritis Rheum. 2010 Jan;62(1):93-104. doi: 10.1002/art.25038.

Functional autoantibodies against serpin E2 in rheumatoid arthritis

H Maciejewska-Rodrigues [1], M Al-Shamisi, H Hemmatazad, C Ospelt, M C Bouton, D Jäger, A P Cope, P Charles, D Plant, J H W Distler, R E Gay, B A Michel, A Knuth, M Neidhart, S Gay, A Jüngel

Affiliations + expand

PMID: 20039430 DOI: 10.1002/art.25038

Free article

Synovial inflammation

PLoS One. 2015 Aug 25;10(8):e0135979. doi: 10.1371/journal.pone.0135979. eCollection 2015.

SERPINE2 Inhibits IL-1α-Induced MMP-13 Expression in Human Chondrocytes: Involvement of ERK/NF-κB/AP-1 Pathways

Anna Santoro [1], Javier Conde [2], Morena Scotece [2], Vanessa Abella [3], Ana Lois [2], Veronica Lopez [2], Jesus Pino [4], Rodolfo Gomez [2], Juan J Gomez-Reino [5], Oreste Gualillo [2]

Affiliations + expand

PMID: 26305372 PMCID: PMC4549255

Cartilage degradation

Cell Mol Life Sci. 2015 Oct;72(20):3999-4011. doi: 10.1007/s00018-015-1972-5. Epub 2015 Jun 25.

Protease nexin-1 regulates retinal vascular development

Sonia Selbonne [1 2], Deborah Francois [1 2], William Raoul [3 4 5 6], Yacine Boulaftali [1 2], Florian Sennlaub [3 4 5], Martine Jandrot-Perrus [1 2], Marie-Christine Bouton [1 2], Véronique Arocas [7 8]

Affiliations + expand

PMID: 26109427 PMCID: PMC11113785 DOI: 10.1007/s00018-015-1972-5

Angiogenesis

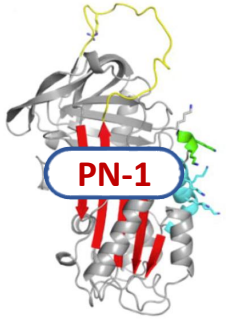
ial inflammation

Angiogenesis

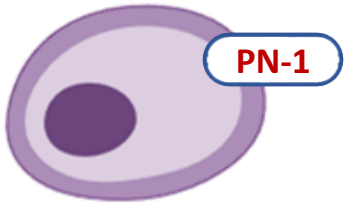
lage degradation

Adapted from Berntorp and *al, Nature Reviews*, 2021

Role of PN-1 in HA ?

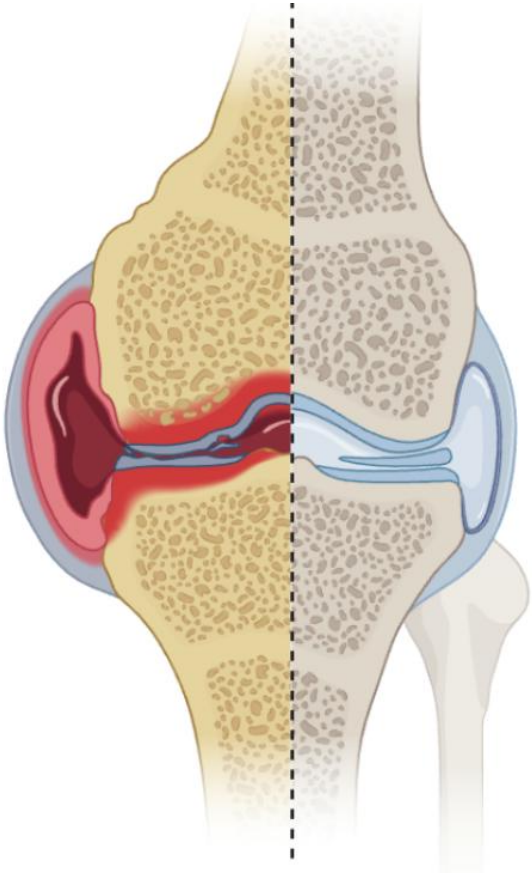


Role of chondrocyte PN-1 in HA ?



Chondrocyte

?

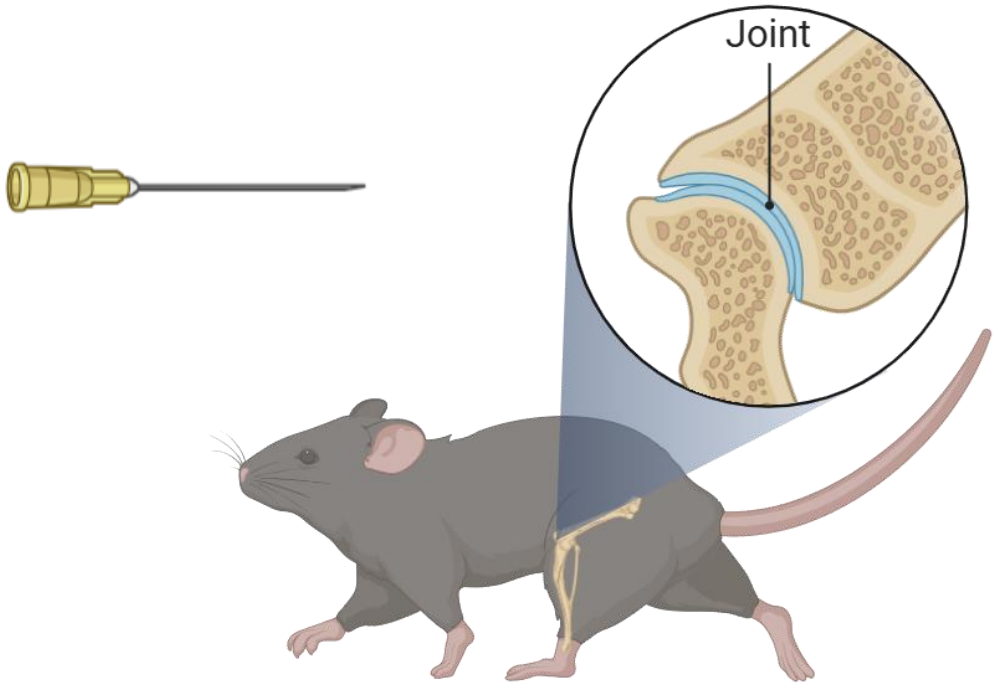


Hemophilic arthropathy (HA)

In vivo model of Hemophilic arthropathy

Hemarthrosis

D0 **D2** **D5** **D10** **D14**



WT (n=8) **PN1**$^{-/-}$ (n=6) **F8**$^{-/-}$ (n=9) **F8**$^{-/-}$**PN1**$^{-/-}$ (n=13)

BioRender.com
Valentino and al, *Hemophilia*, 2004

In vivo model of Hemophilic arthropathy

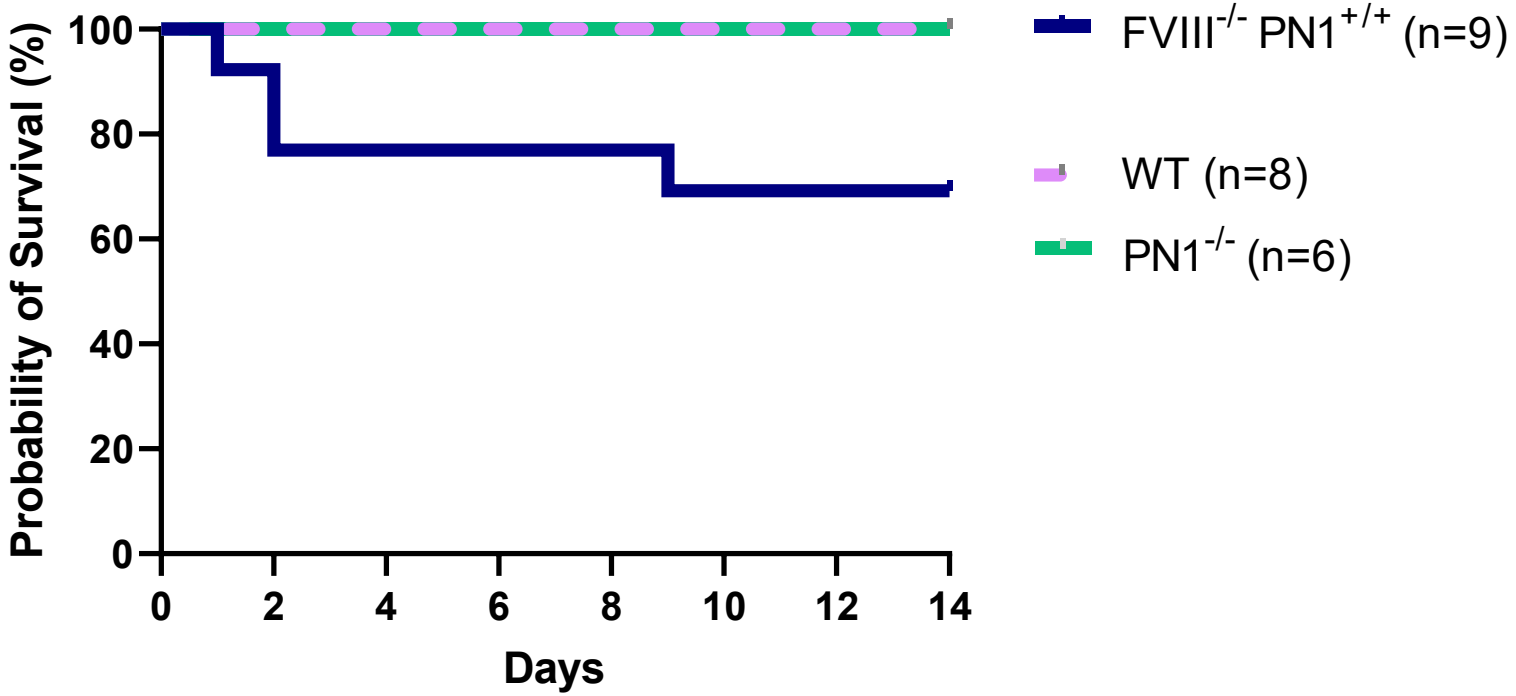
Survival | *Knee Size* | *Severity Score*

0	1	2	3
Absence of Blood	Blood	Blood + Distended knee	Blood + Distended knee + Tensed knee

BioRender.com
Valentino and al, *Hemophilia*, 2004

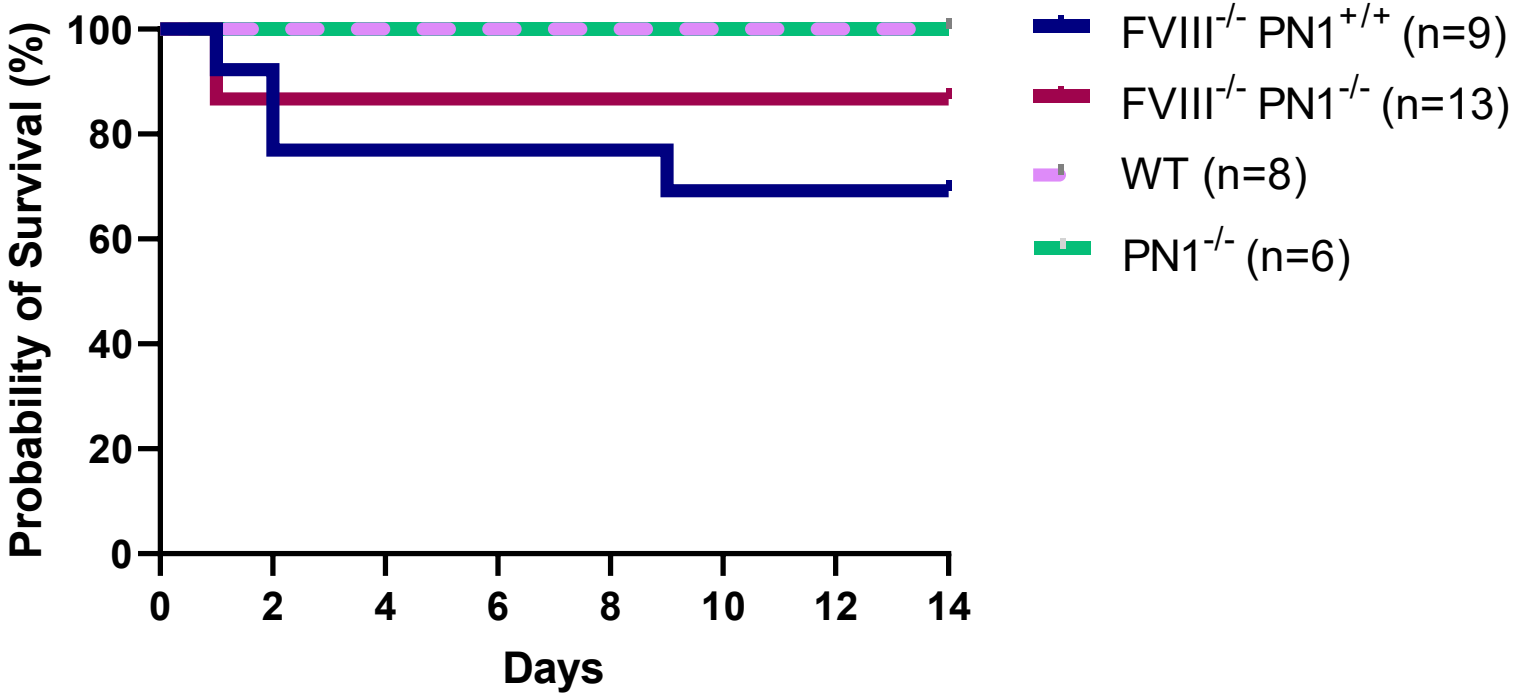
In vivo model of Hemophilic arthropathy

Survival



In vivo model of Hemophilic arthropathy

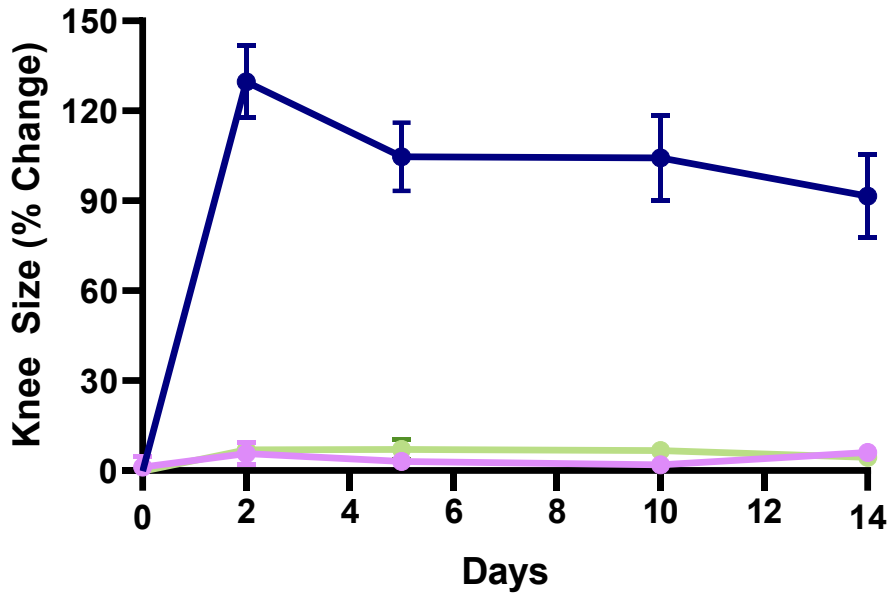
Survival



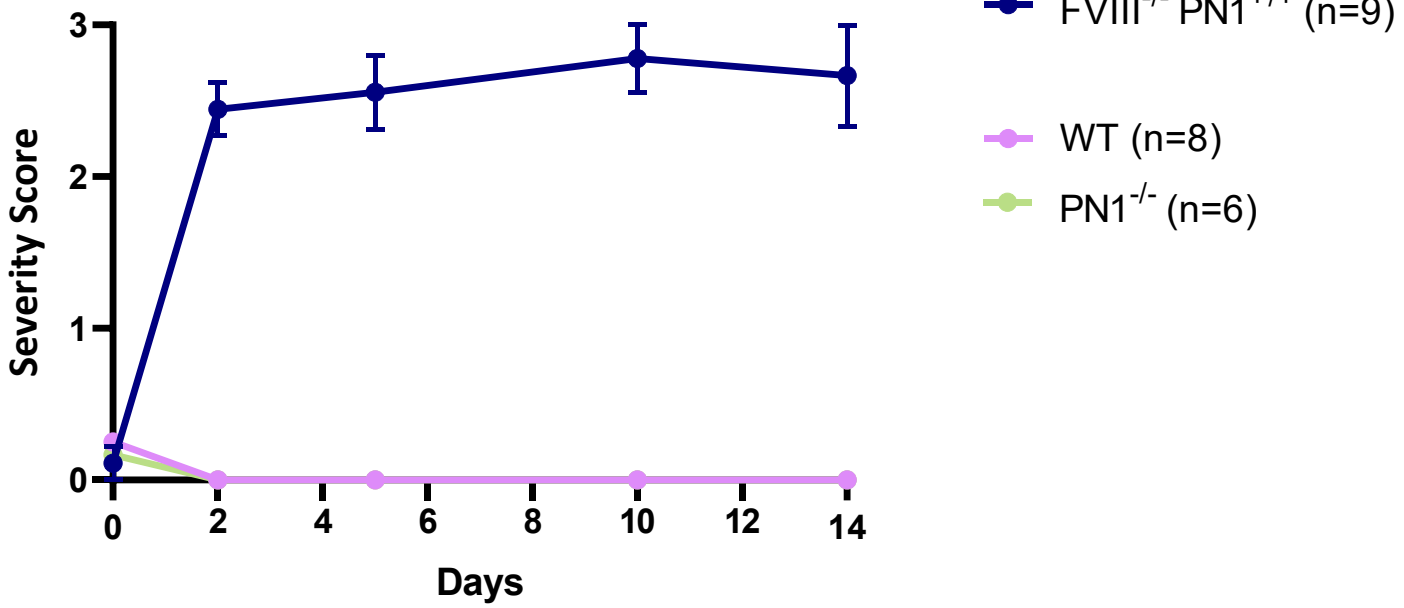
→ **PN1 deficiency limits mortality in hemophilic mice**

In vivo model of Hemophilic arthropathy

Knee Size

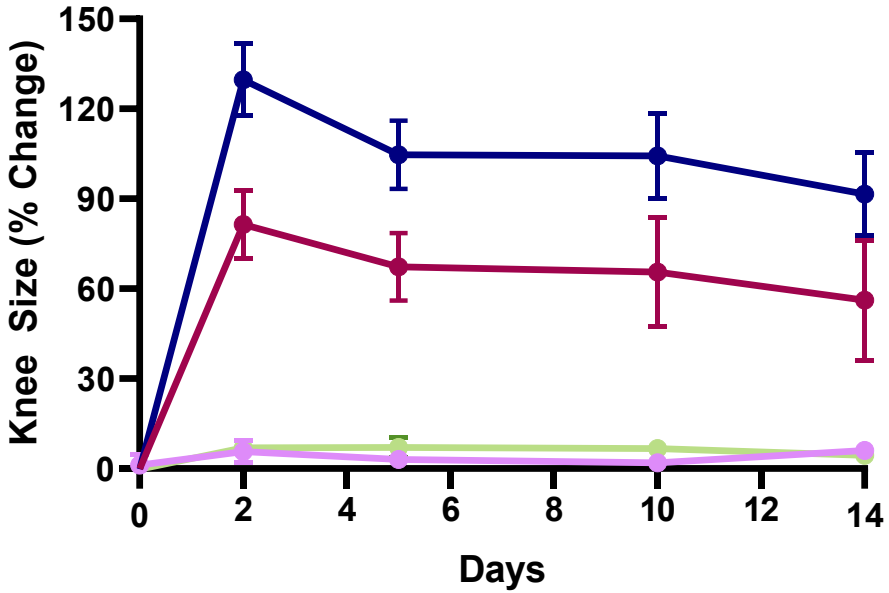


Severity Score

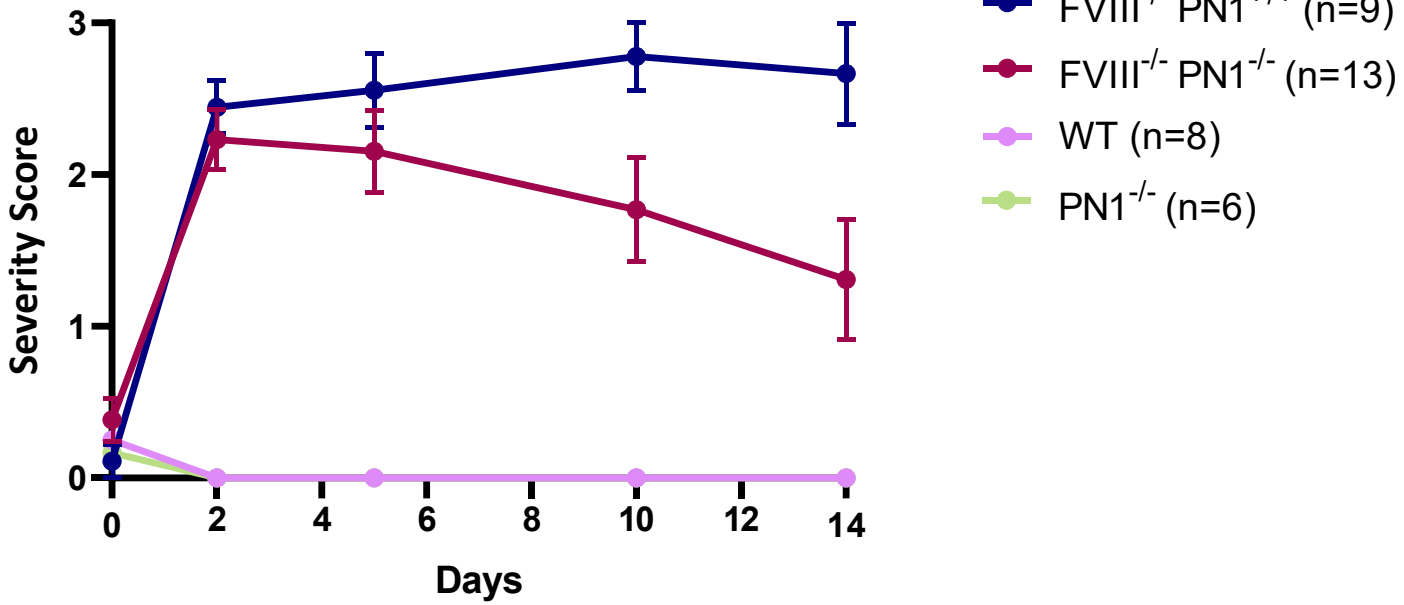


In vivo model of Hemophilic arthropathy

Knee Size



Severity Score



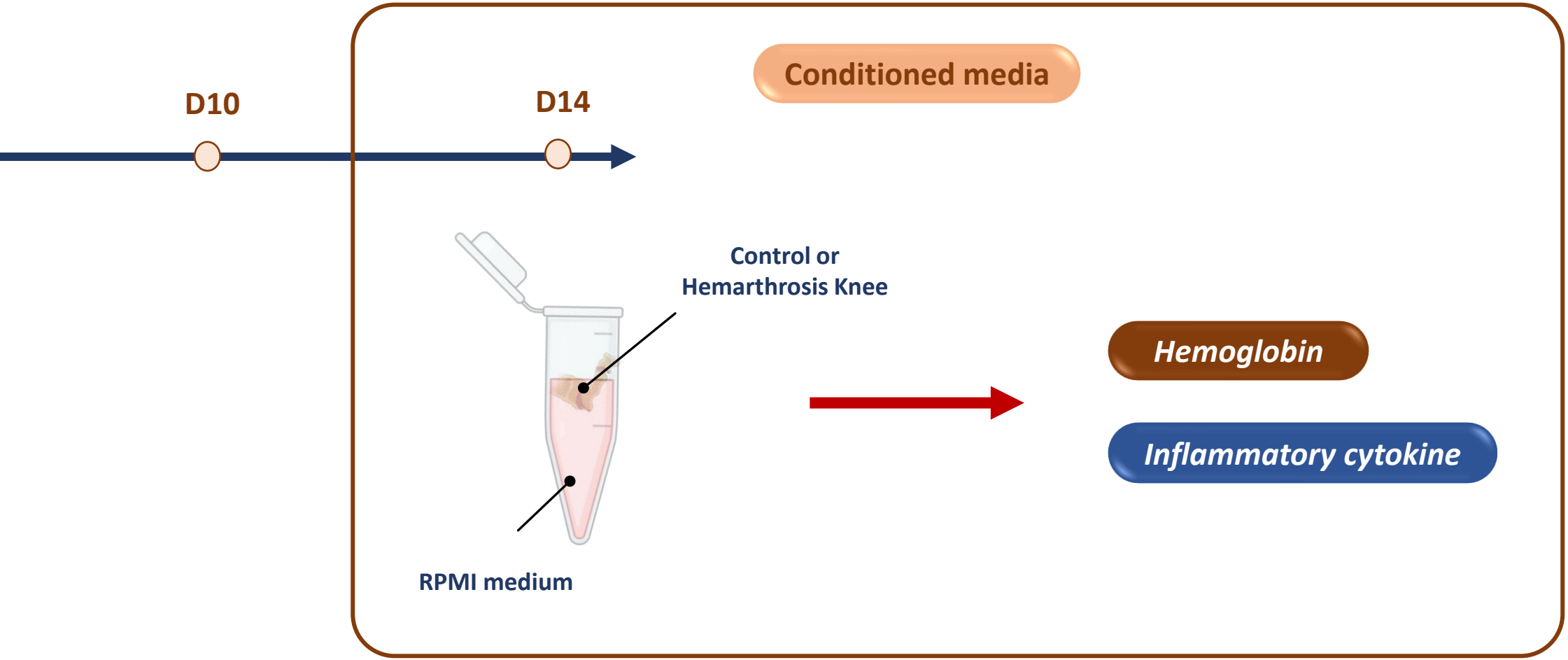
→ **PN1 deficiency limits Knee size and severity score at day 14 in hemophilic mice**

SFTH SOCIÉTÉ FRANÇAISE DE THROMBOSE ET D'HÉMOSTASE

In vivo model of Hemophilic arthropathy

BioRender.com
Valentino and al, *Hemophilia*, 2004

In vivo model of Hemophilic arthropathy



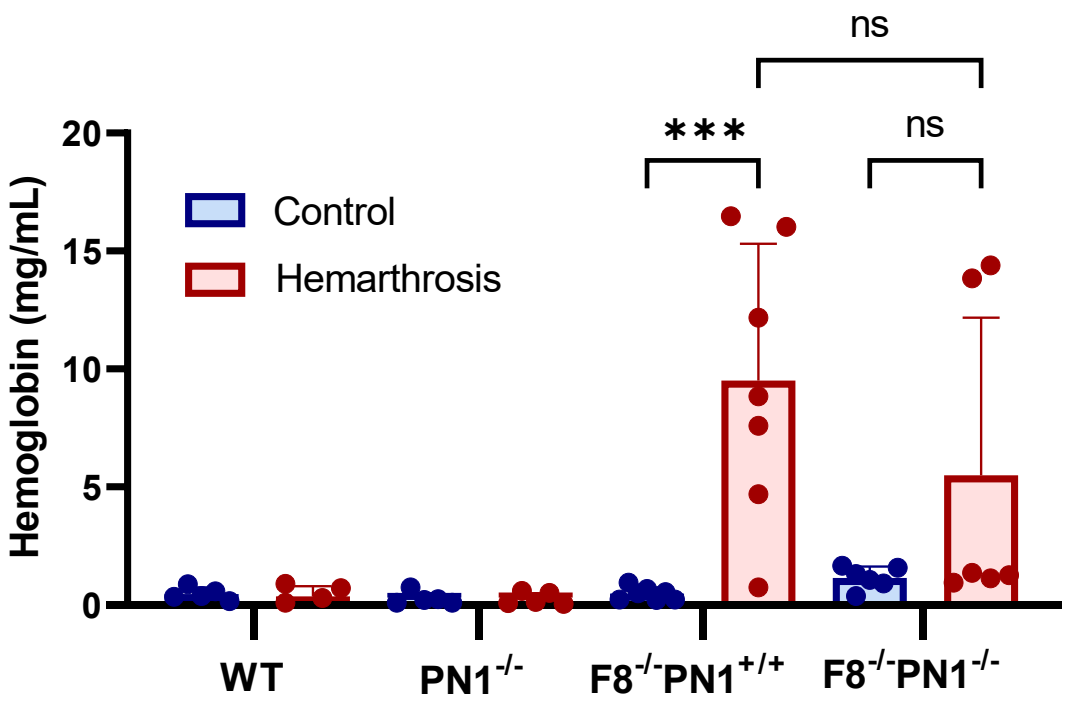
BioRender.com
Valentino and al, *Hemophilia*, 2004

Conditioned media

Day 14

In vivo model of Hemophilic arthropathy

Hemoglobin



→ By day 14, PN1 deficiency reduces hemoglobin level in hemophilic mice knees

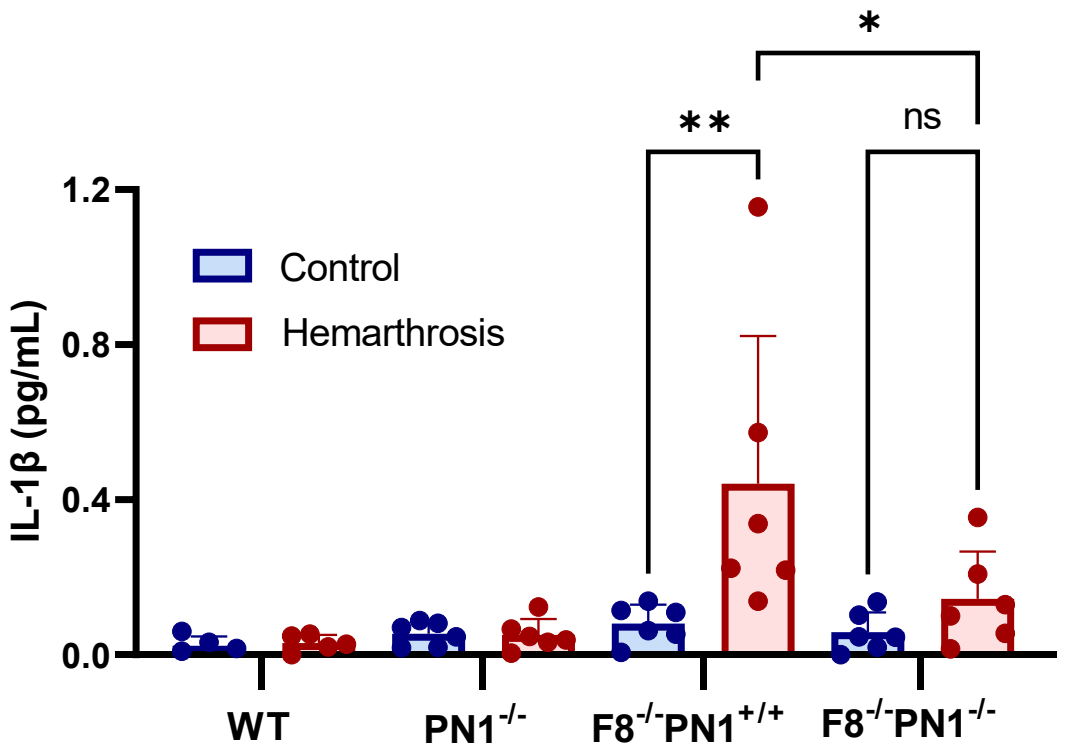
SFTH SOCIÉTÉ FRANÇAISE DE THROMBOSE ET D'HÉMOSTASE

Conditioned media

Day 14

In vivo model of Hemophilic arthropathy

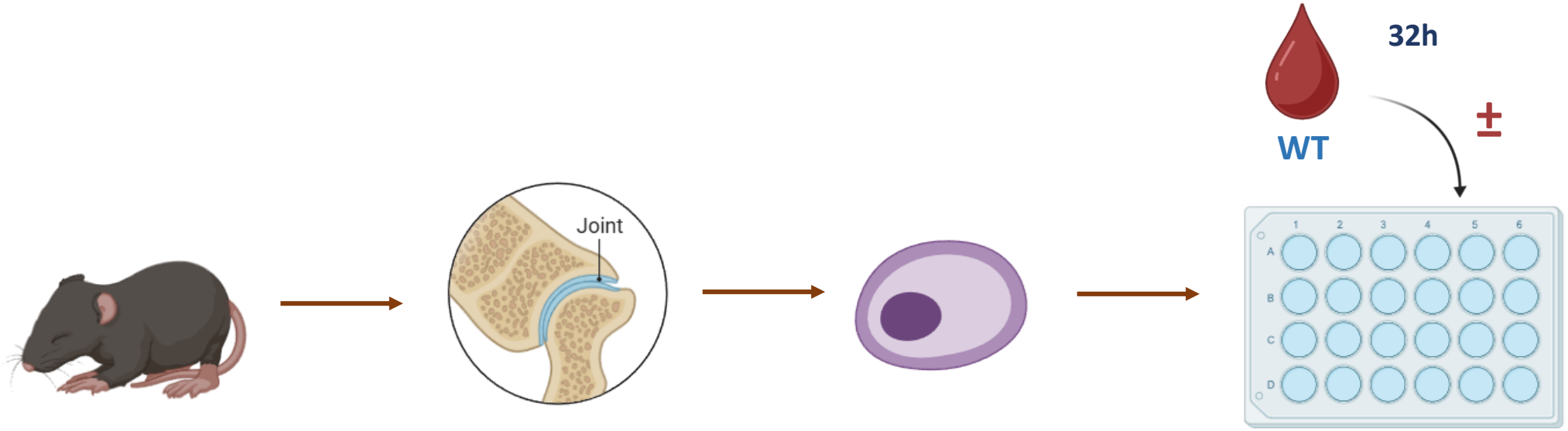
Inflammatory cytokine



→ By day 14, PN1 deficiency reduces inflammatory cytokine levels in hemophilic mice knees

SFTH SOCIÉTÉ FRANÇAISE DE THROMBOSE ET D'HÉMOSTASE

In vitro model of Hemophilic arthropathy : role of chondrocyte PN1



5 days old mice

WT (n=9)

PN1$^{-/-}$ (n=3)

Collection of cartilage

Isolation of chondrocyte

Cell culture

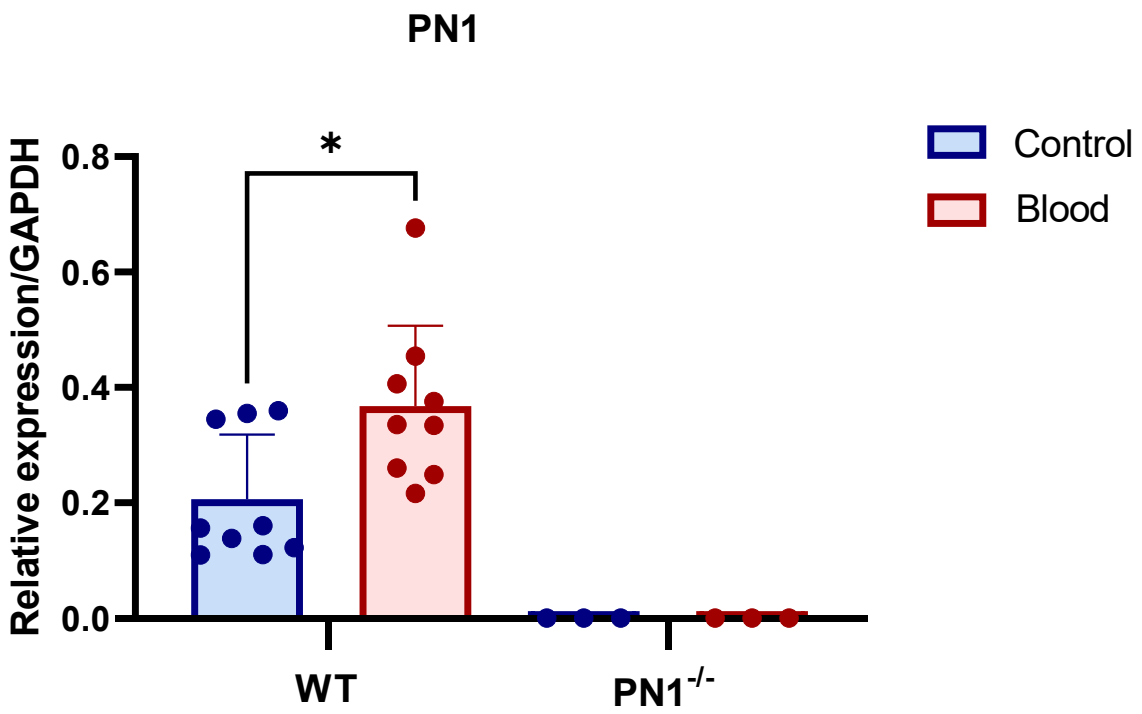
BioRender.com

Théron and al, *Hemasphere*, 2023

In vitro model of Hemophilic arthropathy : role of chondrocyte PN1

WT and PN1$^{-/-}$
Chondrocyte

PN1 expression

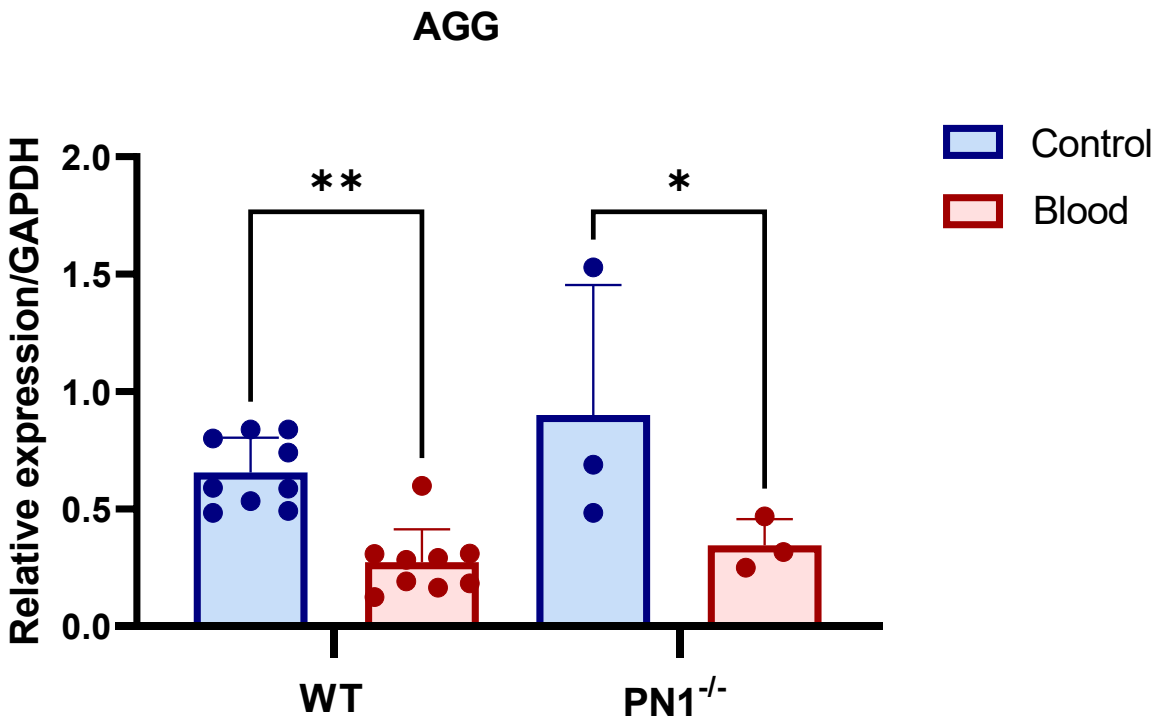


→ **Blood exposure induces PN1 overexpression in WT chondrocytes**

In vitro model of Hemophilic arthropathy : role of chondrocyte PN1

WT and PN1$^{-/-}$ Chondrocyte

Chondrocyte marker expression



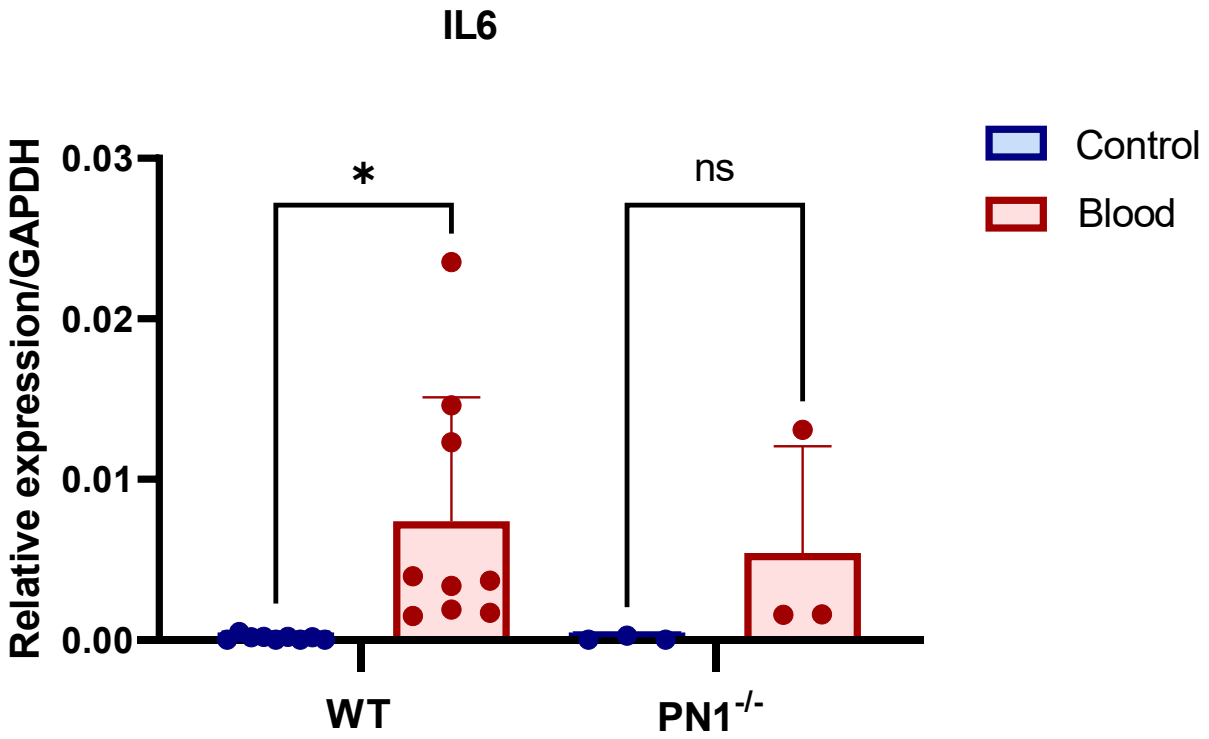
→ **Blood exposition decreases Aggrecan expression in both WT and PN1$^{-/-}$ chondrocytes**

SFTH SOCIÉTÉ FRANÇAISE DE THROMBOSE ET D'HÉMOSTASE

In vitro model of Hemophilic arthropathy : role of chondrocyte PN1

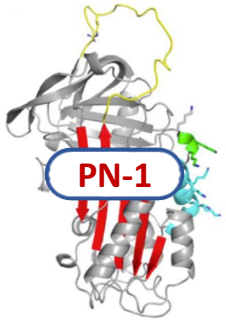
WT and PN1$^{-/-}$
Chondrocyte

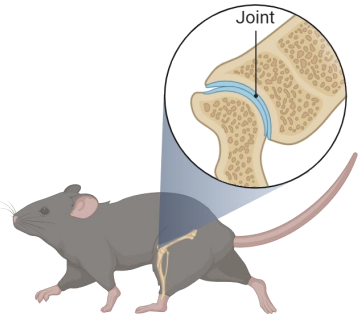
Inflammatory cytokine expression



→ **Inflammatory cytokine rise in WT chondrocytes increase after blood exposure**
But not in PN1$^{-/-}$ chondrocytes

Role of PN-1 in HA ?

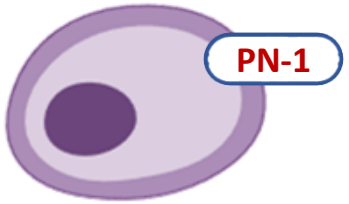




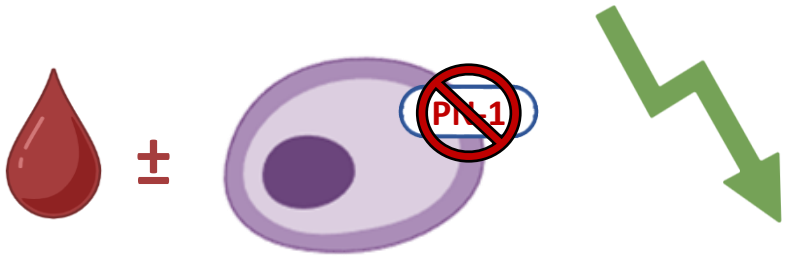
$F8^{-/-}PN1^{-/-}$ (n=13)

- **Mortality & Severity**
- **<u>Conditioned media</u> :**
  Less blood & inflammation

Role of chondrocyte PN-1 in HA ?



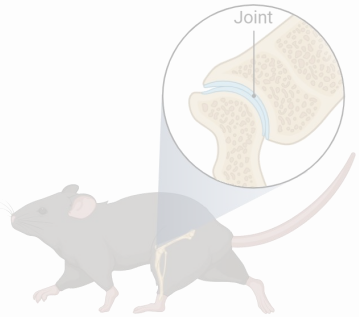
Chondrocyte



- **Inflammation**

HA : Hemophilic arthropathy

Role of PN-1 in HA ?

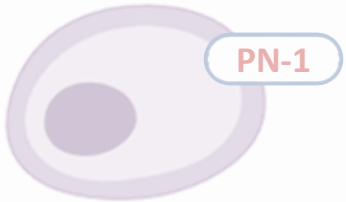


$F8^{-/-}PN1^{-/-}$ (n=13)

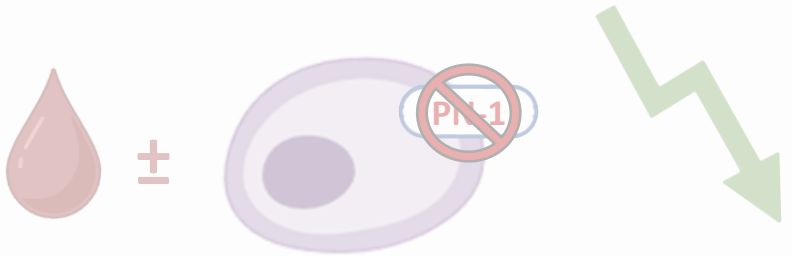
- Mortality & Severity
- Conditioned media : Less blood & inflammation

Targeting PN-1 to reduce hemophilic arthropathy ? To be continued…

Role of chondrocyte PN-1 in HA ?



Chondrocyte



- Inflammation

Thank you for your attention !

ECOLE DOCTORALE
Hématologie · Oncogenèse · Biothérapies

Laboratory for Vascular Translational Science
LVTS UMRS 1148
Inserm · Université Paris Cité · Sorbonne Paris Nord

Team 6

Marie-Christine BOUTON
Véronique AROCAS
Martine JANDROT-PERRUS
Stéphane LOYAU
Déborah FRANÇOIS
Benjamin RICHARD
Yacine BOULAFTALI
Clémence MAUPU
Garance ENNESSER
Junjie YU (Jay)
Irvin SAUTET
Carlotta TURNATURI
Tirza BRAUN
Laura SADIK-PREIRA

Team 2

Carine LE GOFF

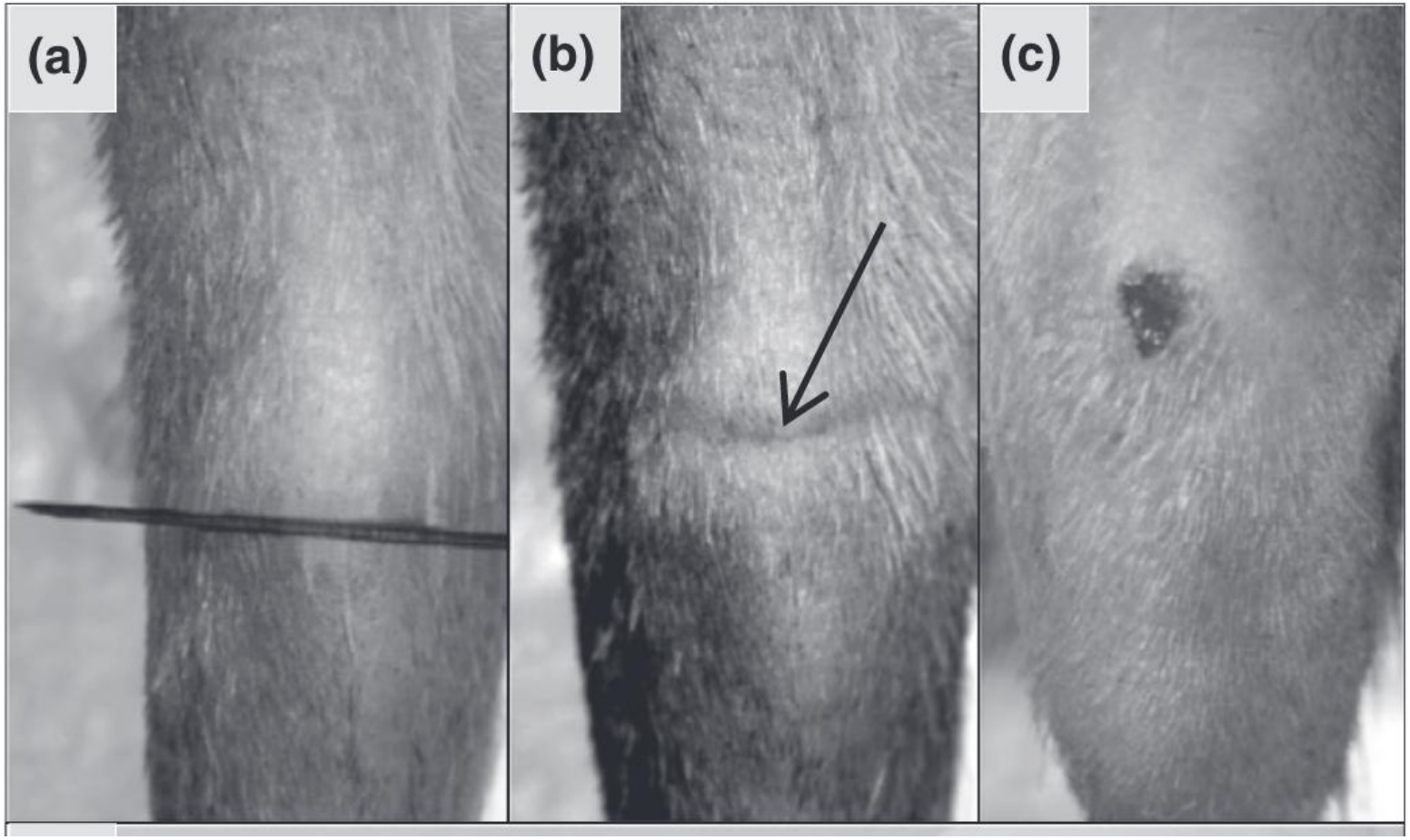
Animal facility

Emma SYLVAIN
Thomas LELANT

crsa
CENTRE DE RECHERCHE SAINT-ANTOINE | PARIS

Xavier HOUARD
Audrey PIGENET

Induction of joint bleeding



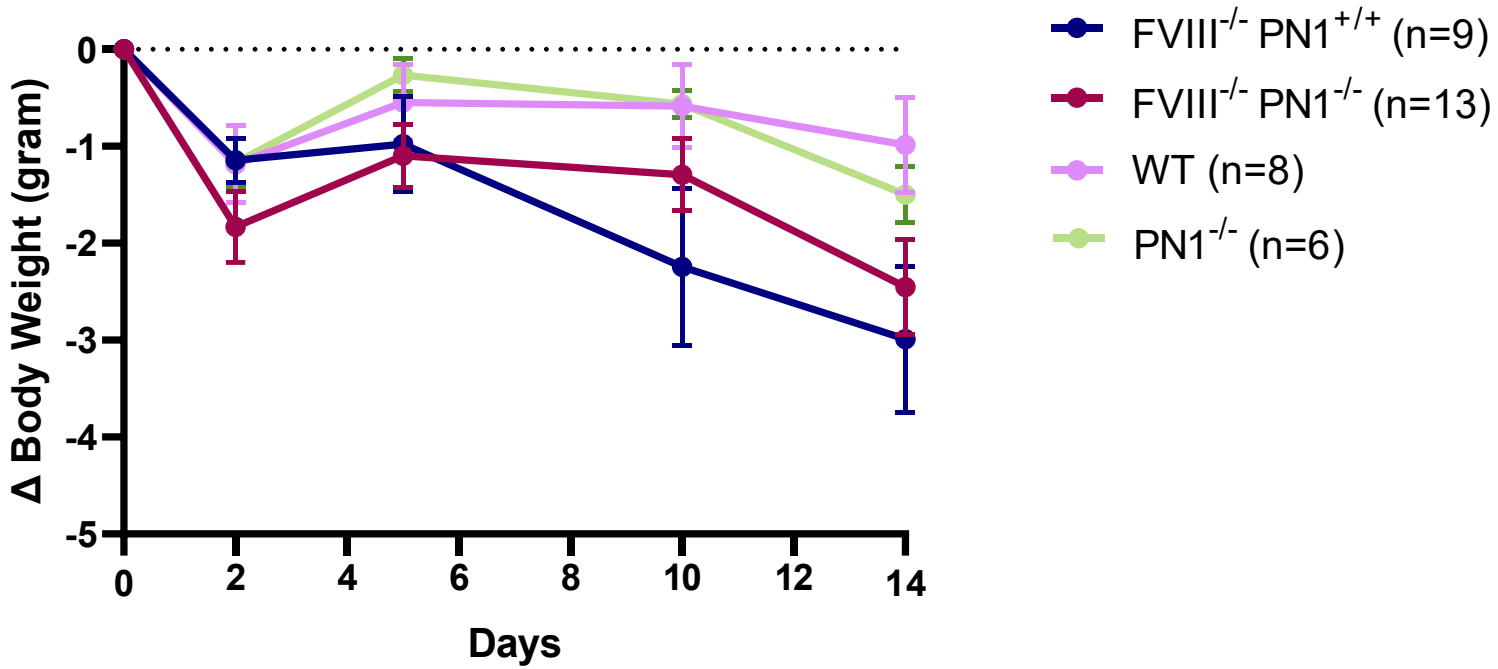
Hakobyan N. and *al, Haemophilia,* 2016

Induction of joint bleeding

Hakobyan N. et *al, Haemophilia,* 2016

In vivo model of Hemophilic arthropathy

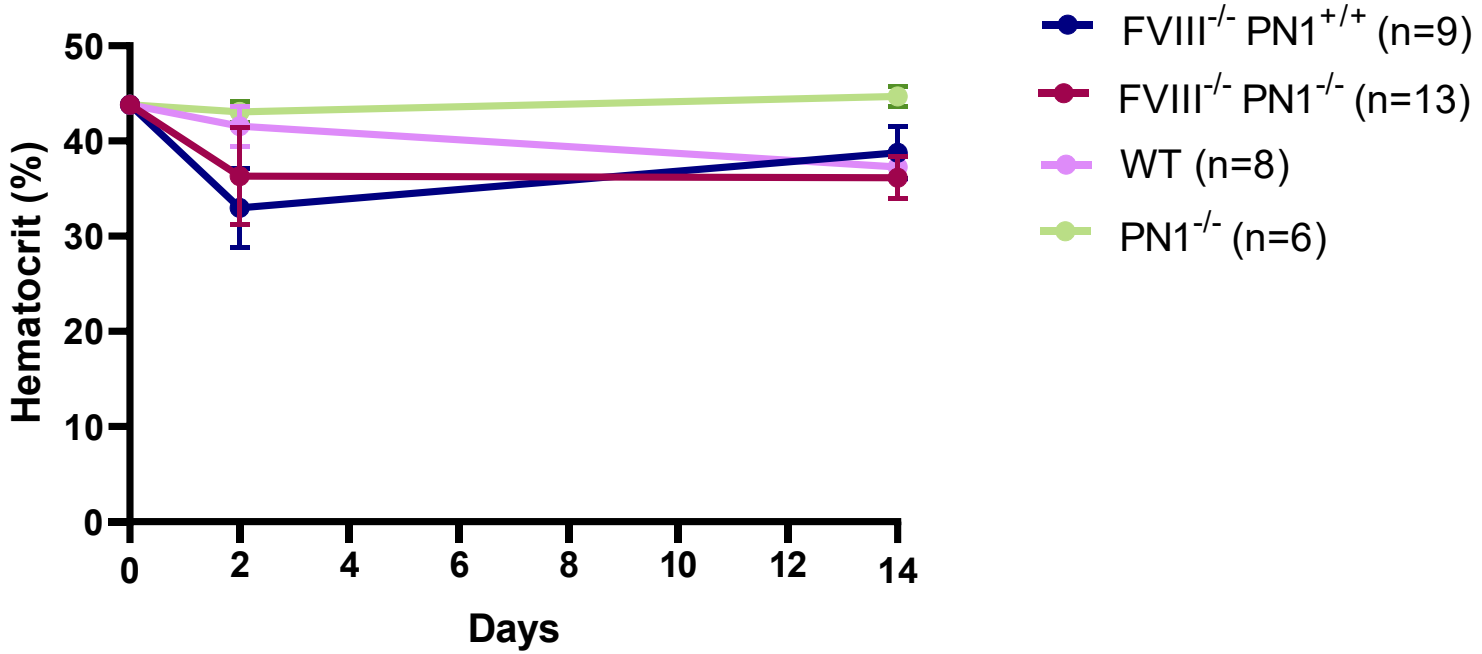
Weight



→ **Hemophilic mice (no matter PN1 expression) lose more weight than WT at day 14**

In vivo model of Hemophilic arthropathy

Hematocrit

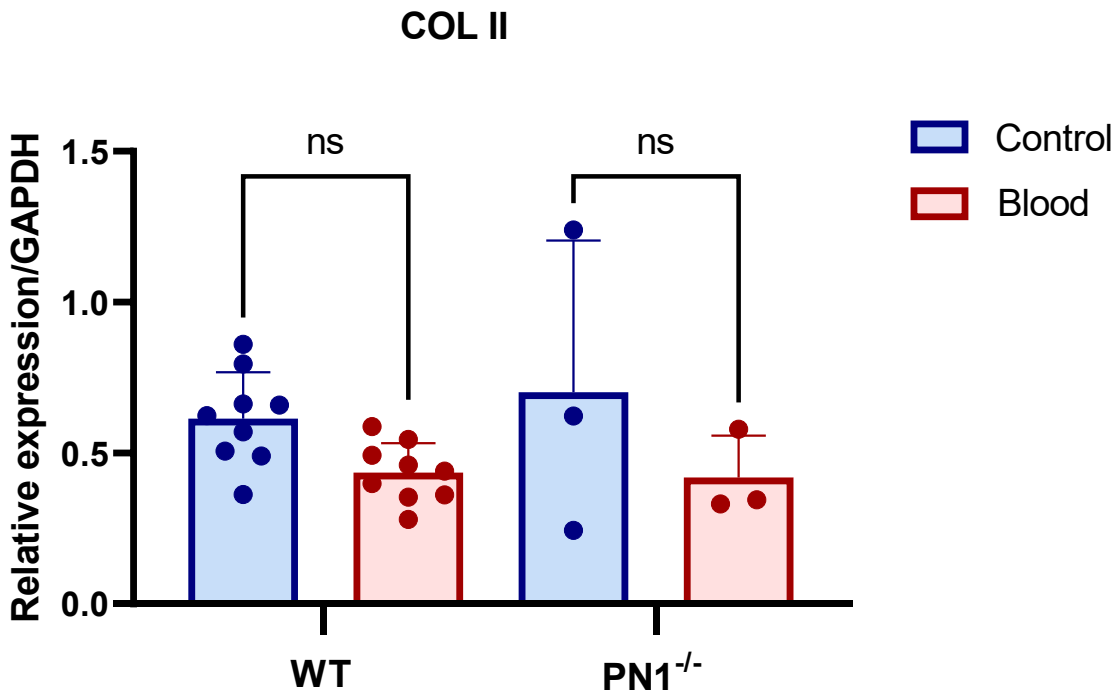


→ Hemophilic mice (no matter PN1 expression) lose mor blood at day 2 than control mice

In vitro model of Hemophilic arthropathy : role of chondrocyte PN1

WT and PN1$^{-/-}$ Chondrocyte

Chondrocytes markers expression



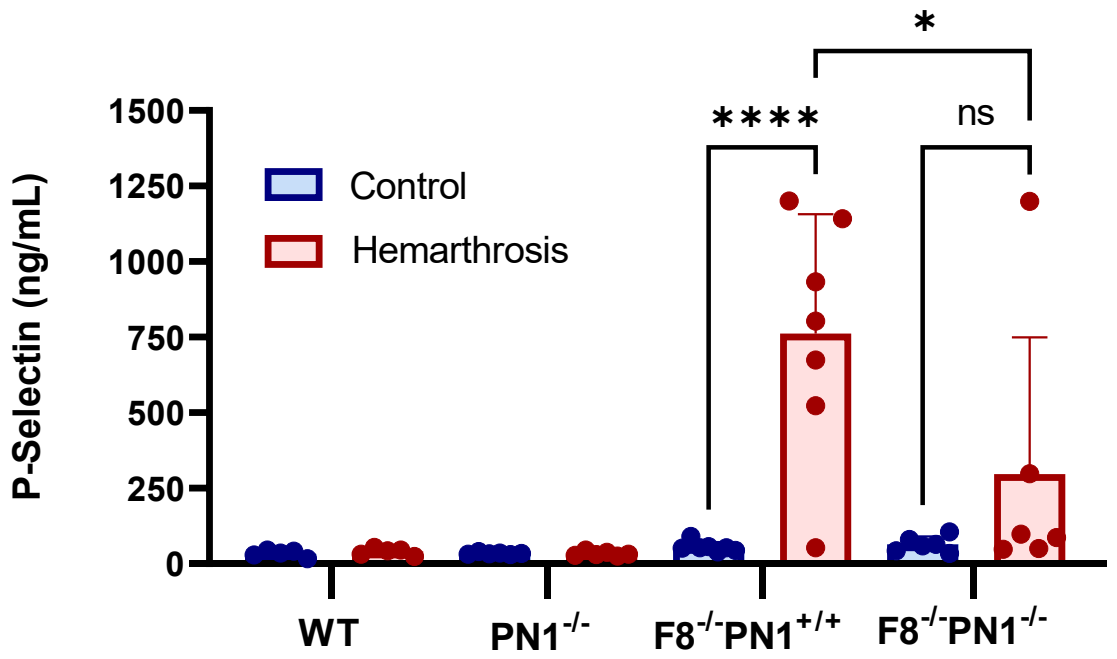
→ **Blood exposition decreases Collagen II expression in both WT and PN1$^{-/-}$ chondrocytes**

In vivo model of Hemophilic arthropathy

Conditioned media

Day 14

Inflammatory cytokine

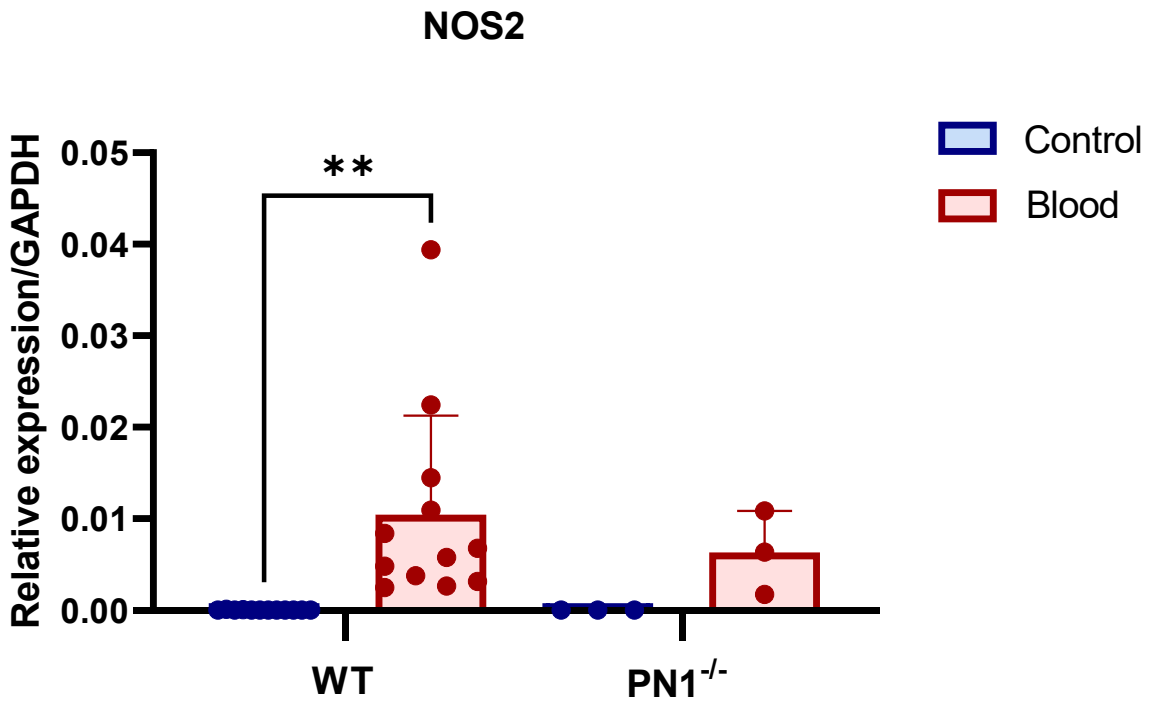


→ By day 14, PN1 deficits reduces inflammatory cytokine levels in hemophilic mice knees

In vitro model of Hemophilic arthropathy : role of chondrocyte PN1

WT and PN1$^{-/-}$
Chondrocyte

Inflammatory markers expression



→ **Inflammatory cytokine rise in WT chondrocytes increase after blood exposure**
But not in PN1$^{-/-}$ chondrocytes