

8° WORKSHOP IN EMATOLOGIA TRASLAZIONALE

DELLA SOCIETÀ ITALIANA DI EMATOLOGIA SPERIMENTALE

Firenze - Auditorium CTO - A.O.U. Careggi, 22-23 giugno 2023

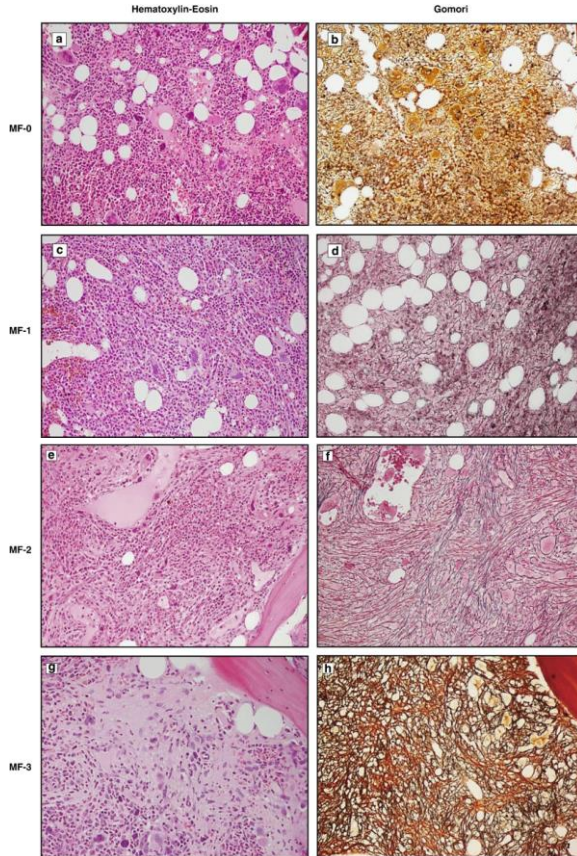


ERK1/2 INHIBITION PREVENTS BONE MARROW FIBROSIS BY REDUCING PLASMATIC OSTEOPONTIN IN A MYELOFIBROSIS MOUSE MODEL

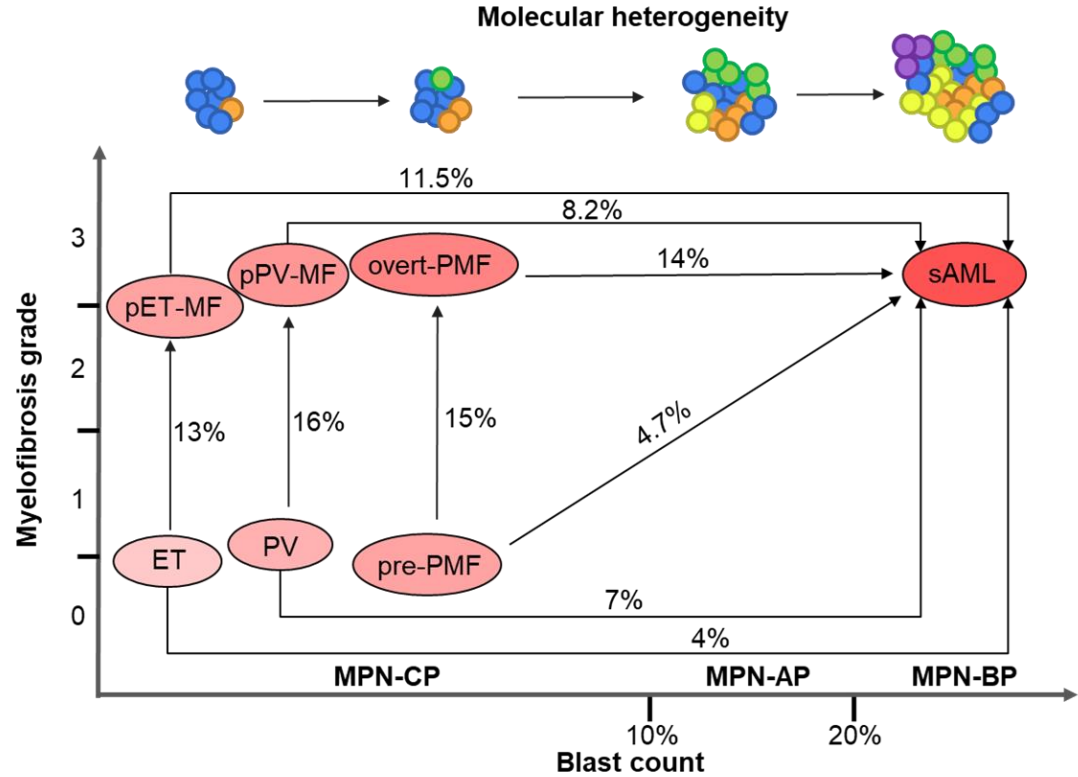
Sebastiano Rontauroli, PhD

*Centre for Regenerative Medicine "Stefano Ferrari", Department of Biomedical, Metabolic and Neural Sciences,
University of Modena and Reggio Emilia, Modena*

Primary Myelofibrosis (PMF)



Gianelli et al, Modern Pathology 2015



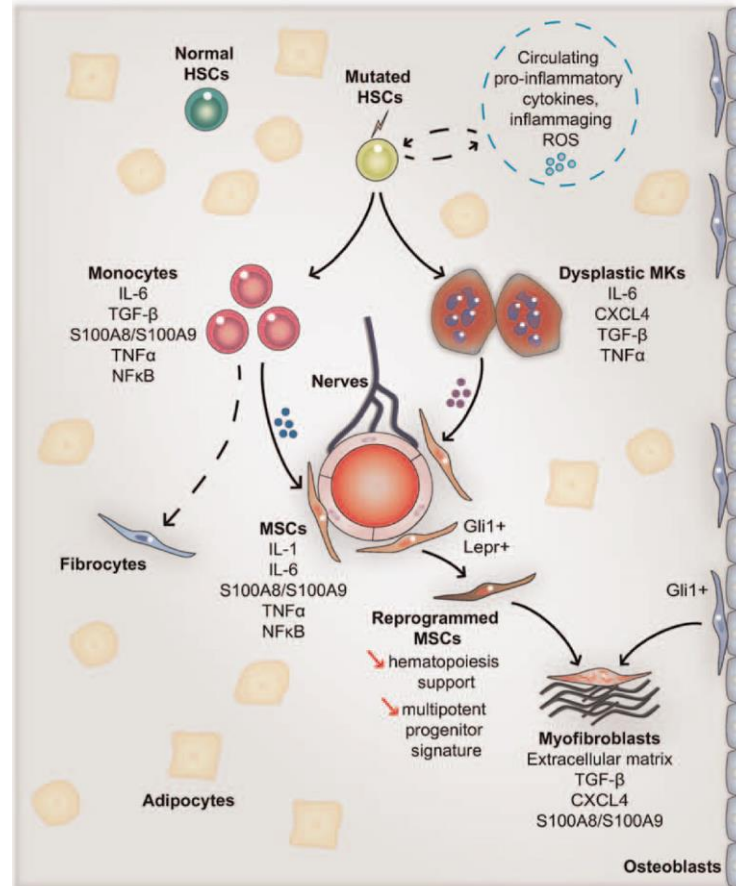
Rontauroli et al, Int J Mol Sci 2022

«bad seeds in bad soil»

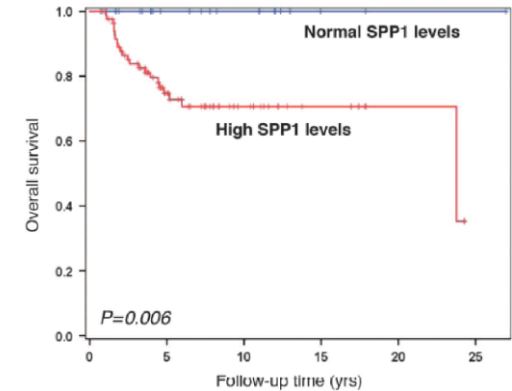
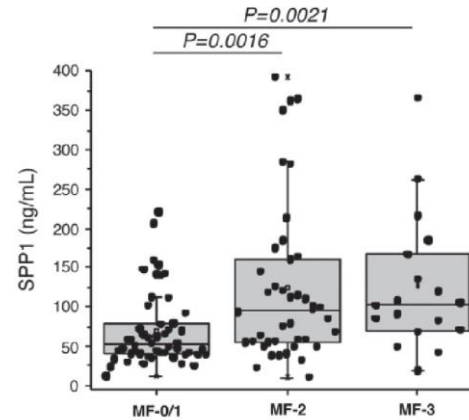
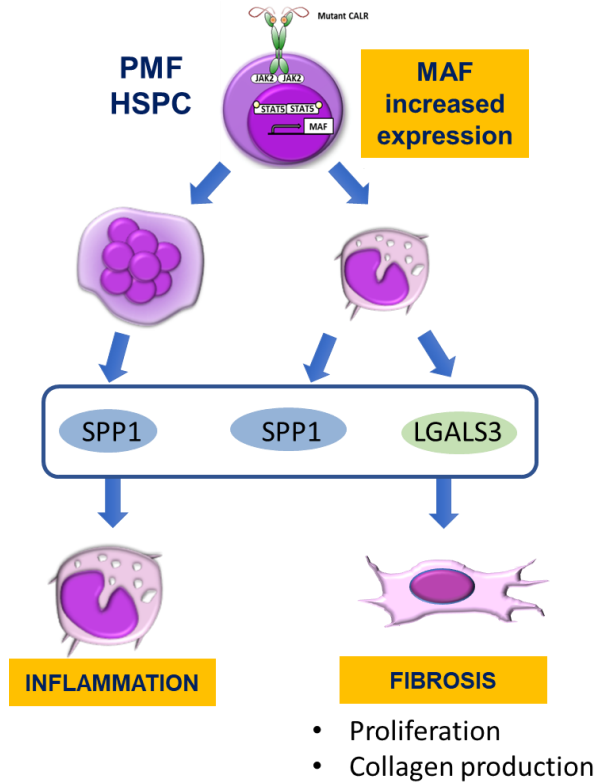
KEY POINTS

- Malignant hematopoietic cells create a chronically inflamed microenvironment via secretion of pro-inflammatory cytokines that severely disrupts the normal bone marrow niche.
- The bone marrow niche, particularly stromal cells, can also contribute to chronic inflammation in MPN, perpetuating a disease-permissive environment.
- Specifically targeting stromal inflammation, together with JAK inhibition, is a promising approach to reduce bone marrow fibrosis and treat MPN.

Gleitz et al. ,CO Hematol, 2021

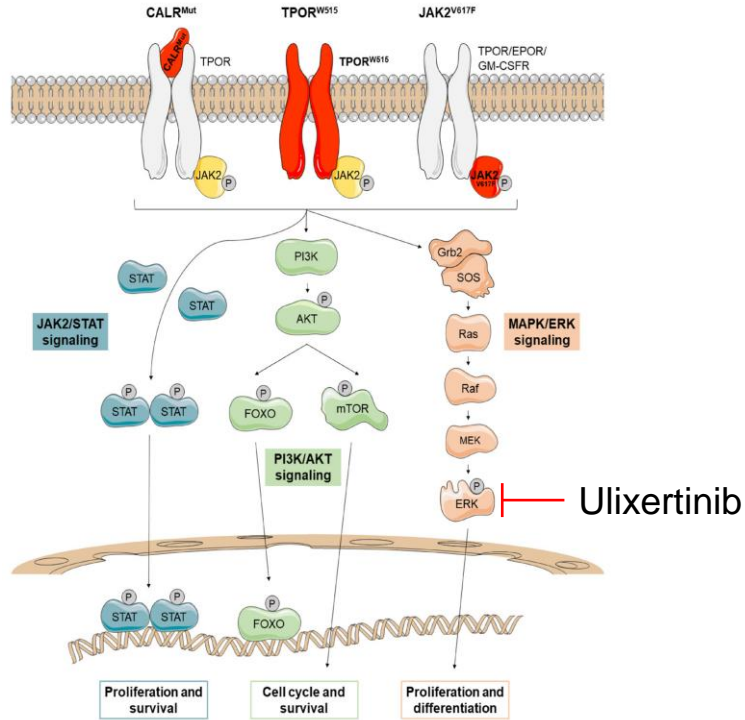


Involvement of MAF/SPP1 axis in the development of bone marrow fibrosis in PMF patients

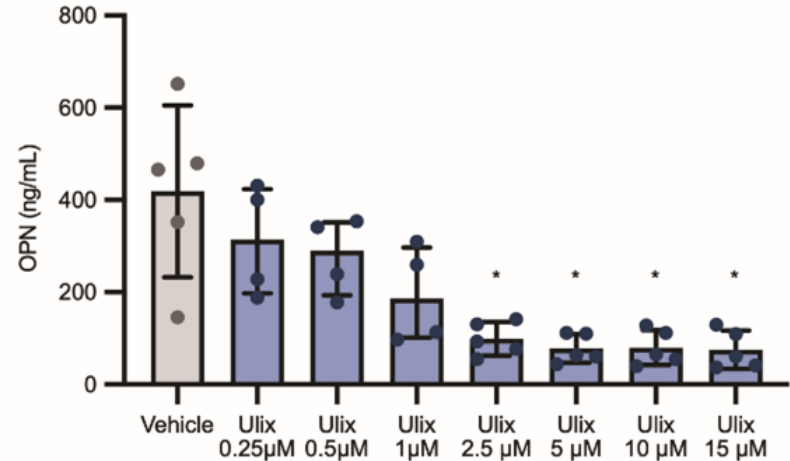


Higher SPP1 plasma levels correlate with a more severe fibrosis degree and a shorter OS in PMF patients

ERK1/2 inhibition reduces OPN production by primary CD14+ monocytes in vitro

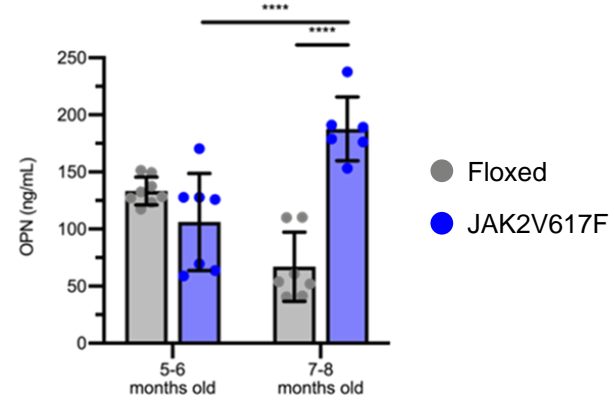
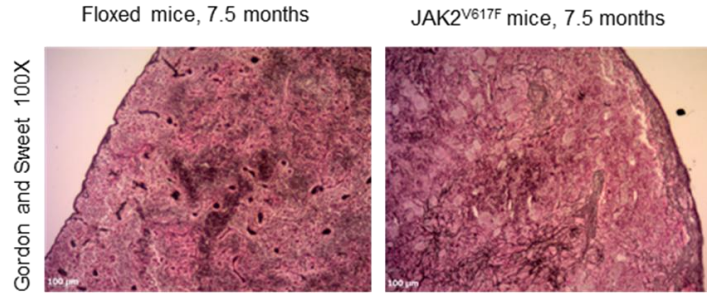


96 h



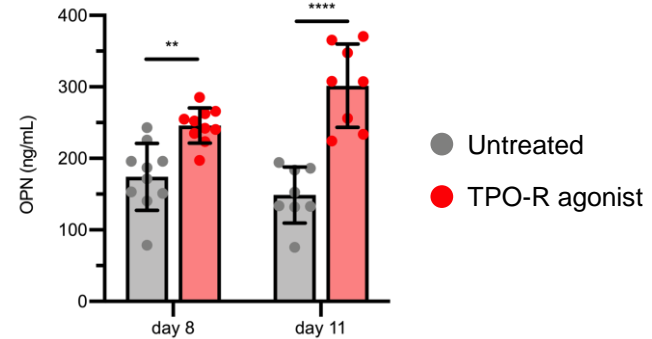
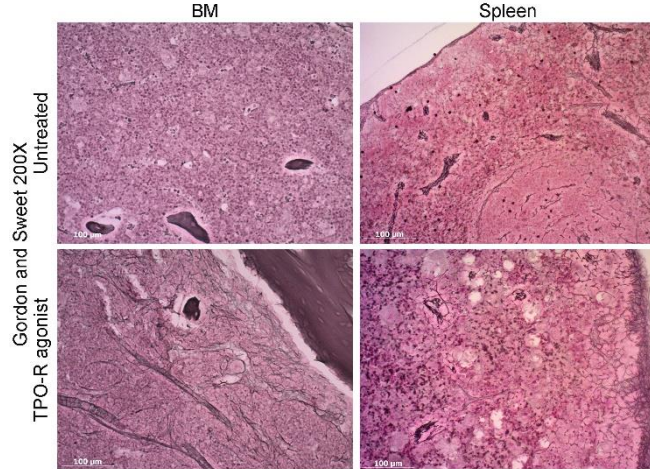
OPN plasma levels are increased in mice developing BM fibrosis

JAK2 V617F Knock-In mice (*Hasan, Blood 2013*)

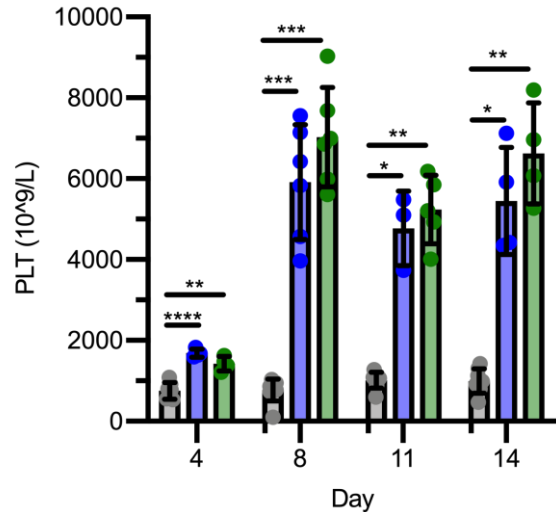
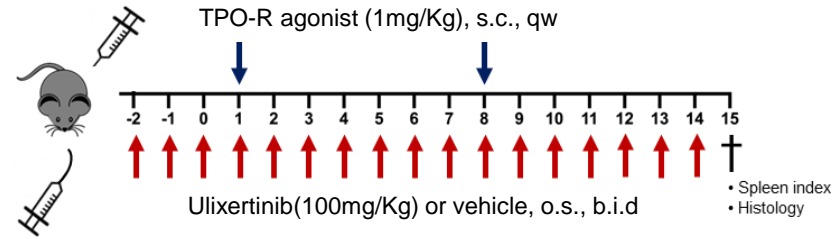


TPO-R agonist treated mice (*Maekawa, Leukemia 2017*)

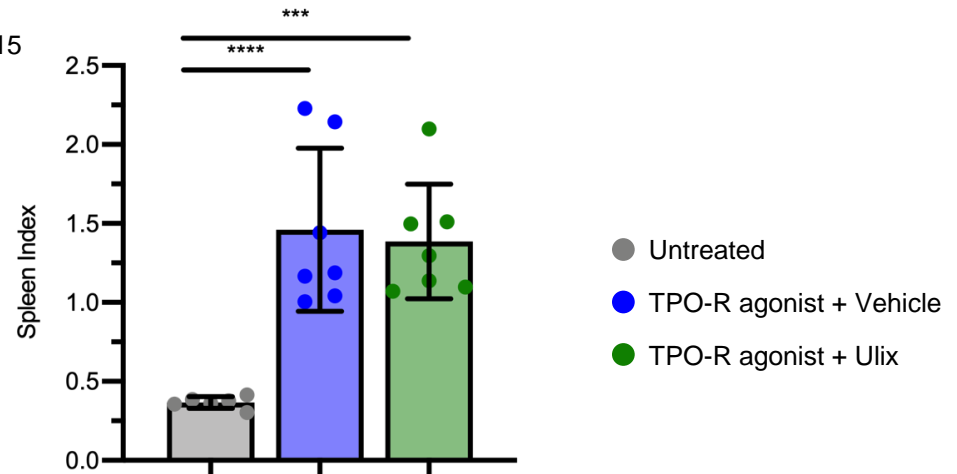
Day 15



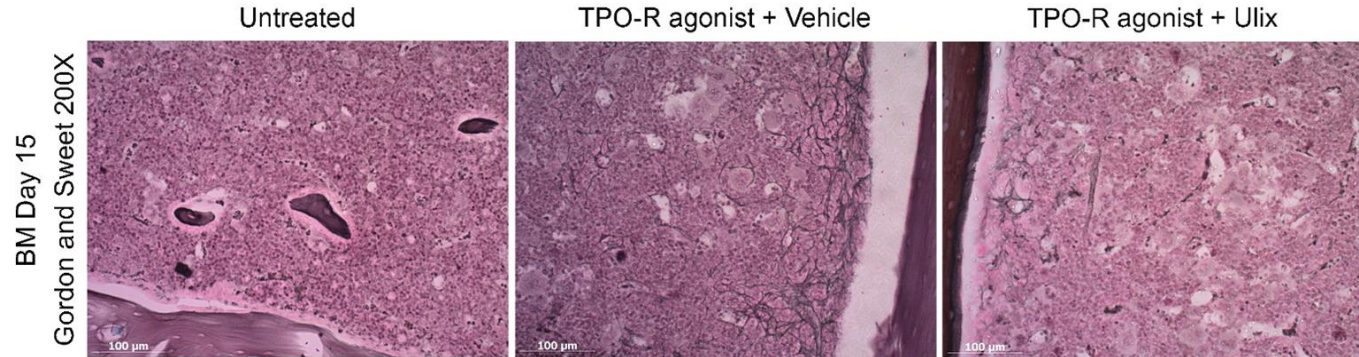
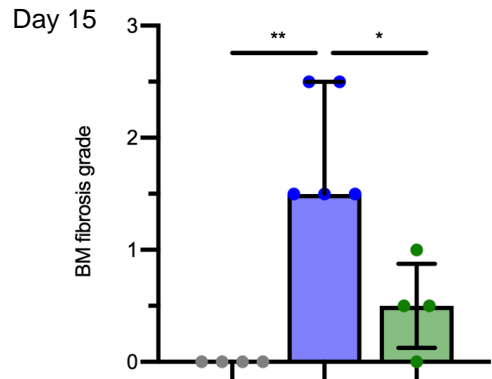
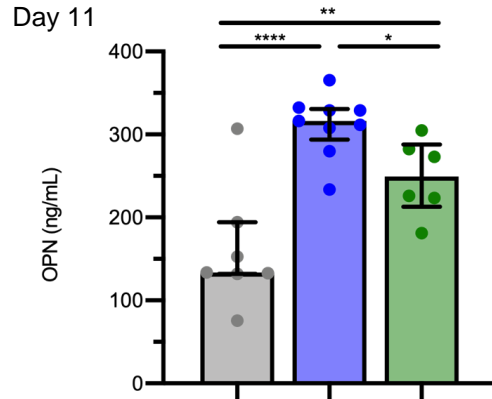
ERK1/2 inhibition does not affect thrombocytosis and splenomegaly in MF mice



Day 15

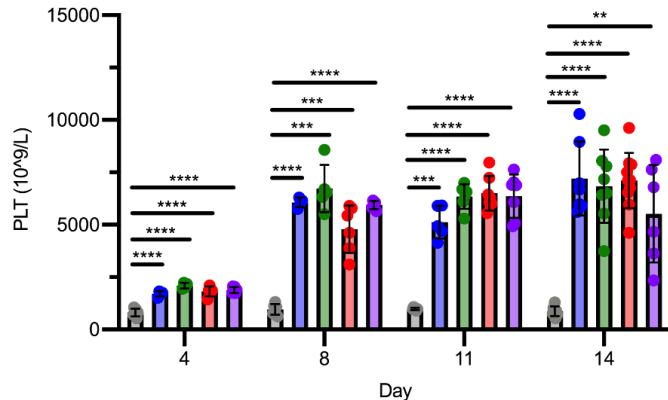
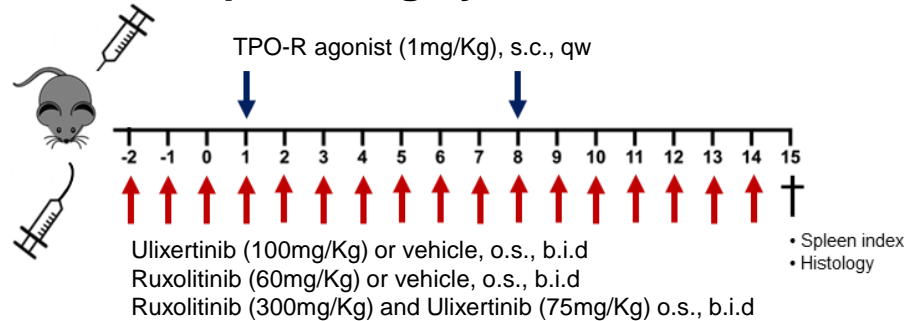


Ulixertinib constrains OPN production and BM fibrosis in TPO-R agonist treated mice

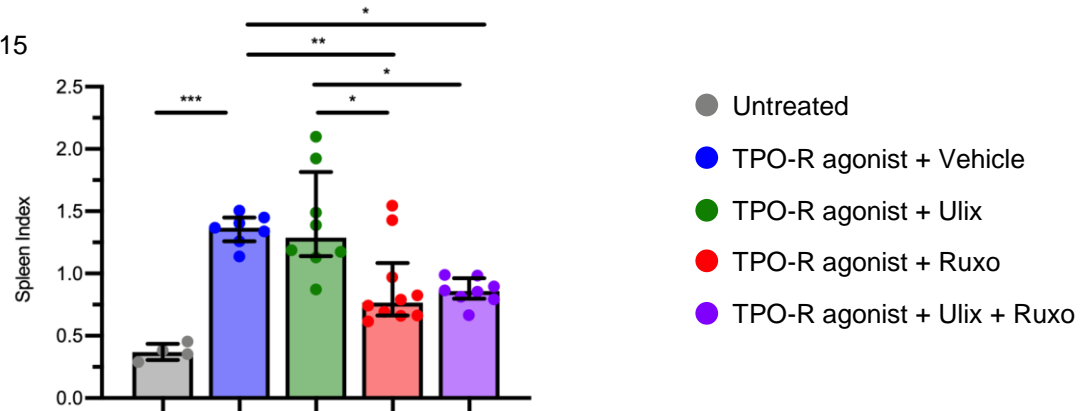


- Untreated
- TPO-R agonist + Vehicle
- TPO-R agonist + Ulix

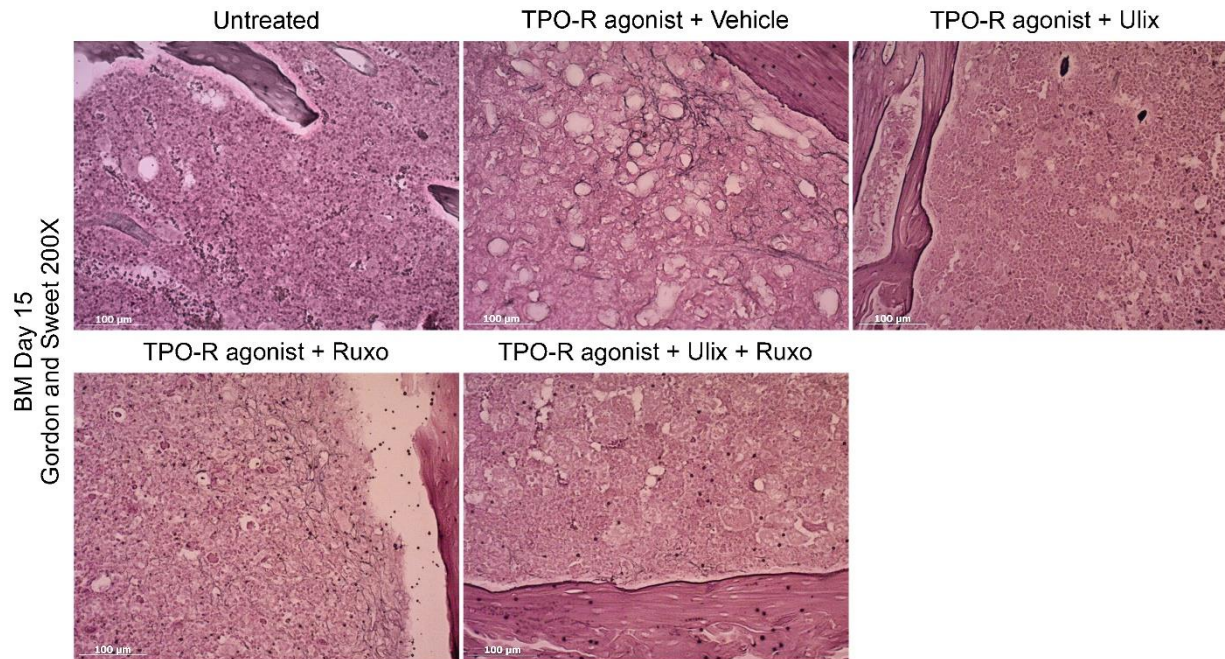
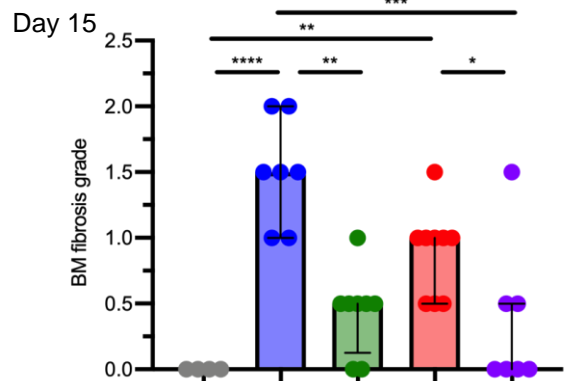
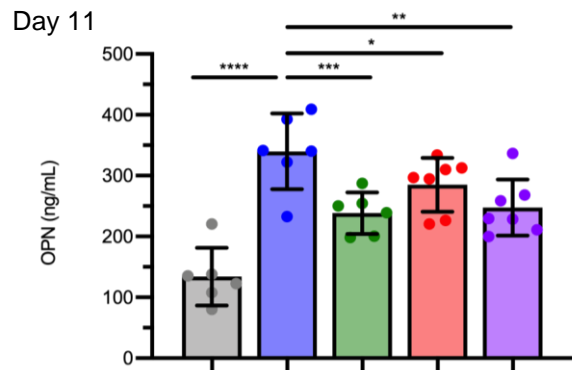
Combined ERK1/2 and JAK1/2 inhibition does not affect thrombocytosis but improves splenomegaly in MF mice



Day 15

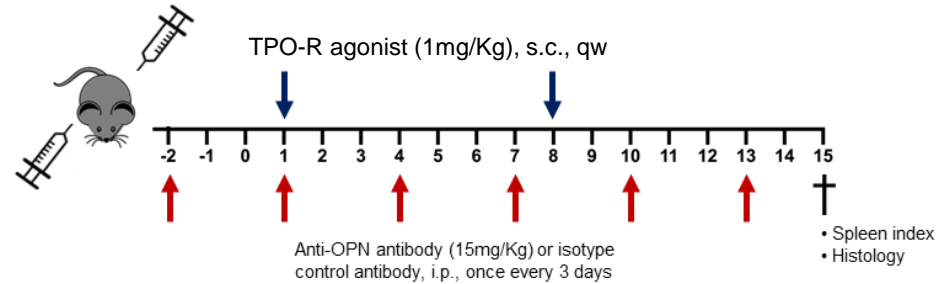


The combination of Ulixertinib and Ruxolitinib reduces OPN plasma levels and BM fibrosis in MF mice



- Untreated
- TPO-R agonist + Vehicle
- TPO-R agonist + Ulix
- TPO-R agonist + Ruxo
- TPO-R agonist + Ulix + Ruxo

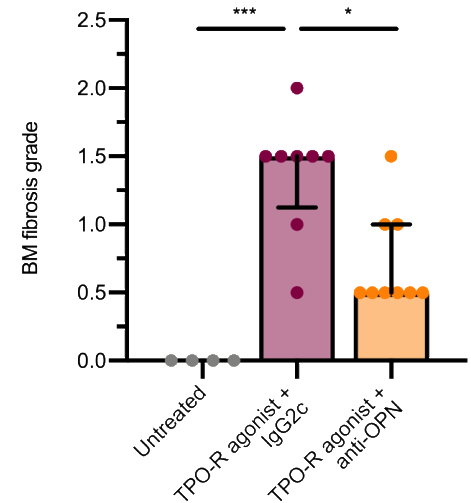
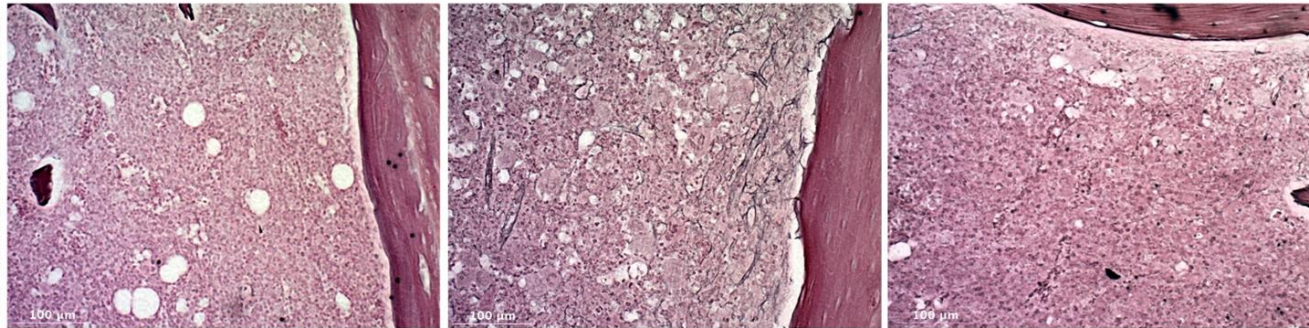
Treatment with anti-OPN neutralizing antibody recapitulates the antifibrotic effect of Ulixertinib



Untreated

TPO-R agonist + IgG2c

TPO-R agonist + anti-OPN



Conclusions

- OPN is a profibrotic molecule, is increased in PMF patients plasma and correlates to the presence of overt fibrosis.
- Plasmatic OPN is increased also in myelofibrosis mouse models and correlates with the presence of BM fibrosis
- ERK1/2 inhibition reduces OPN production by monocytes in vitro
- ERK1/2 inhibition constrains BM fibrosis development in mice through the reduction of OPN plasma levels.

www.nature.com/leu

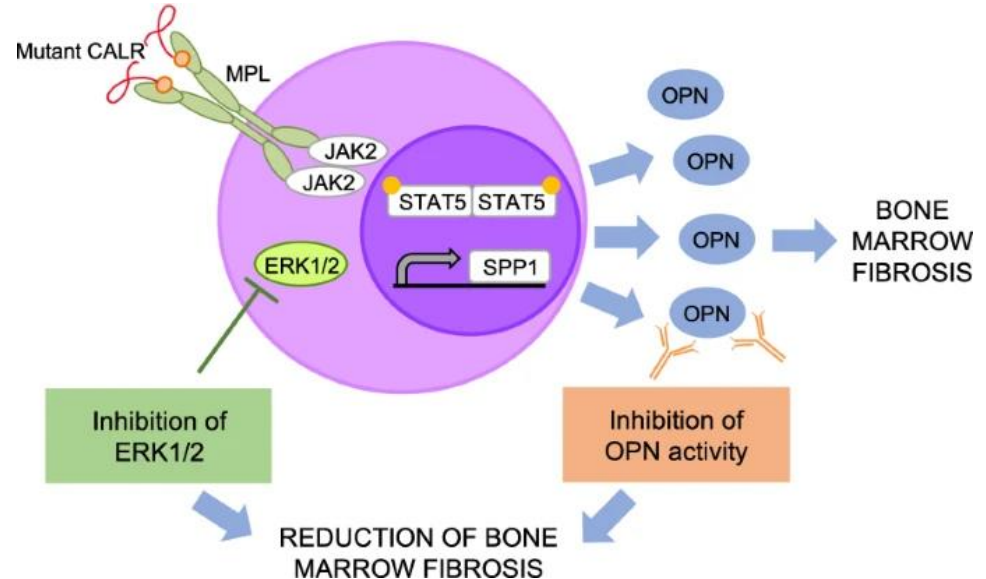
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CHRONIC MYELOPROLIFERATIVE NEOPLASMS

Inhibition of ERK1/2 signaling prevents bone marrow fibrosis by reducing osteopontin plasma levels in a myelofibrosis mouse model

Elisa Bianchi^{1,2,11}, Sebastiano Rontautoli^{1,3,11}, Lara Tavernari^{1,2,11}, Margherita Mirabile^{1,2}, Francesca Pedrazzi^{1,2}, Elena Genovese^{1,3}, Stefano Sartini^{1,2}, Massimiliano Dall'Ora⁴, Giulia Grisendi⁵, Luca Fabbiani⁶, Monica Maccaferri⁷, Chiara Carretta^{1,2}, Sandra Parenti^{1,2}, Sebastian Fantini⁸, Niccolò Bartalucci⁹, Laura Calabresi⁷, Manjola Ballu⁷, Paola Guglielmelli¹⁰, Leonardo Potenza⁴, Enrico Tagliafico⁴, Lorena Losi¹⁰, Massimo Dominici¹⁰, Mario Luppi⁴, Alessandro Maria Vannucchi⁸ and Rossella Manfredini^{1,3,11}



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UNIVERSITÀ
DEGLI STUDI
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Rossella Manfredini
Elisa Bianchi
Lara Tavernari
Margherita Mirabile

Francesca Pedrazzi
Elena Genovese
Chiara Carretta
Sandra Parenti

A.M. Vannucchi
Paola Guglielmelli
Niccolò Bartalucci
Laura Calabresi
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