XIX CONGRESSO NAZIONALE SIES 2026

Dissecting the role of CCL2/CCR2 axis in Myelofibrosis: Translational Evidence from Murine Models to Human Cells

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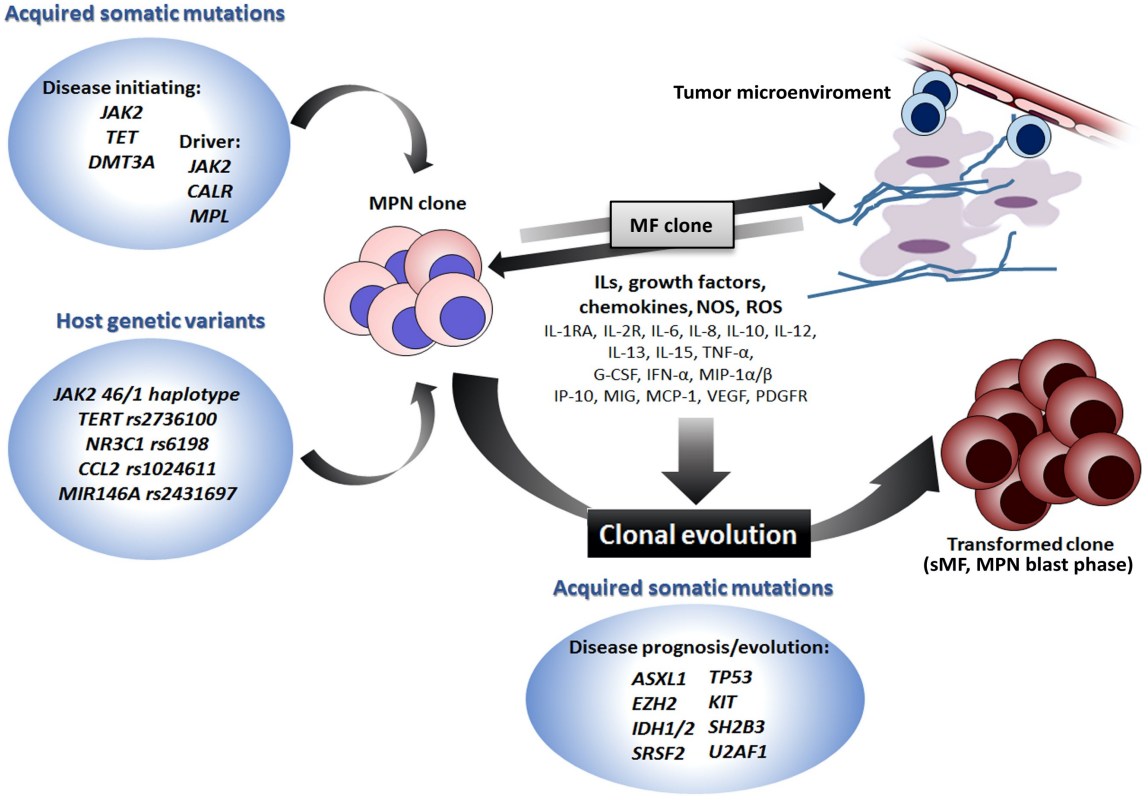
Firenze | 4-6 marzo 2026
Palazzo degli Affari

Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
NONE							

MPNs as the paradigm of inflammation-related cancer development



INCREASED LEVELS OF PRO-INFLAMMATORY/PRO-FIBROTIC CYTOKINES AND CHEMOKINES

↓

«INFLAMED» MICROENVIRONMENT

↓

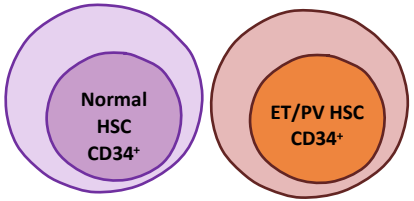
CLONAL EVOLUTION

FIBROTIC TRANSFORMATION

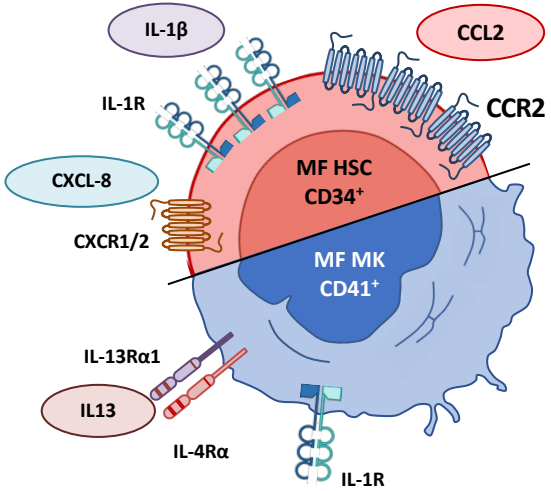
Reviewed in: Masselli E. et al. Cells 2020

Activation of chemokine/cytokines axis in MF

- IL-1/IL-1R Axis (Rai S et al, Nat Commun 2022; Rahman MF, et al, Nat Commun, 2022)
- CXCL8/CXCR1/2 Axis (Dunbar AJ et al, Blood 2023)
- IL4/IL13 Axis (Melo-Cardenas J, et al, Blood, 2022)



- **CCL2/CCR2 Axis** (Masselli E et al., Cancers, 2021)



Pozzi G. et al., *Biomedicines*, 2023

CCL2/CCR2 AXIS IN MF

BRIEF COMMUNICATION
Leukemia
Chronic myeloproliferative neoplasms
The -2518 A/G polymorphism of the monocyte chemoattractant protein-1 as a candidate genetic predisposition factor for secondary myelofibrosis and biomarker of disease severity

Elena Masselli[1] · Cecilia Carubbi[1] · Benedetta Cambò[2] · Giulia Pozzi[1] · Giuliana Gobbi[1] · Prisco Mirandola[1] Elena Follini[2] · Luca Pagliaro[2] · Daniela Di Marcantonio[3] · Francesco Bonatti[4] · Antonio Percesepe[4] · Stephen M. Sykes[5] · Franco Aversa[2] · Marco Vitale[1,5]

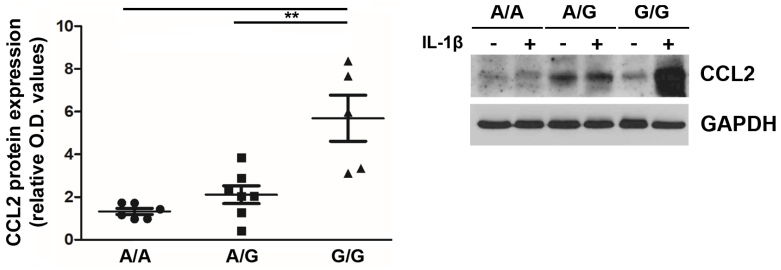
cancers
MDPI
Article
Impact of the rs1024611 Polymorphism of *CCL2* on the Pathophysiology and Outcome of Primary Myelofibrosis

Elena Masselli [1], Cecilia Carubbi [1], Giulia Pozzi [1], Antonio Percesepe [2], Rita Campanelli [3], Laura Villani [3], Giuliana Gobbi [1], Sabrina Bonomini [4], Giovanni Roti [5], Vittorio Rosti [3], Margherita Massa [6], Giovanni Barosi [3] and Marco Vitale [1,*]

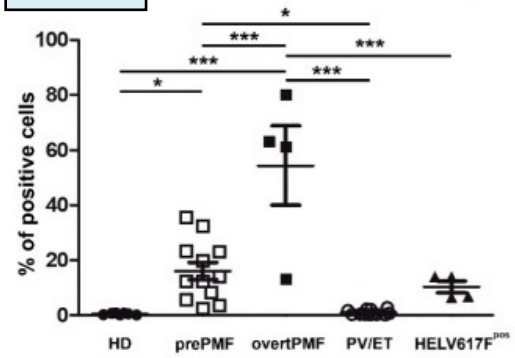
frontiers | Frontiers in Oncology
Tracking fibrosis in myeloproliferative neoplasms by CCR2 expression on CD34+ cells

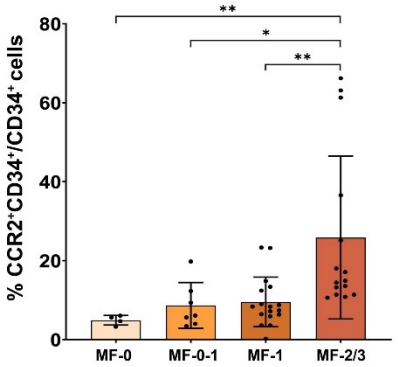
Giulia Pozzi[1†], Cecilia Carubbi[1†], Giuliana Gobbi[1], Sara Tagliaferri[1], Prisco Mirandola[1], Marco Vitale[1,2*] and Elena Masselli[1,2*]

CCL2



CCR2

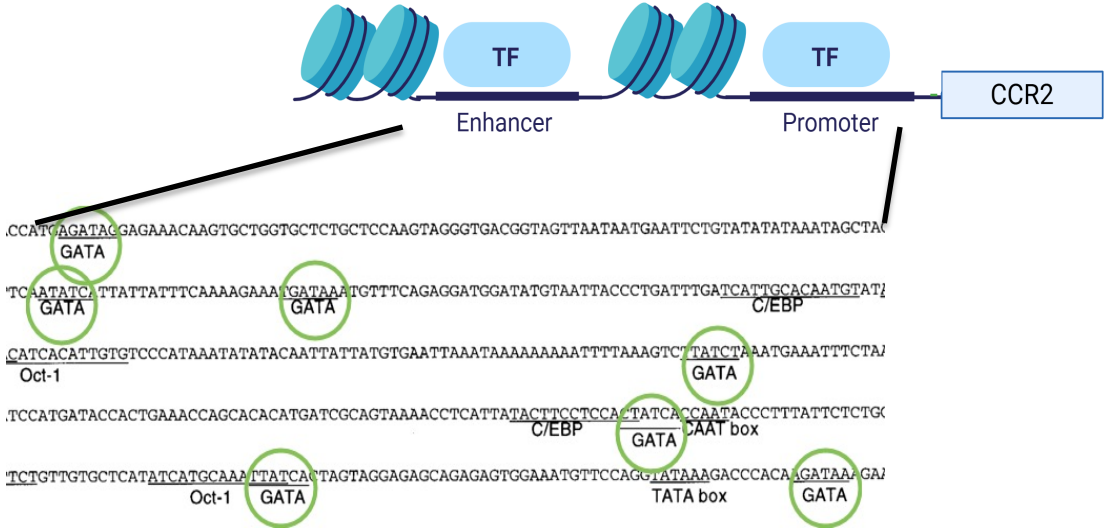




- **CCL2** overexpression in MF is underpinned by the rs1024611 SNP in *CCL2* promoter enhancing gene transcription
- **CCR2** is selectively expressed by CD34+ MF cells and correlates with the degree of BM fibrosis

GATA and CCR2

What can regulate the selective expression of CCR2 in myelofibrosis?

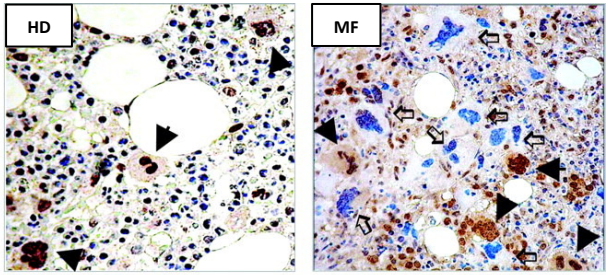


(Yamamoto K. et al., J Biol Chem, 1998)

The **5'-flanking region** of the *CCR2* gene has potential binding sites for GATA family transcription factors

GATA-1 and Myelofibrosis

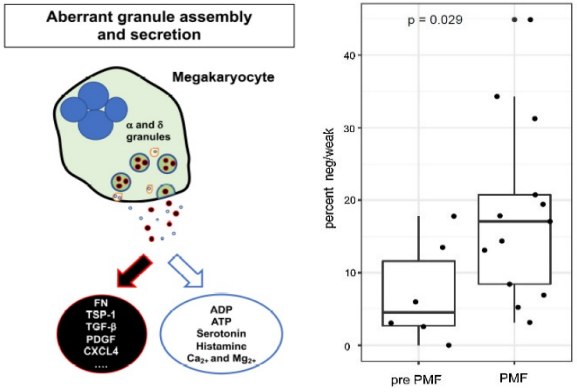
→ Reduced expression of GATA-1 is associated with aberrant megakaryocytopoiesis in MF



GATA-1pos MKs
GATA-1neg MKs

Vannucchi AM et al. Am J Pathol 2005

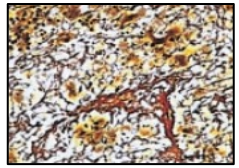
→ In MF Mks are source of pro-fibrotic and pro-inflammatory cytokines and the % of GATA-1^{neg} MKs correlates with the grading of BM fibrosis



Malara A et al., Mediterr J Hematol Infect Dis. 2018
Varricchio L and Hoffman R, Front Oncol 2022
Sangiorgio VFI et al. Leukemia Research 2021

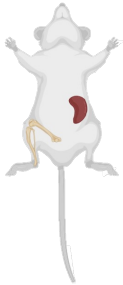
→ GATA-1^{low} mice are a well-established mouse model for MF

GATA-1low

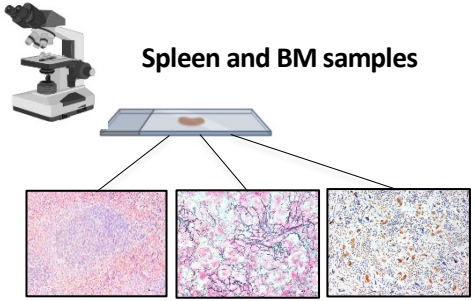


Vannucchi AM...Migliaccio AR, Blood,2002
Migliaccio AR, et al. Blood 2009
Zingariello. M...Migliaccio AR, Blood Cancer Journal 2017

Materials and methods

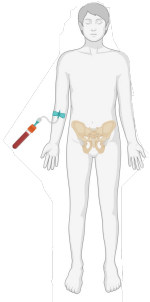


Murine samples: GATA-1^{low} mice vs CD1 mice

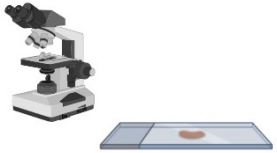


Spleen and BM samples

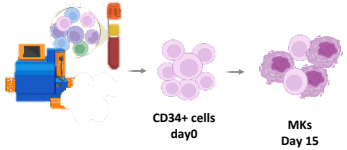
H&E | Reticulin staining | CCR2 IHC



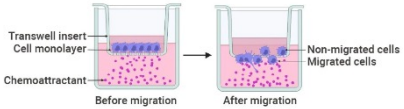
Human samples: MF patients vs HD



Immunofluorescence on BM biopsies



CD34⁺ cells in vitro differentiation



Migration assays on cell lines

Fundings

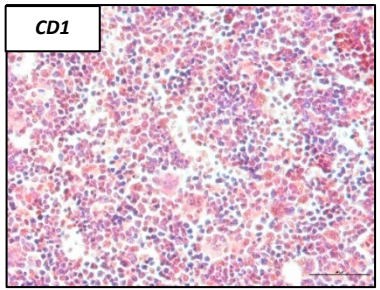
RICERCA FINALIZZATA 2021

PRIN 2022

FIL 2021

GATA-1^{low} mice: Bone Marrow analysis

H&E



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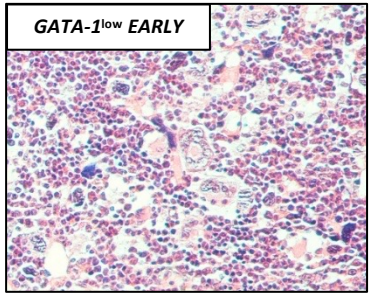

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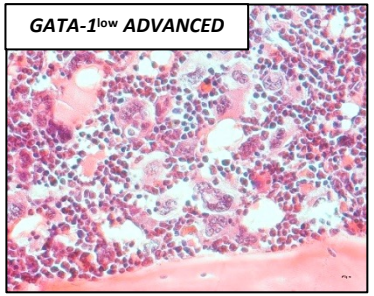

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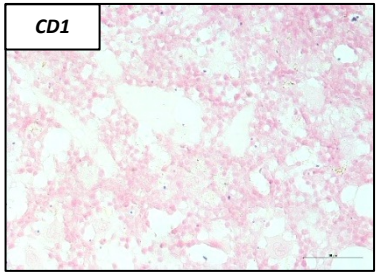
Reticulin staining



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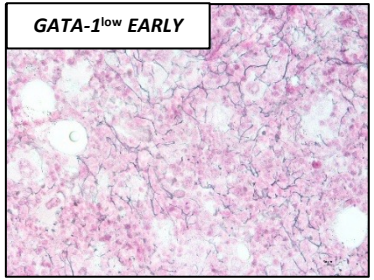

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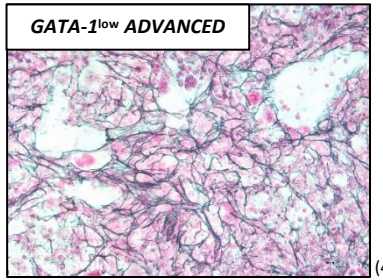

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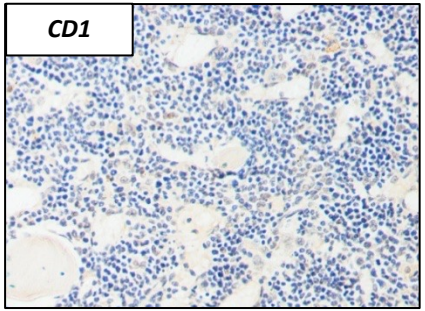
CCR2 IHC



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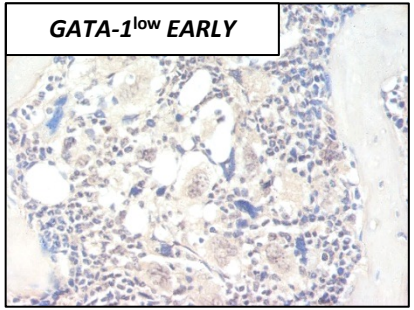

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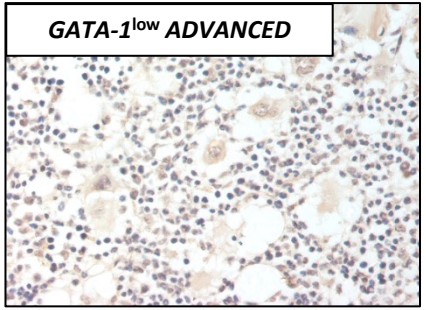

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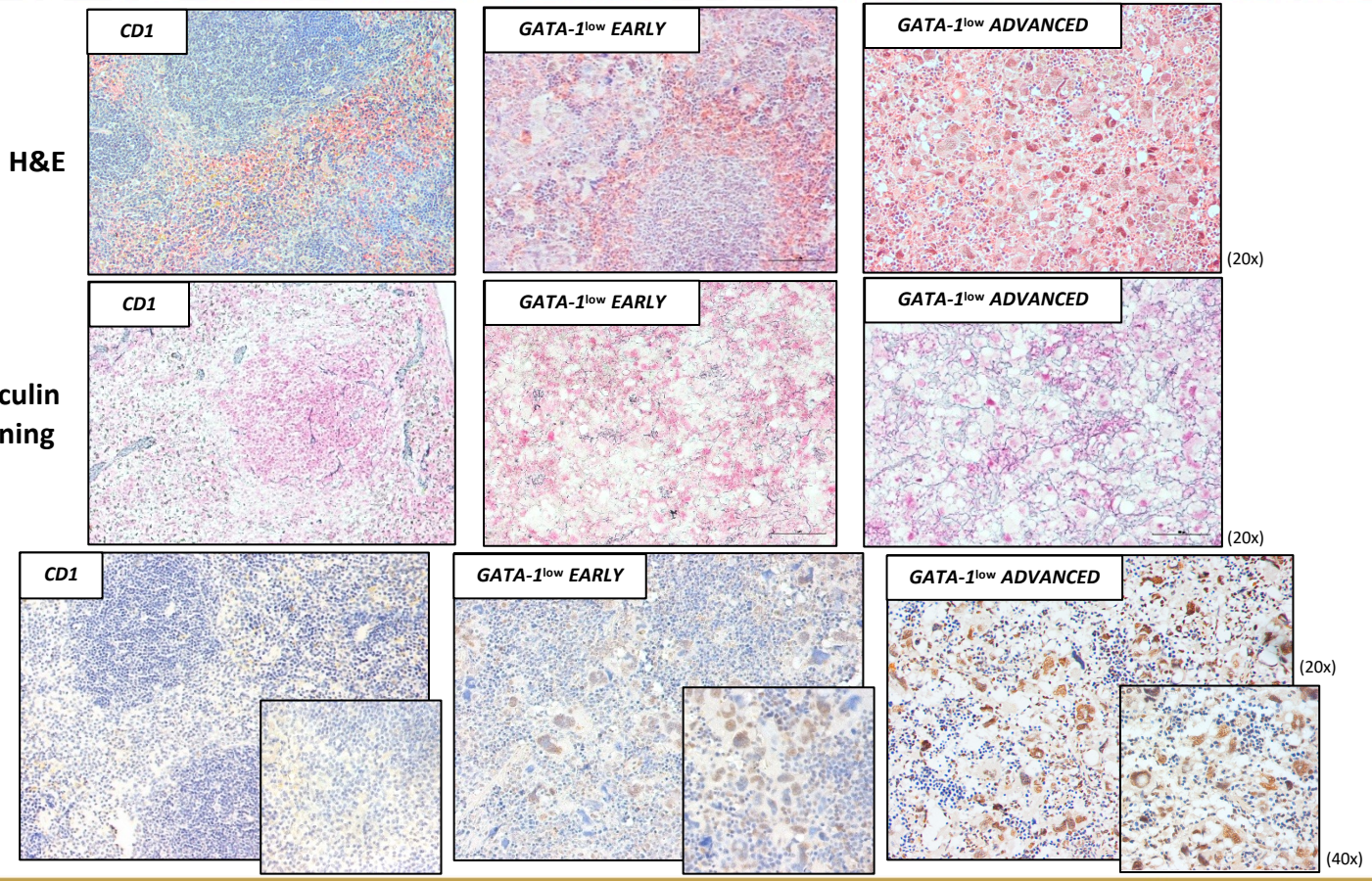
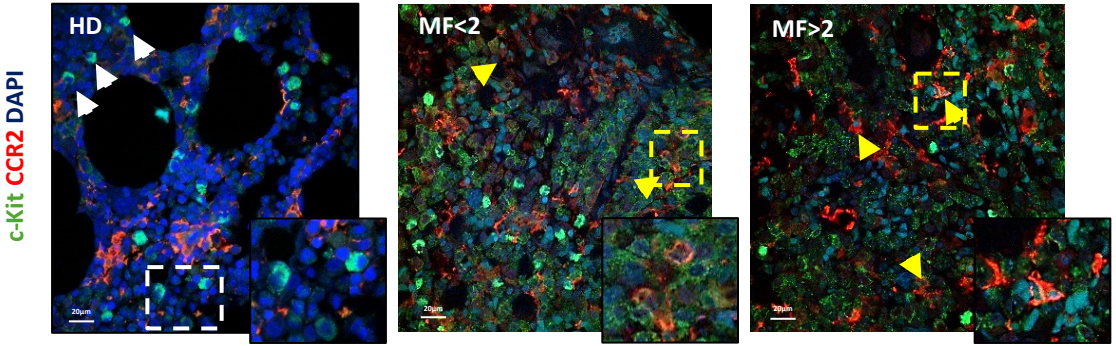
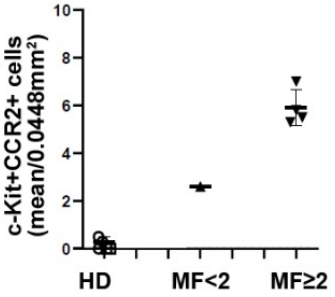
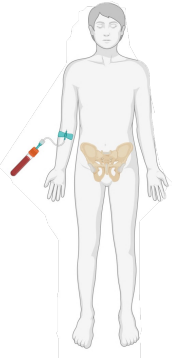
GATA-1^{low} mice: Spleen analysis

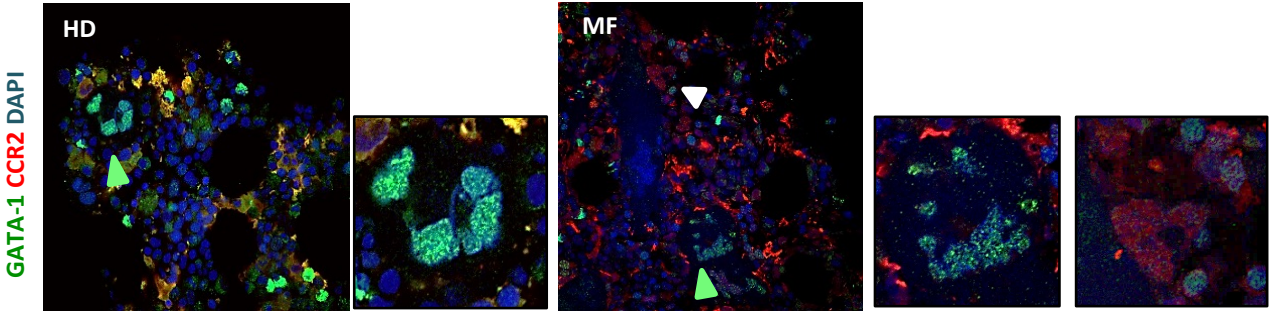


CCR2 expression in MF BM





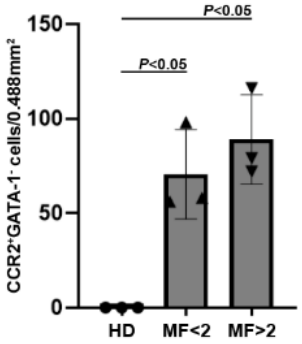




Mature CCR2⁻GATA-1⁺ MK

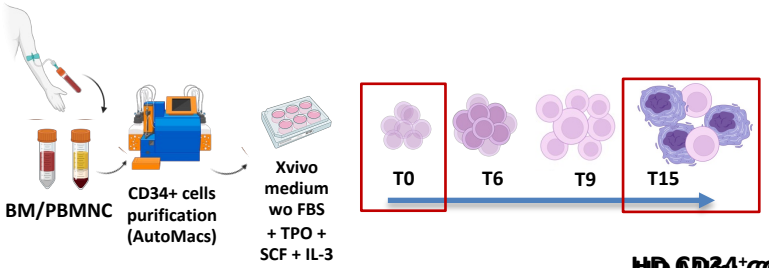
Mature CCR2⁻GATA-1⁺ MK

Immature atypical CCR2⁺GATA-1⁻ MK



CD34+ cells and ex-vivo differentiated MKs from MF and HD showed mutually exclusive CCR2/GATA-1 expression

HD/MF patients

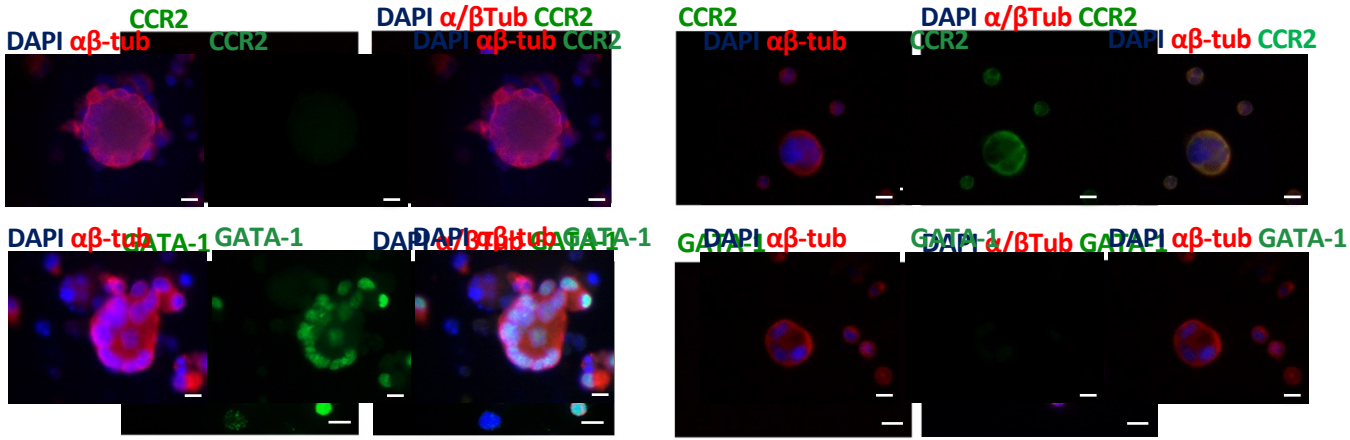


HD CD34⁺ cells: CCR2⁺/GATA-1⁺

HD MKs: CCR2⁺/GATA-1⁺

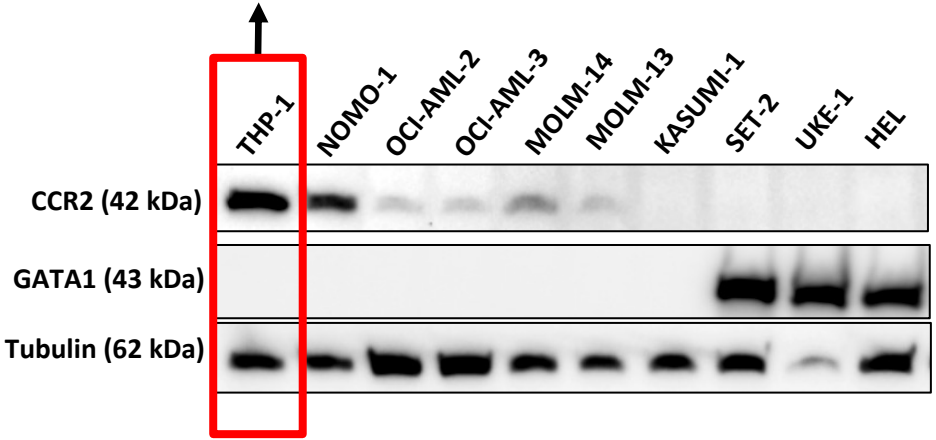
MF CD34⁺ cells: CCR2⁺/GATA-1⁻

MF MKs: CCR2⁺/GATA-1⁻

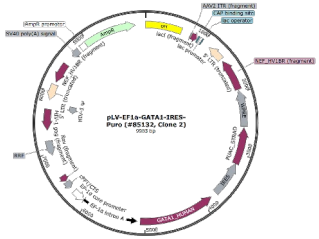


Mutually exclusive CCR2/GATA-1 expression in cell lines

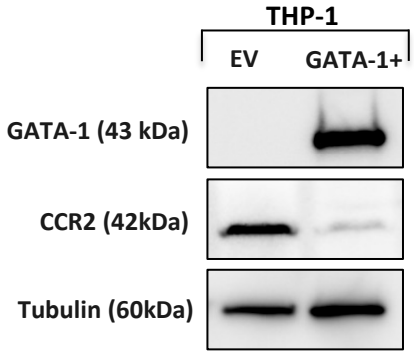
Acute monocytic leukemia

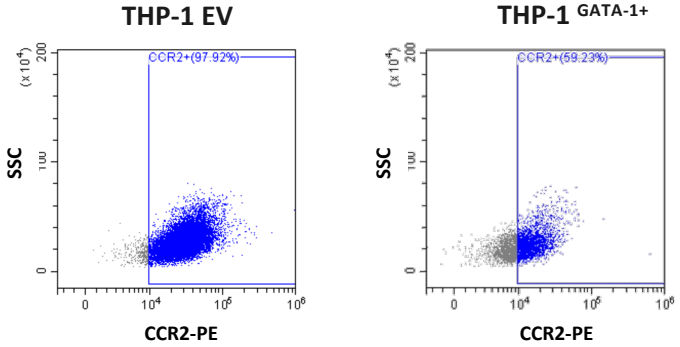


GATA-1 overexpression in THP-1 cell lines

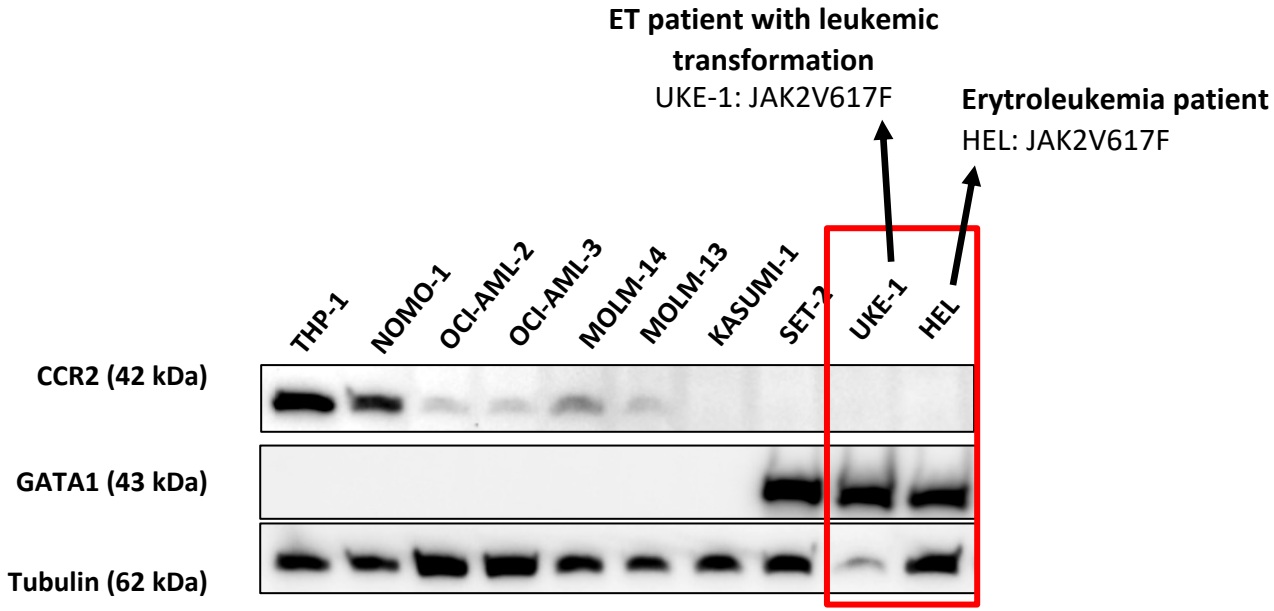


pLV-EF1a-GATA1-IRES-Puro (Addgene #85132)

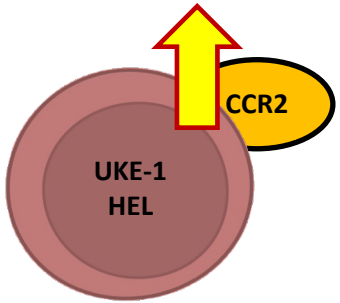


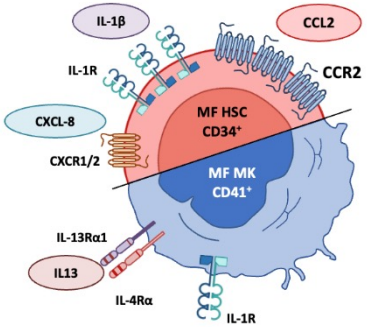


CCR2 overexpression in UKE-1 and HEL cells



CCR2 overexpression in UKE-1 and HEL cells





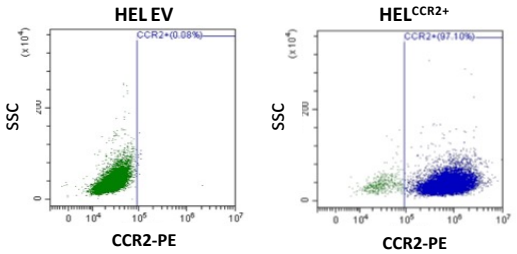
CCL2 chemotaxis

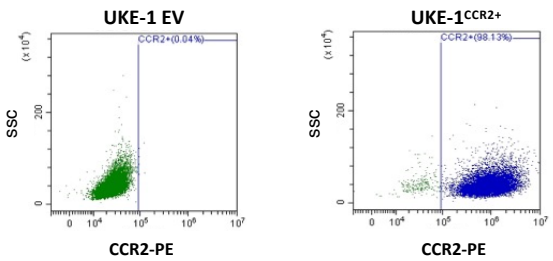
↓

Extramedullary hematopoiesis

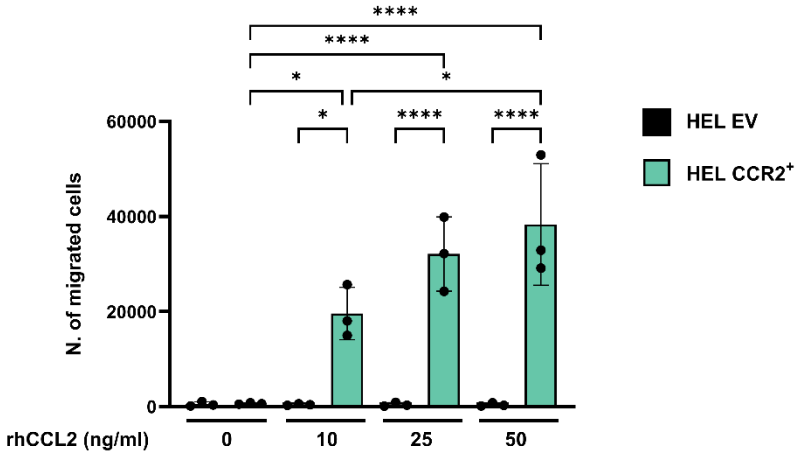
- HEL
  - EV
  - CCR2+
    - 0 ng/ml hCCL2
    - 10 ng/ml hCCL2
    - 25 ng/ml hCCL2
    - 50 ng/ml hCCL2
- UKE-1
  - EV
  - CCR2+
    - 0 ng/ml hCCL2
    - 10 ng/ml hCCL2
    - 25 ng/ml hCCL2
    - 50 ng/ml hCCL2

Transwell assay: 100’000 cells in the upper chamber, 16h migration

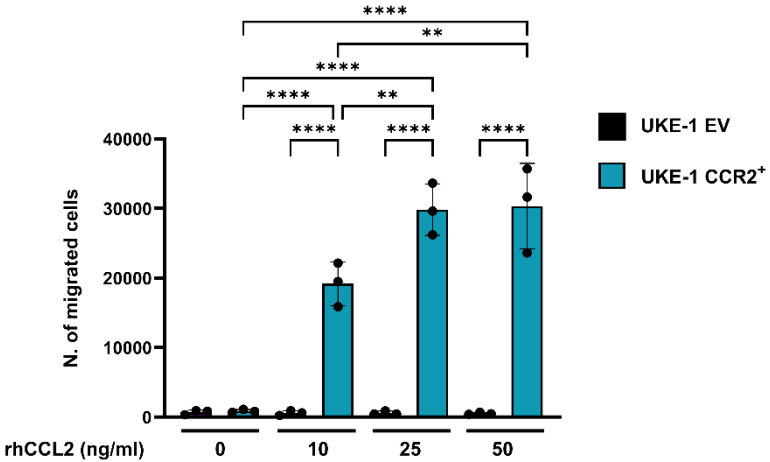




HEL cells – lower chamber (migrated cells)



UKE-1 cells – lower chamber (migrated cells)



Take Home Messages

- **In GATA-1^{low} mice**, the BM and spleen show profound morphological alterations, including a massive infiltration of CCR2^{pos} **megakaryocytes**

- **In MF patients**, BM displayed cKit+/CCR2+ cells and **heterogeneous MK populations**, with immature, aberrant GATA^{neg}CCR2^{pos} MKs co-exhisting with more differentiated GATA^{pos}CCR2^{neg} MKs

- CD34+ cells from MF and HD showed mutually exclusive CCR2/GATA-1 expression (MF CD34+ cells: CCR2^{pos}/GATA^{neg})
  Ex-vivo differentiated MKs from MF and HD showed mutually exclusive CCR2/GATA-1 expression (MF MKs: CCR2^{pos}/GATA^{neg})

- Functional experiments in MPN cell lines demonstrate a reciprocal expression of CCR2 and GATA, suggesting a potential role of **GATA-1 as a repressor of CCR2 expression**

Acknowledgments

Laboratorio di Anatomia Umana e Biologia Applicata al Sistema Ematopoietico
Dep. of Medicine and Surgery, University of Parma

UNIVERSITÀ DI PARMA

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Orsola di Martino
Samuele Cortellazzi
Rossana Vairo
Francesca Zampino
Cristina Micheloni

Marco Vitale
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Thank you for your attention