UNIKLINIK RWTH AACHEN
Centrum für Integrierte Onkologie – CIO Aachen

CRU344 RWTH Aachen University

GERMAN STUDY GROUP MPN

Inflammation in MPNs

Prof. Dr. med. Steffen Koschmieder
Department of Hematology, Oncology, Hemostaseology, and SCT
RWTH Aachen University, Germany

14th Joyce NiblackMemorial Conference on Myeloproliferative Neoplasms

CIO Centrum für Integrierte Onkologie Aachen Bonn Köln Düsseldorf

Disclosures

1. **Employment**
   None

2. **Advisory Board Activity**
   Pfizer, Incyte / Ariad, Novartis, AOP Pharma, BMS, Celgene, Geron, Janssen, CTI, Roche, Baxalta, Sanofi, MPN Hub, Sierra Oncology, Glaxo-Smith Kline, AbbVie, PharmaEssentia, MSD

3. **Stock etc**
   None

4. **Patents, Licences**
   RWTH Aachen University (Patent filed on own BET inhibitors)

5. **Honoraria**
   Novartis, BMS, Pfizer, Incyte, Ariad, Shire, Roche, AOP Pharma, Janssen, Geron, Celgene, Karthos, Abbvie, iOMEDICO, MSD

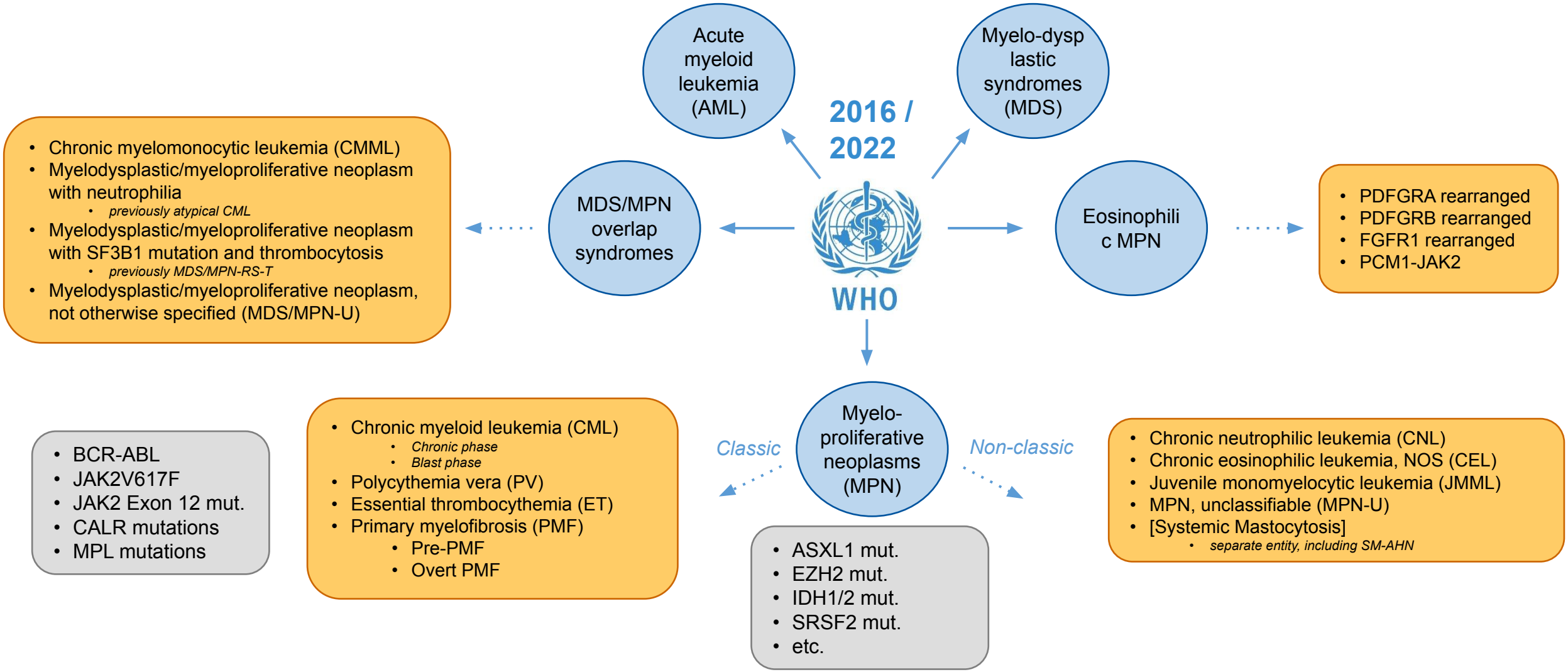
6. **Research Funding**
   Novartis Foundation, BMS, Novartis, AOP Pharma, Janssen/Geron

7. **Other financial disclosures (e.g. travel support)**
   Alexion, Novartis, BMS, Incyte / Ariad, AOP Pharma, Baxalta, CTI, Pfizer, Sanofi, Celgene, Shire, Janssen, Geron, Karthos, Sierra Oncology, Glaxo-Smith Kline, Imago Biosciences, AbbVie, iOMEDICO, MSD

8. **Immaterial disclosures**
   None

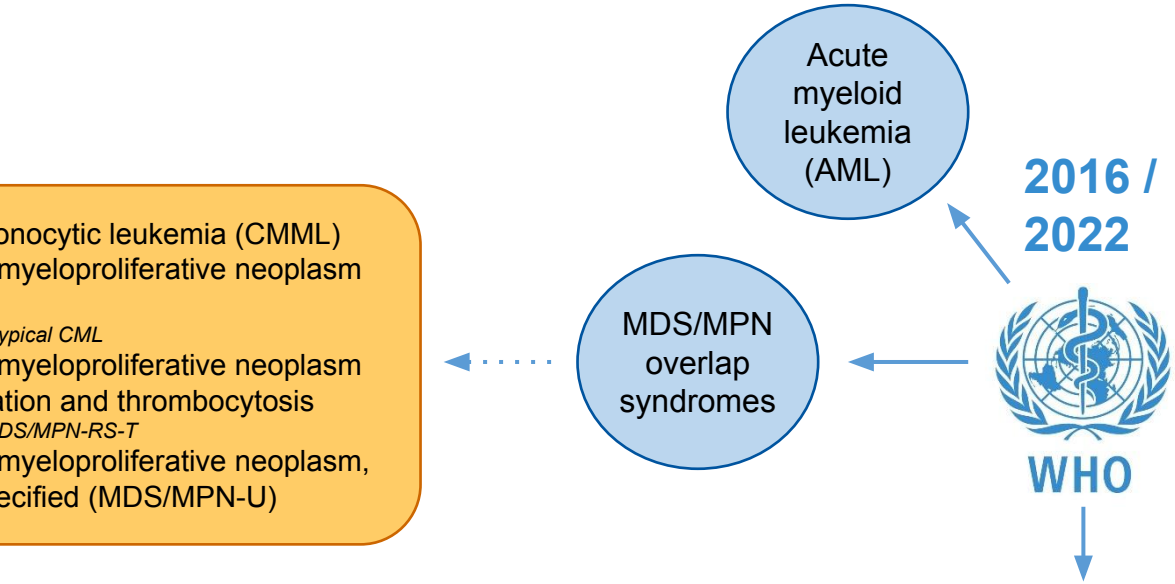
This presentation contains information on off-label therapies

Myeloproliferative Neoplasms (MPN)



Modified from Tefferi & Vainchenker JCO 2011, Arber et al Blood 2016, Khoury et al Leukemia 2022

Myeloproliferative Neoplasms (MPN)



- Chronic myelomonocytic leukemia (CMML)
- Myelodysplastic/myeloproliferative neoplasm with neutrophilia
  - *previously atypical CML*
- Myelodysplastic/myeloproliferative neoplasm with SF3B1 mutation and thrombocytosis
  - *previously MDS/MPN-RS-T*
- Myelodysplastic/myeloproliferative neoplasm, not otherwise specified (MDS/MPN-U)

- PDFGRA rearranged
- PDFGRB rearranged
- FGFR1 rearranged
- PCM1-JAK2

- BCR-ABL
- JAK2V617F
- JAK2 Exon 12 mut.
- CALR mutations
- MPL mutations

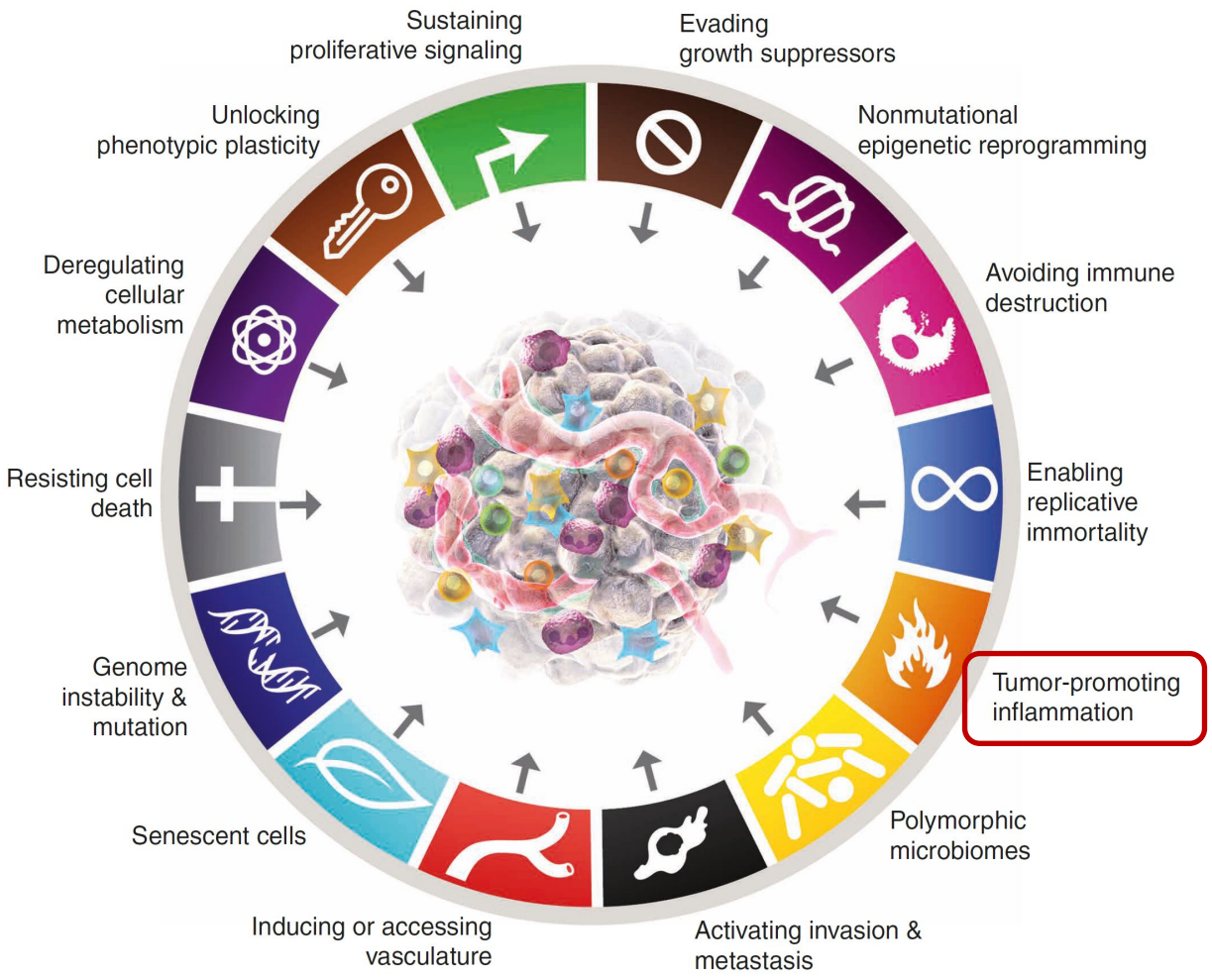
- Chronic myeloid leukemia (CML)
  - *Chronic phase*
  - *Blast phase*
- Polycythemia vera (PV)
- Essential thrombocythemia (ET)
- Primary myelofibrosis (PMF)
  - Pre-PMF
  - Overt PMF

- ASXL1 mut.
- EZH2 mut.
- IDH1/2 mut.
- SRSF2 mut.
- etc.

- Chronic neutrophilic leukemia (CNL)
- Chronic eosinophilic leukemia, NOS (CEL)
- Juvenile monomyelocytic leukemia (JMML)
- MPN, unclassifiable (MPN-U)
- [Systemic Mastocytosis]
  - *separate entity, including SM-AHN*

Modified from Tefferi & Vainchenker JCO 2011, Arber et al Blood 2016, Khoury et al Leukemia 2022

Inflammation and cancer: One of the hallmarks of cancer



Hanahan Cancer Discovery 2022

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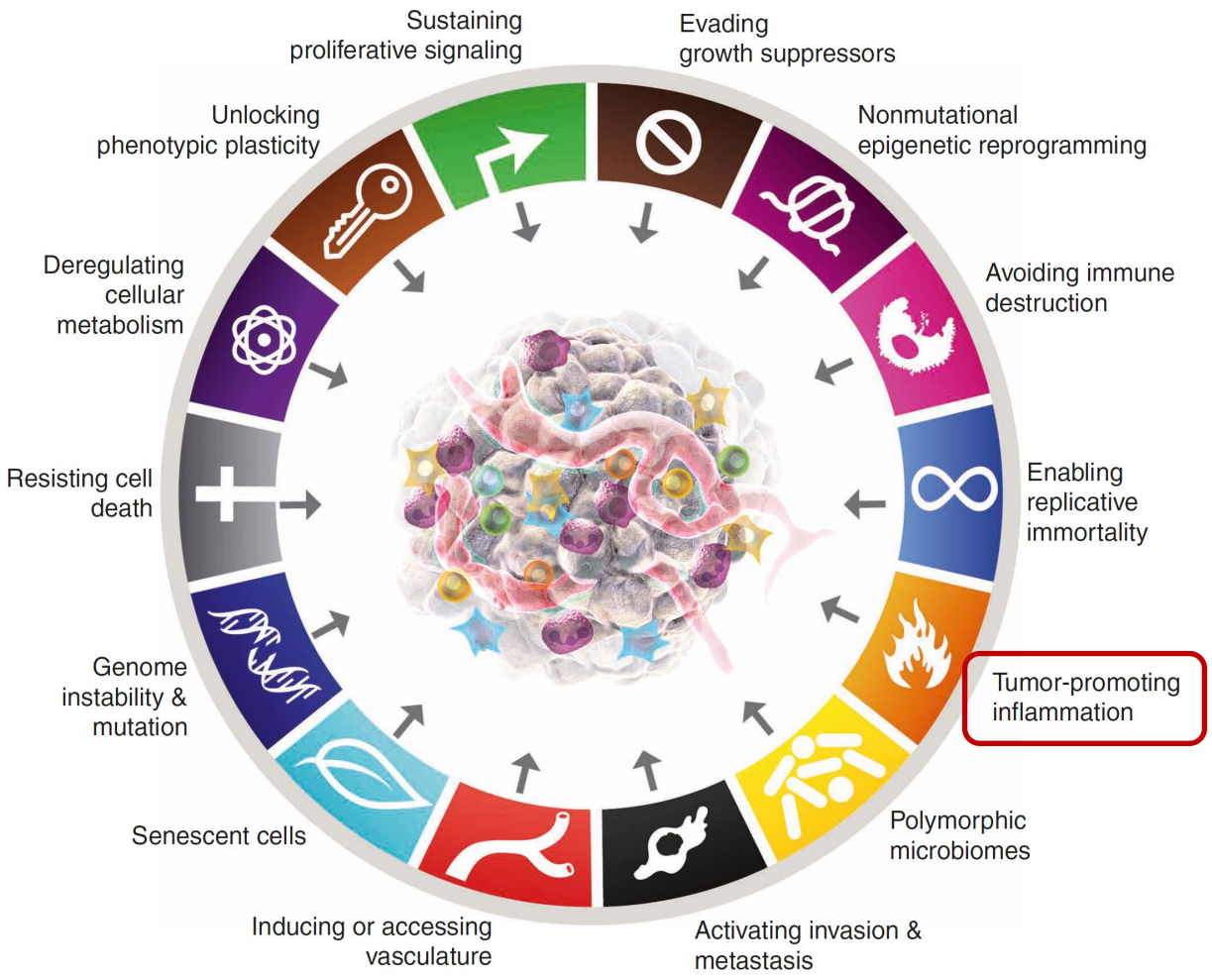

Hanahan Cancer Discovery 2022

Myeloproliferative neoplasms (MPN) are particular cancers…

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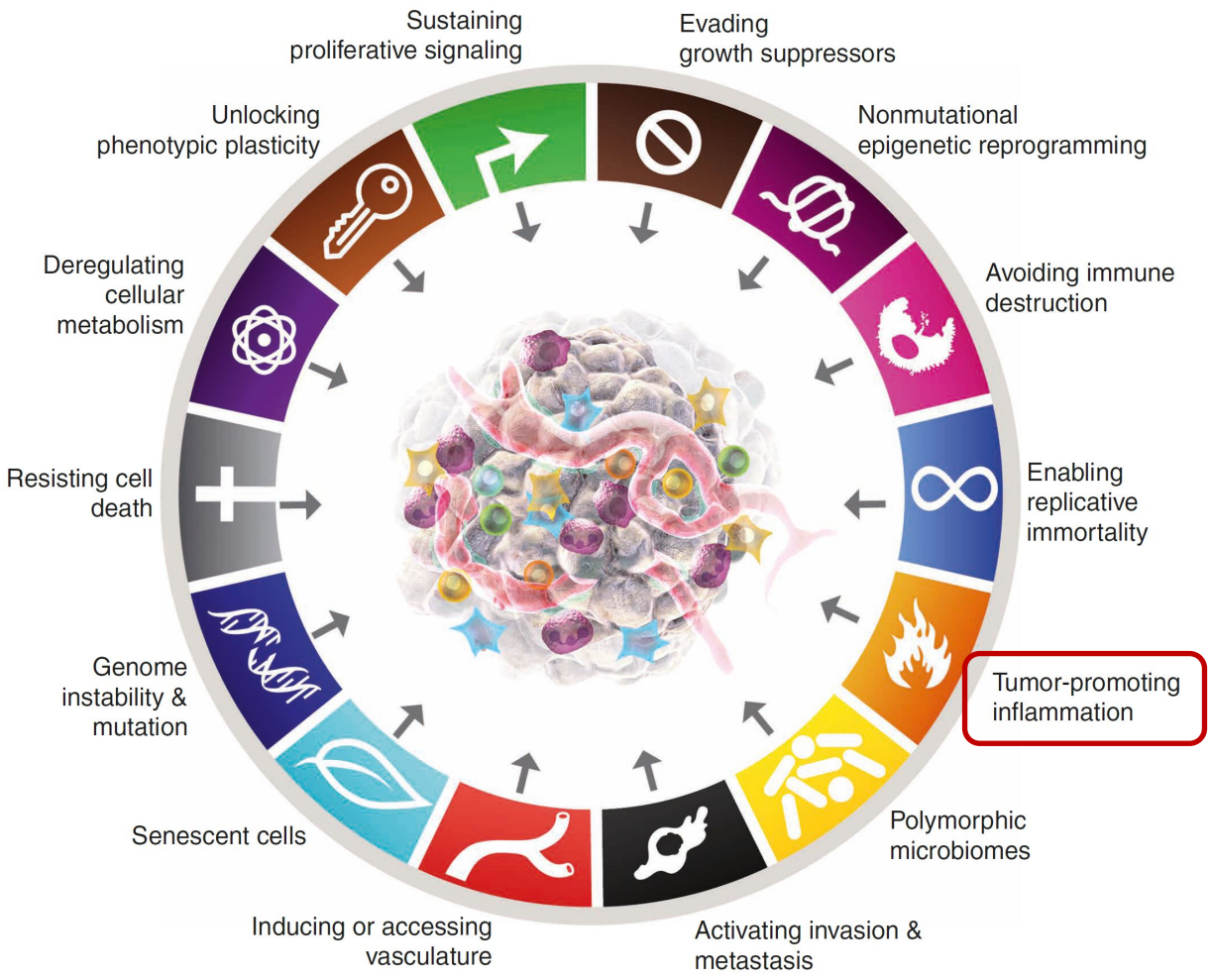


Hanahan Cancer Discovery 2022

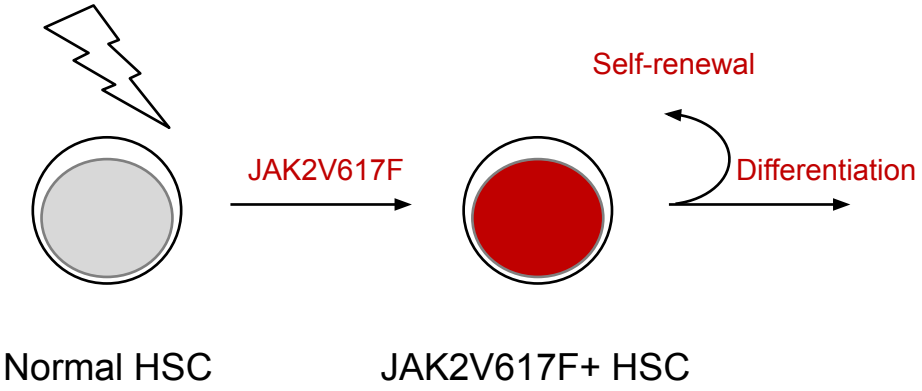
Myeloproliferative neoplasms (MPN) are particular cancers…

…since the clonal cancer cells themselves are inflammatory cells…

Personal view on MPN pathogenesis and the role of inflammation

Koschmieder 2025 (unpublished)

Personal view on MPN pathogenesis and the role of inflammation



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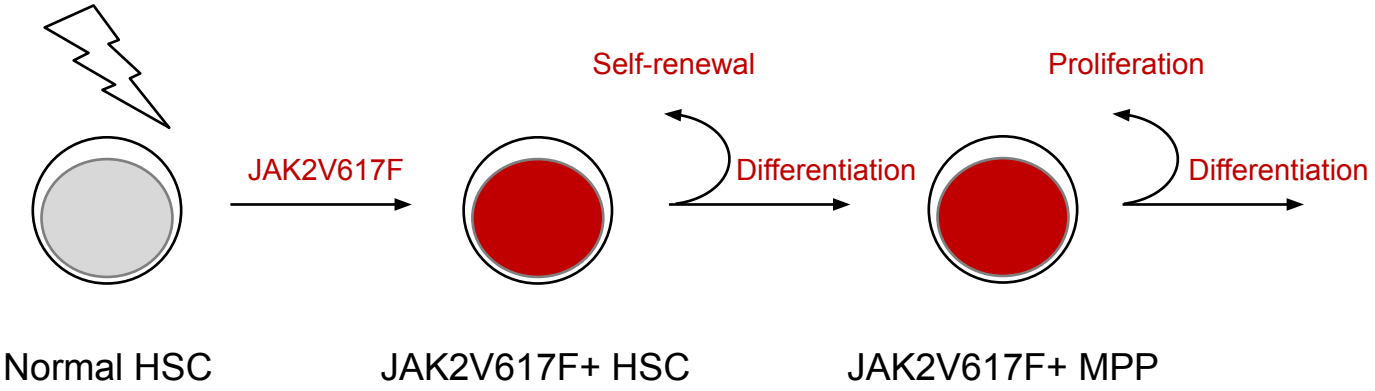

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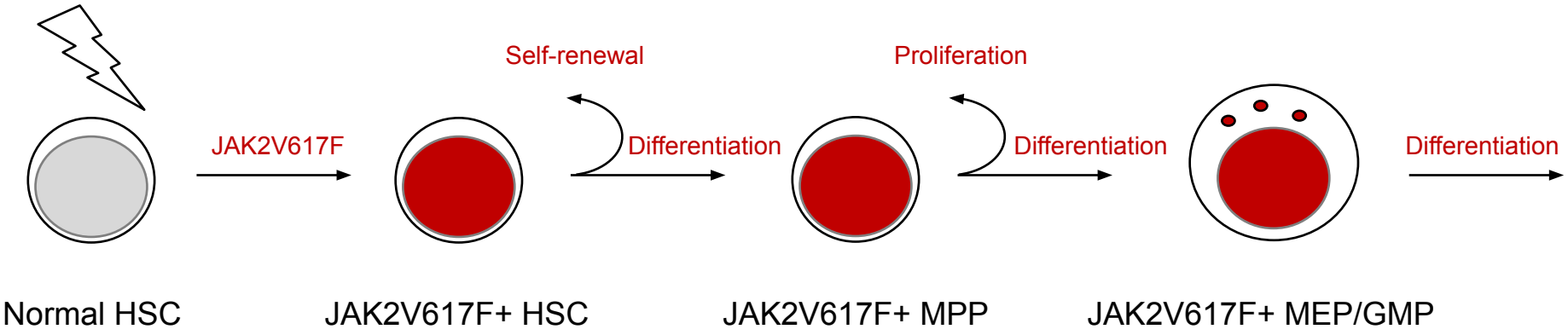

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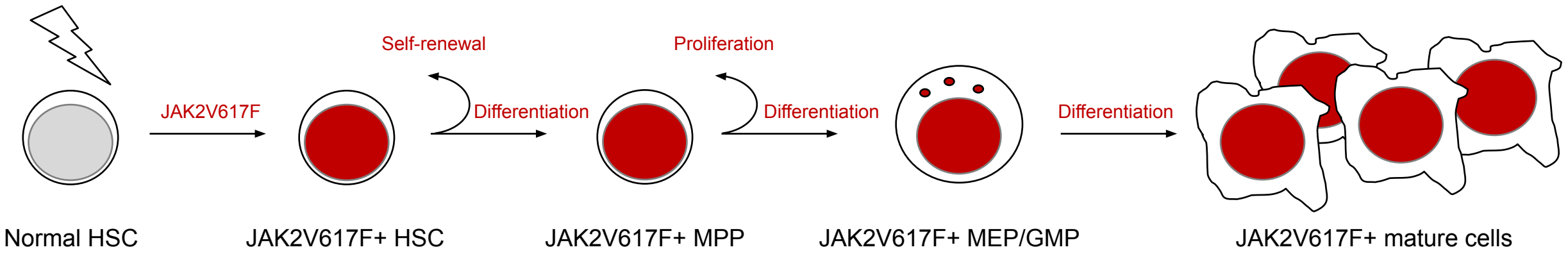

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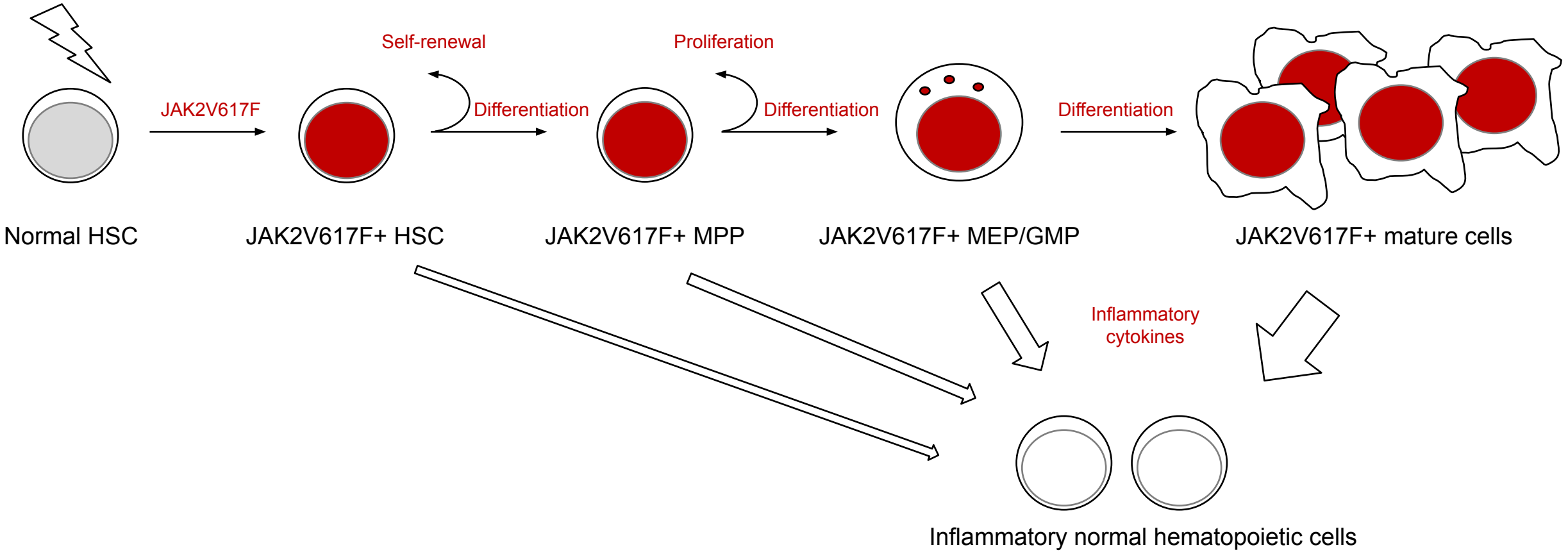

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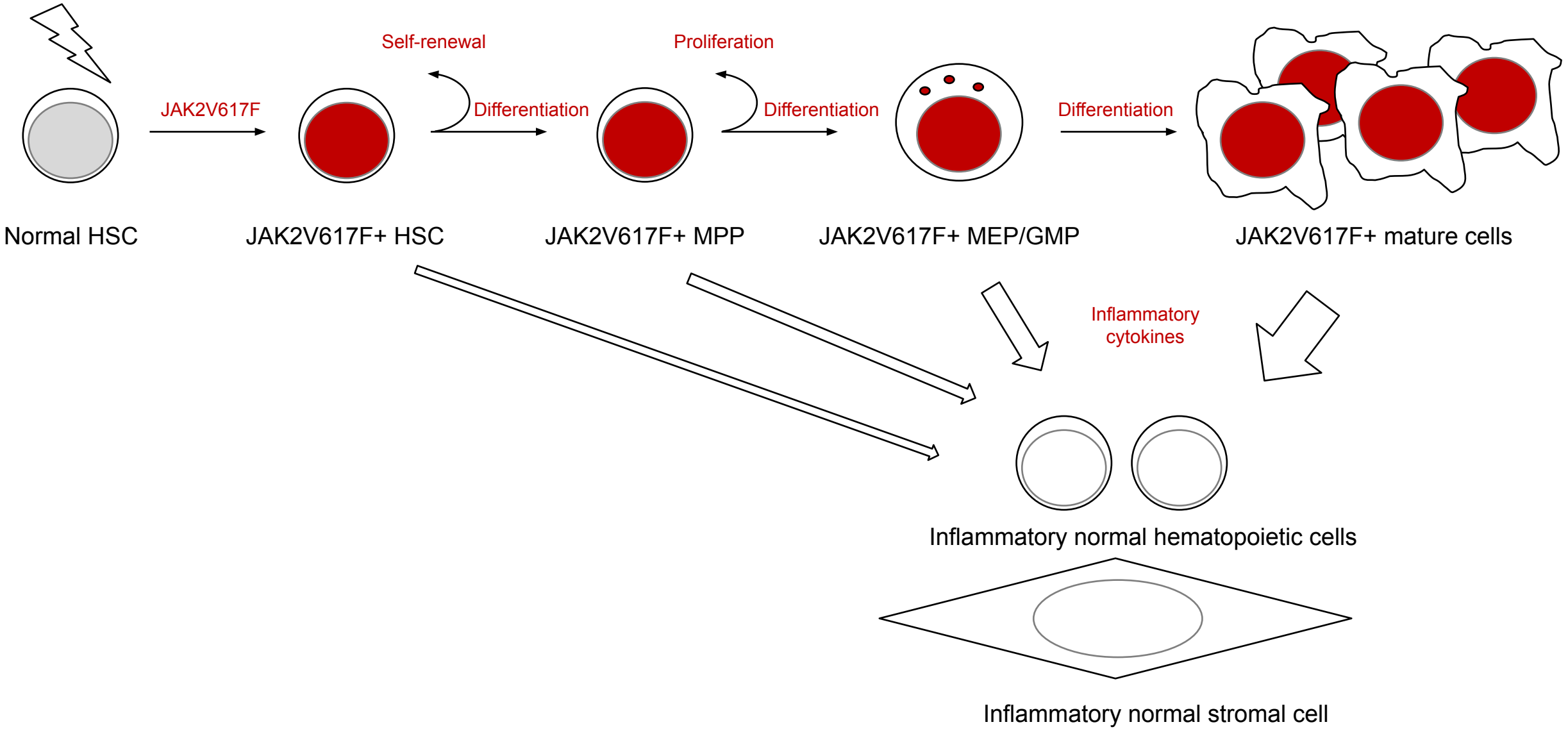

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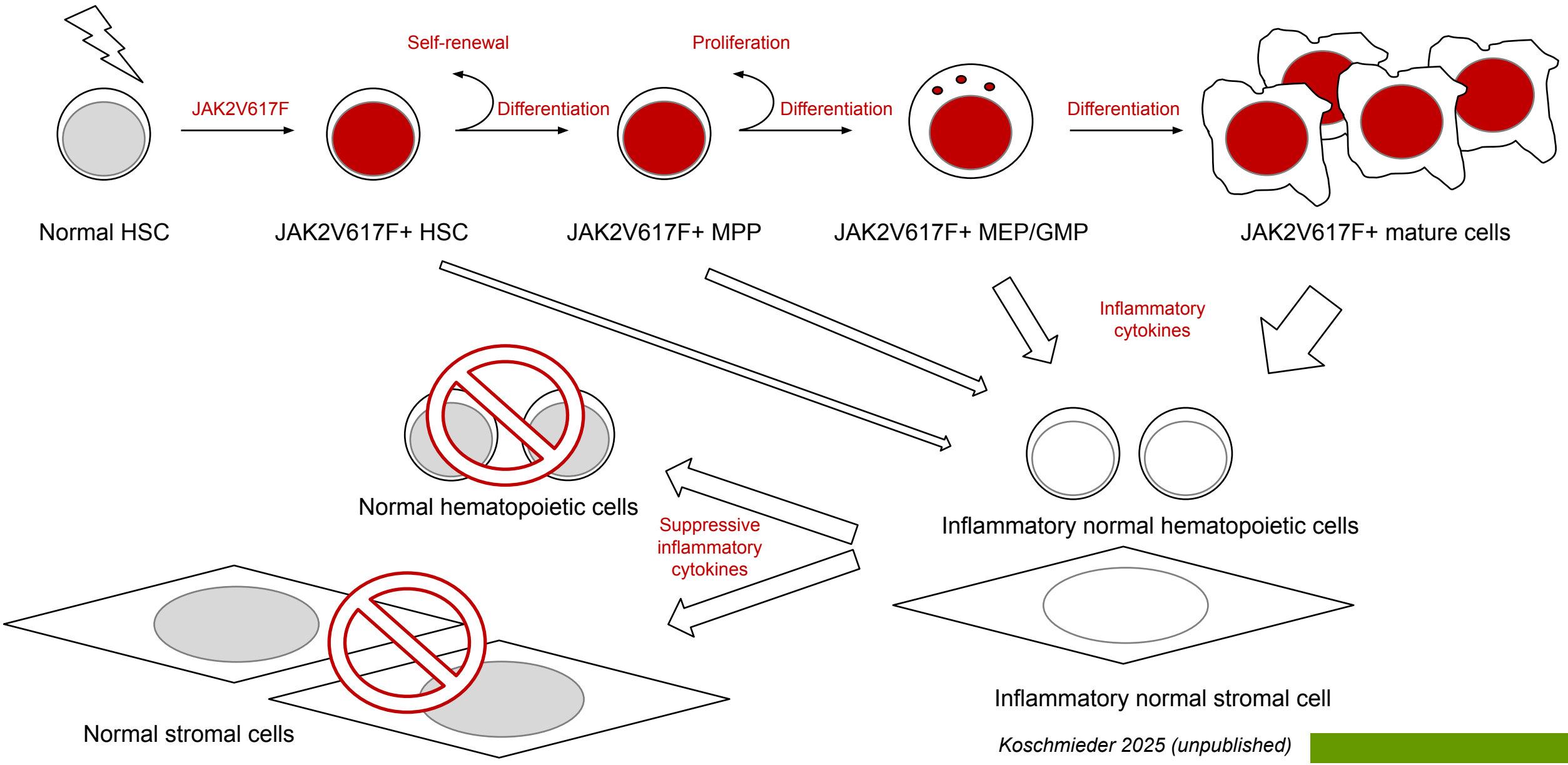

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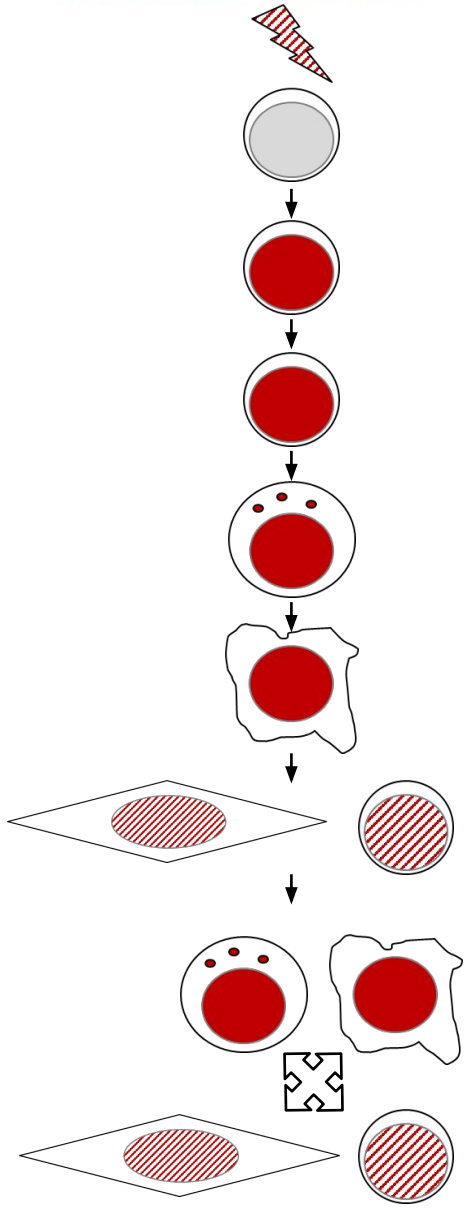
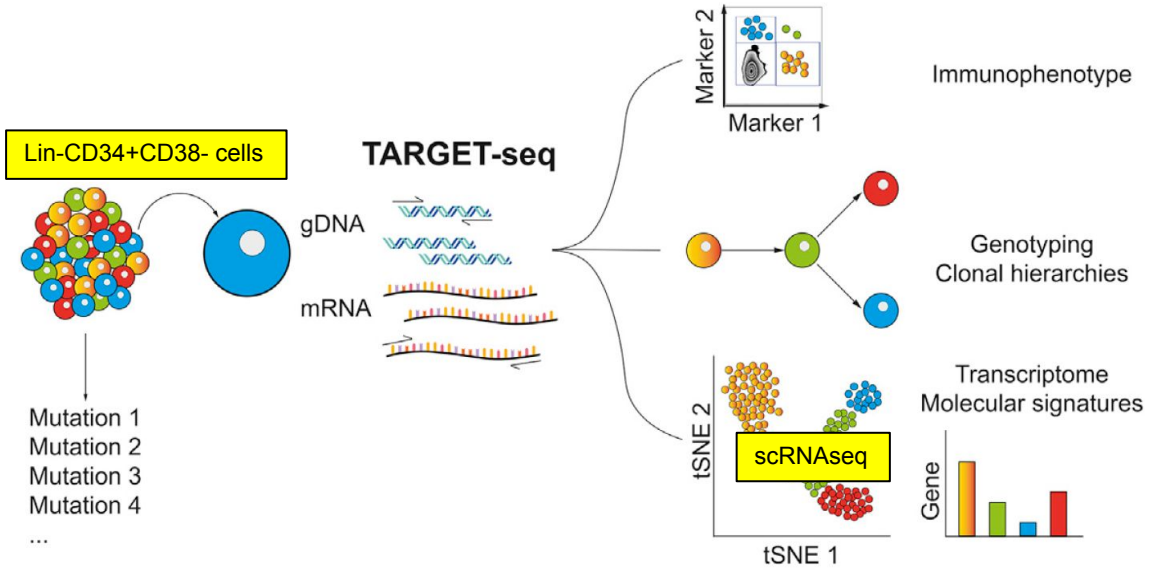


CD34+ cells from MPN patients express inflammatory genes



Modified from Rodriguez-Meira et al Mol Cell 2019

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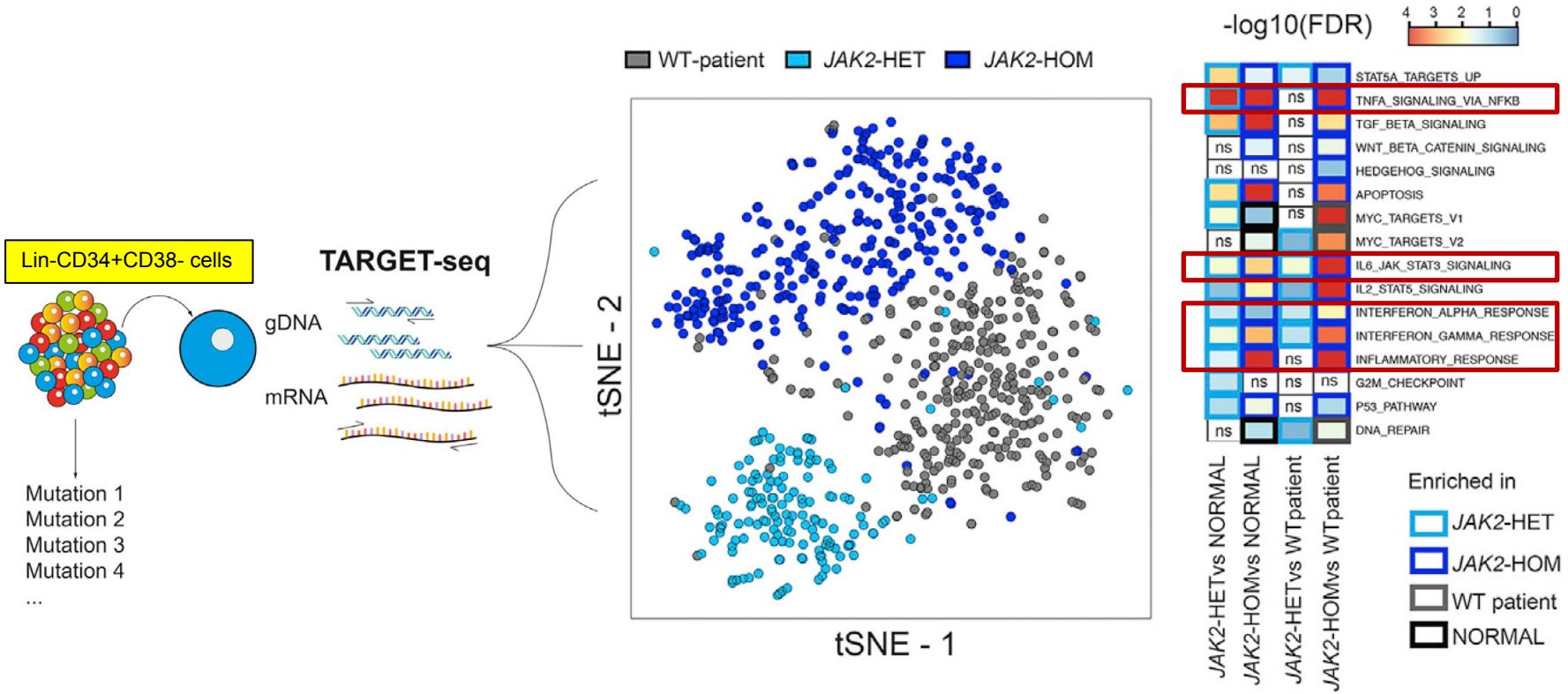

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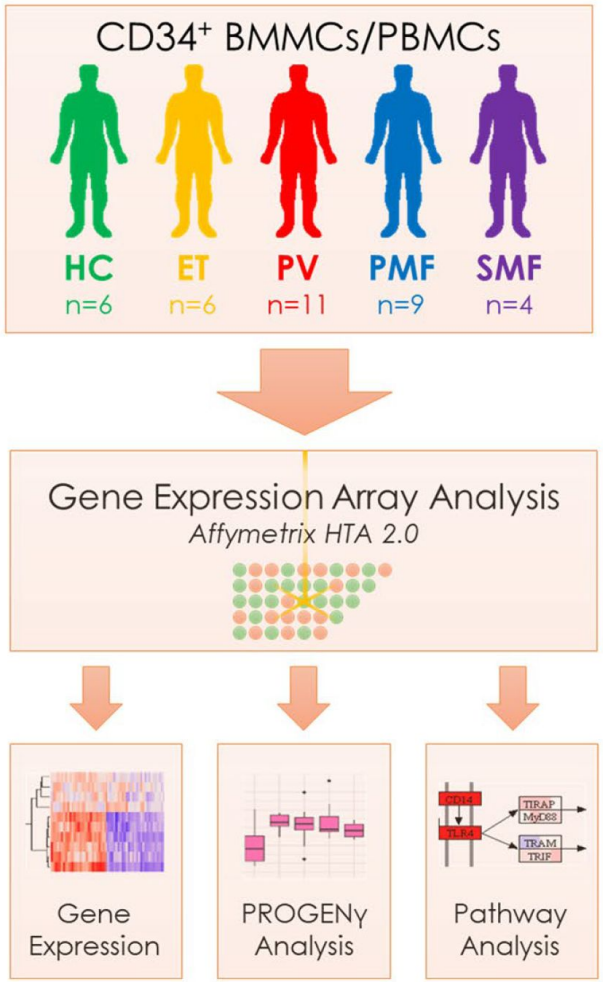

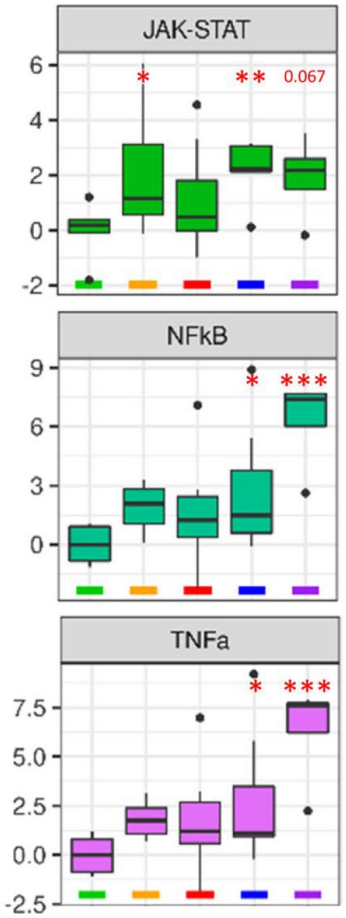

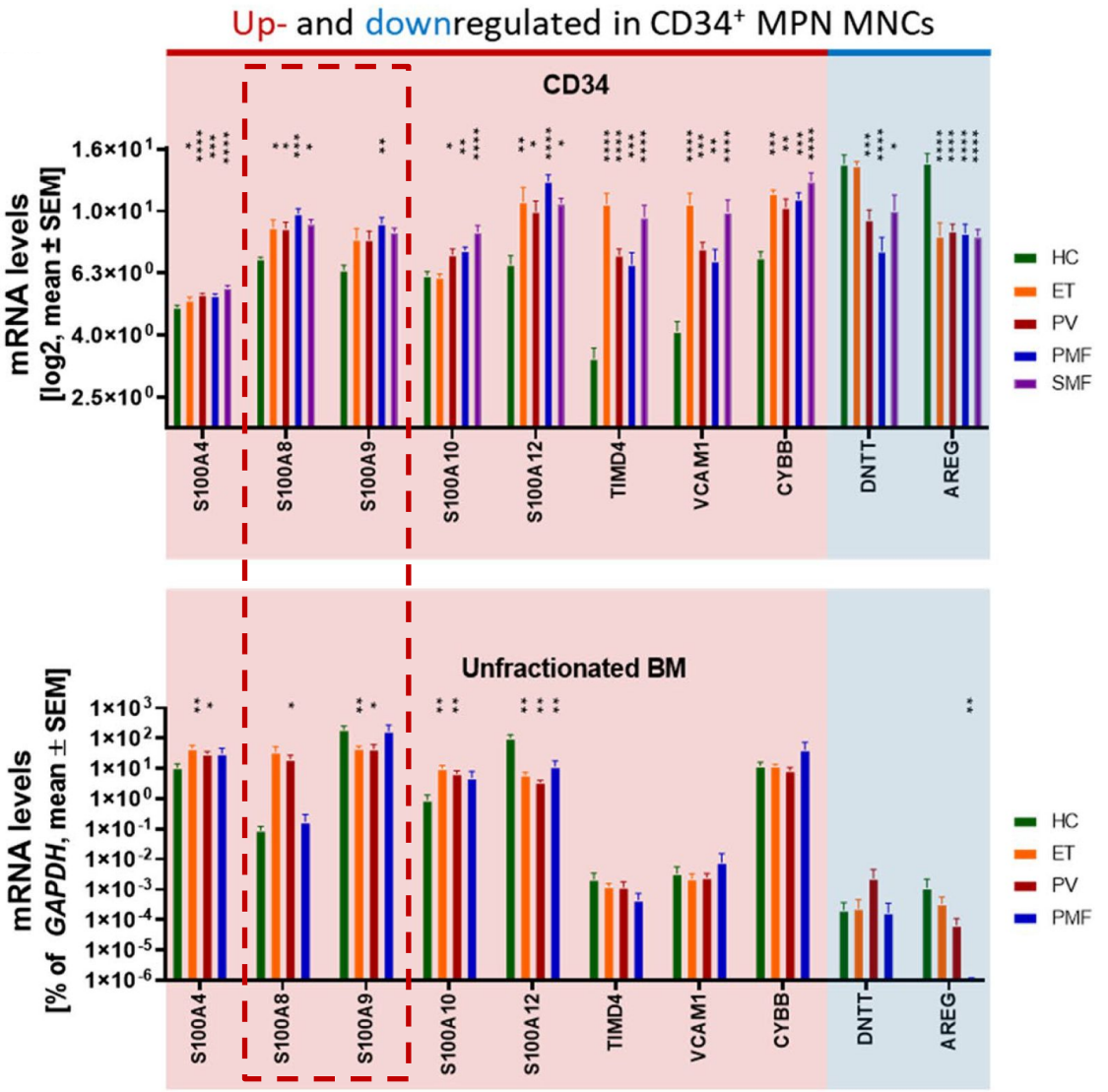

Baumeister et al Ann Hematol 2021

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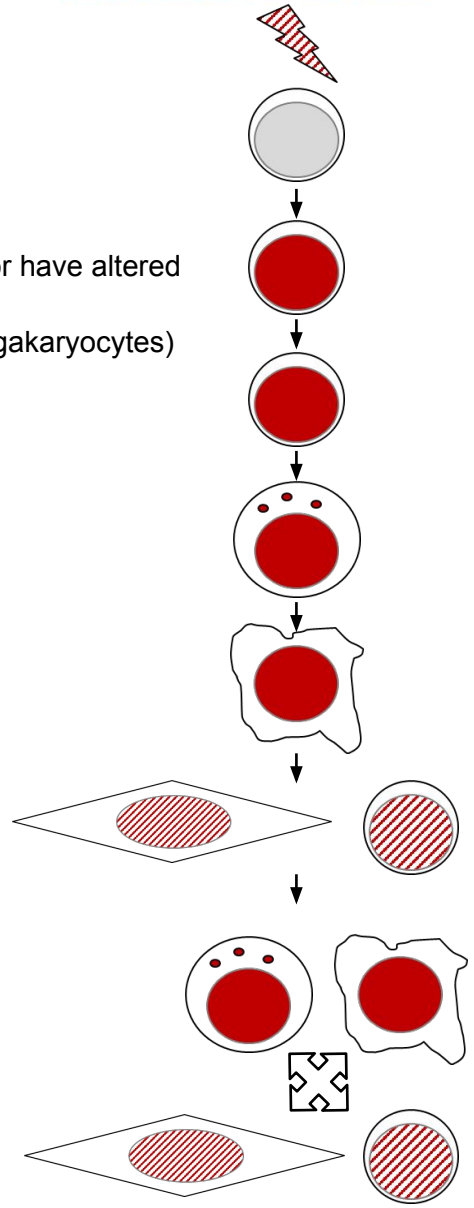
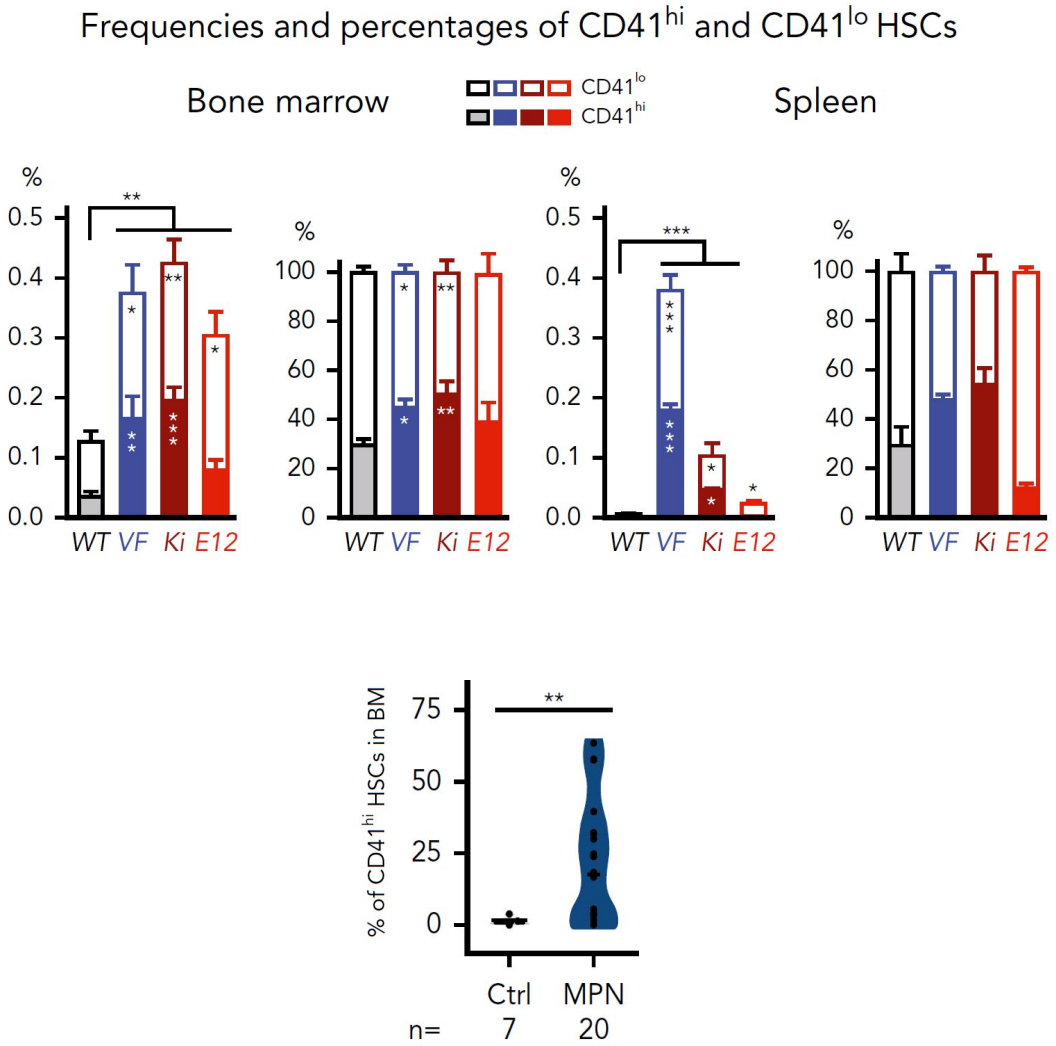


MPN-derived HSCs are skewed towards MKs



MYELOID NEOPLASIA

JAK2-V617F and interferon-α induce megakaryocyte-biased stem cells characterized by decreased long-term functionality

Tata Nageswara Rao,[1] Nils Hansen,[1] Jan Stetka,[1,2] Damien Luque Paz,[1] Milena Kalmer,[3] Julian Hilfiker,[1] Max Endele,[4] Nouraiz Ahmed,[4] Lucia Kubovcakova,[1] Margareta Rybarikova,[1] Hui Hao-Shen,[1] Florian Geier,[1,5] Christian Beisel,[4] Stefan Dirnhofer,[6] Timm Schroeder,[4] Tim H. Brümmendorf,[3] Dominik Wolf,[7] Steffen Koschmieder,[3] and Radek C. Skoda[1]

Modif. From Rao et al Blood 2021, Gleitz et al Blood 2020

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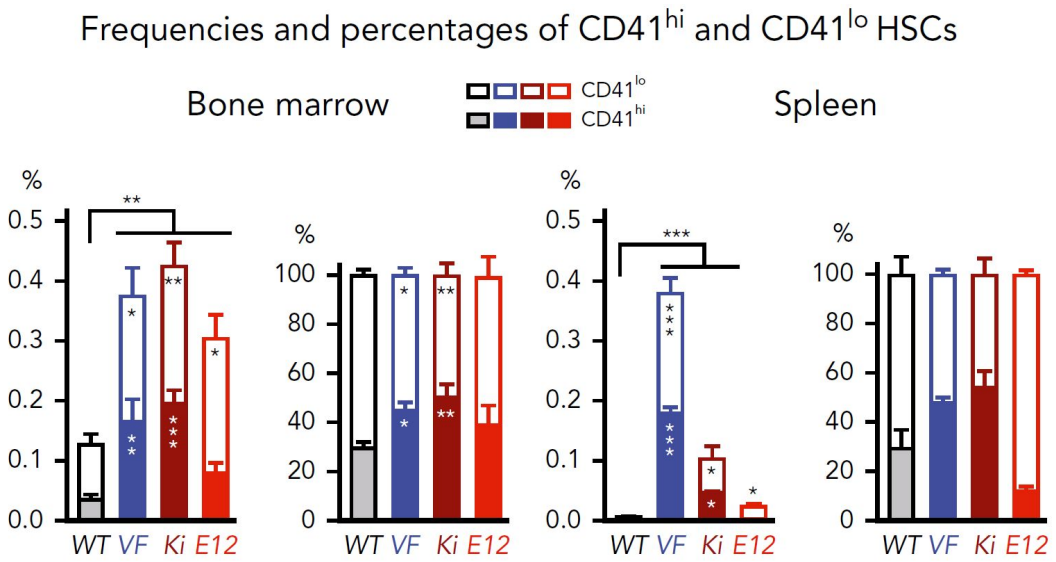

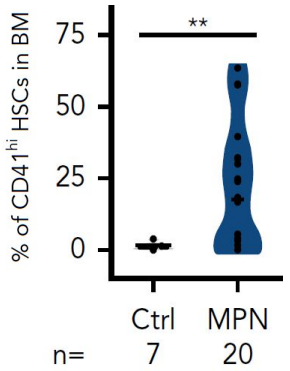

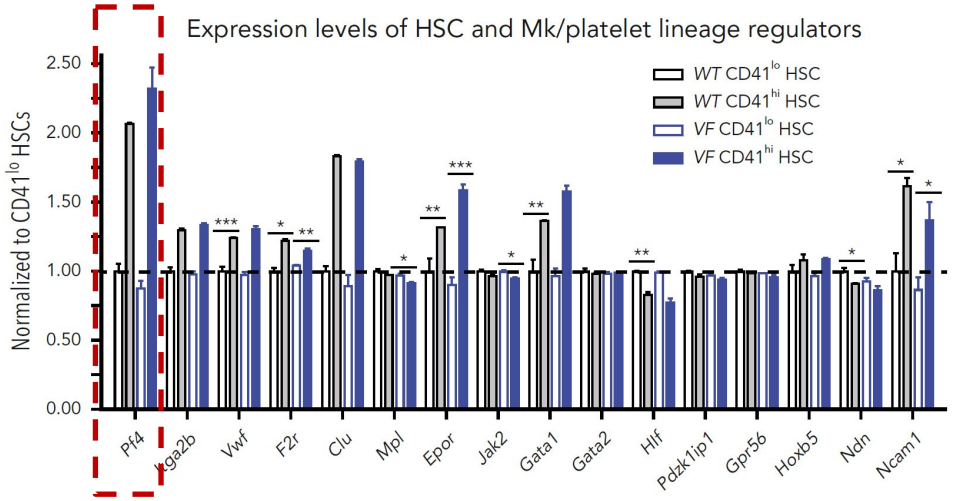

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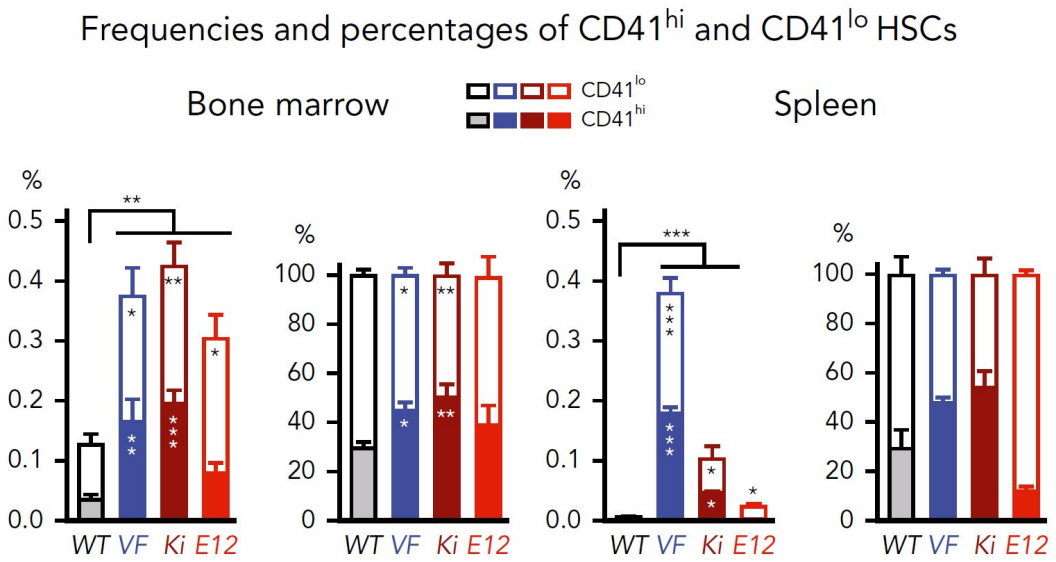
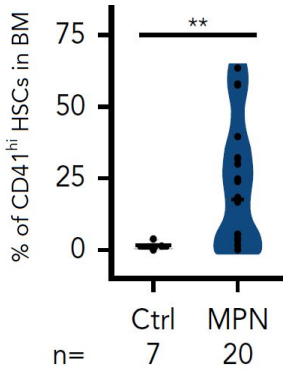
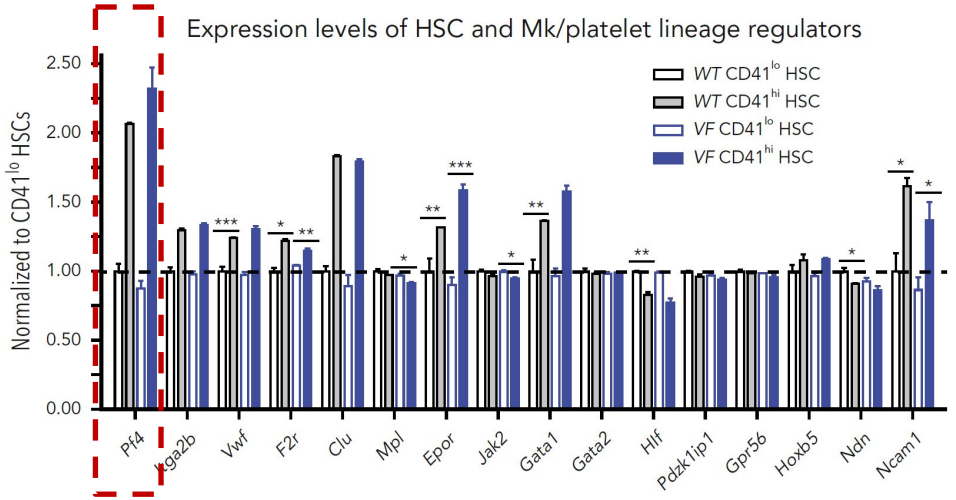
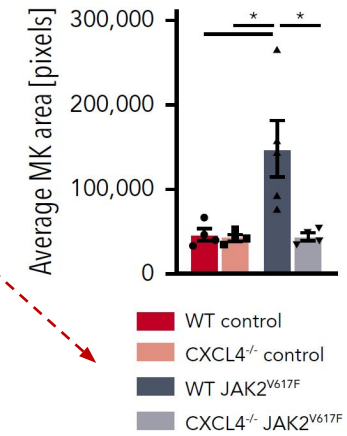




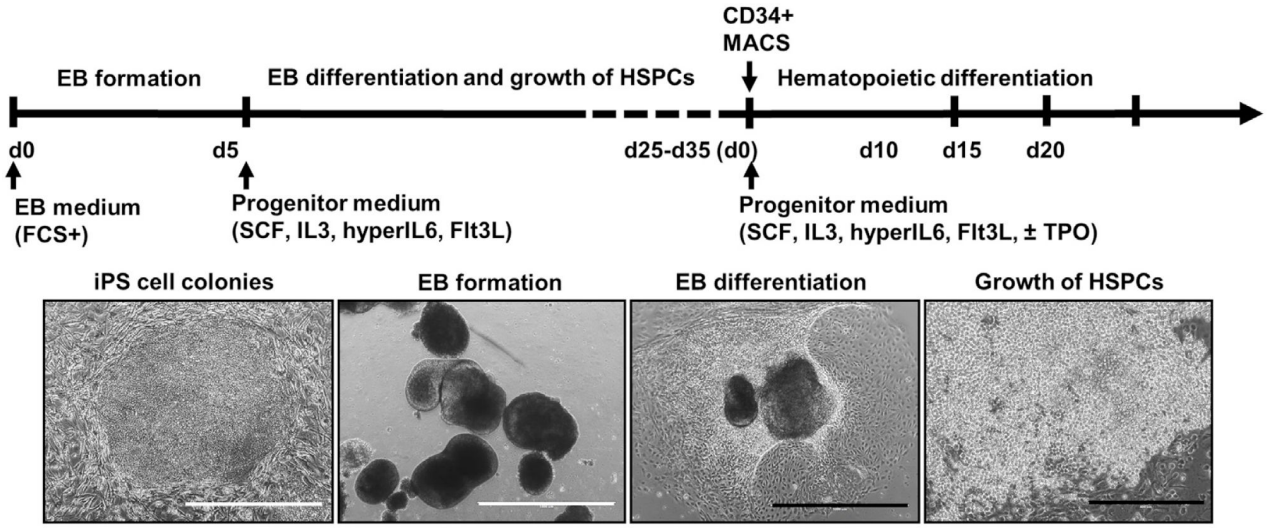


Pf4/Cxcl4 axis



Modif. From Rao et al Blood 2021, Gleitz et al Blood 2020

MPN-derived iPSCs are skewed towards MKs



Stem Cell Reports
Article
OPEN ACCESS

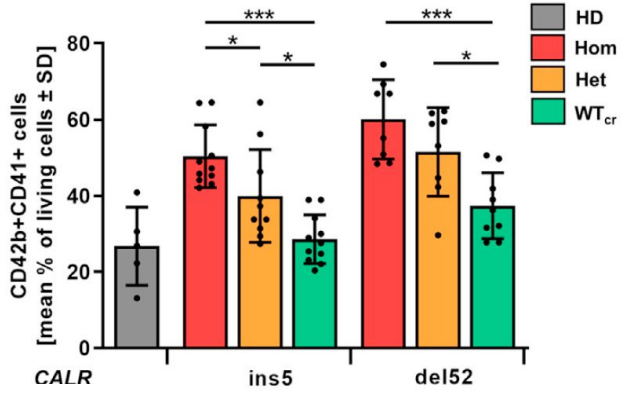
CALR frameshift mutations in MPN patient-derived iPSCs accelerate maturation of megakaryocytes

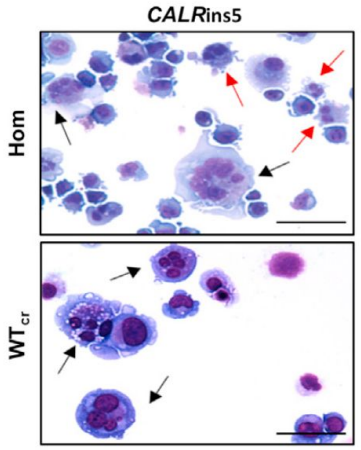
Kathrin Olschok,[1,2,10] Lijuan Han,[1,2,3,10] Marcelo A.S. de Toledo,[1,2] Janik Böhnke,[4,5] Martin Graßhoff,[6] Ivan G. Costa,[6] Alexandre Theocharides,[7] Angela Maurer,[1,2] Herdit M. Schüler,[8] Eva Miriam Buhl,[9] Kristina Pannen,[1,2] Julian Baumeister,[1,2] Milena Kalmer,[1,2] Siddharth Gupta,[1,2] Peter Boor,[9] Deniz Gezer,[1,2] Tim H. Brümmendorf,[1,2] Martin Zenke,[4,5] Nicolas Chatain,[1,2,11] and Steffen Koschmieder[1,2,11,*]

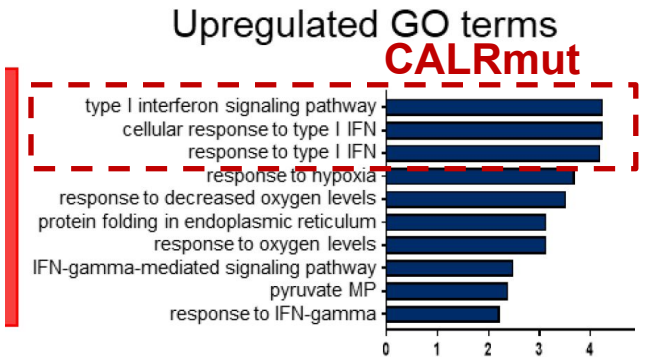
Stem Cell Reports
Article
OPEN ACCESS

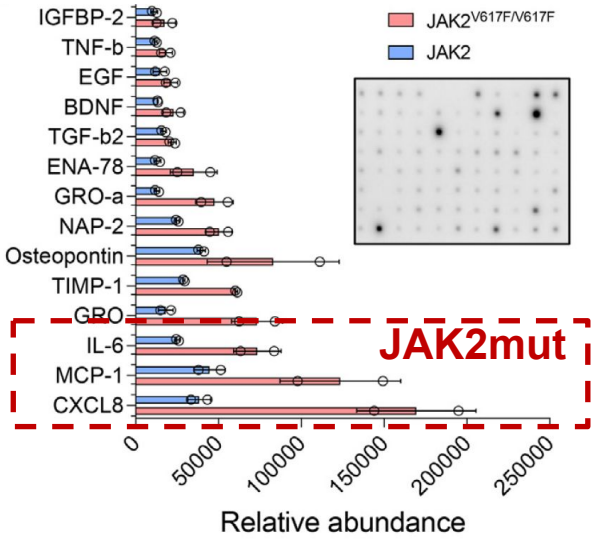
Proinflammatory phenotype of iPS cell-derived JAK2 V617F megakaryocytes induces fibrosis in 3D *in vitro* bone marrow niche

Niclas Flosdorf,[1,2,3,4] Janik Böhnke,[1,2,4] Marcelo A.S. de Toledo,[4,5] Niklas Lutterbach,[3] Vanesa Gómez Lerma,[1,2] Martin Graßhoff,[6] Kathrin Olschok,[4,5] Siddharth Gupta,[4,5] Vithurithra Tharmapalan,[2,4,7] Susanne Schmitz,[3] Katrin Götz,[3] Herdit M. Schüler,[8,9] Angela Maurer,[4,5] Stephanie Sontag,[1,2] Caroline Küstermann,[1,2] Kristin Seré,[1,2,3] Wolfgang Wagner,[2,4,7] Ivan G. Costa,[6] Tim H. Brümmendorf,[4,5] Steffen Koschmieder,[4,5] Nicolas Chatain,[4,5] Miguel Castilho,[10] Rebekka K. Schneider,[3] and Martin Zenke[1,2,4,5,*]









Olschok, Han et al Stem Cell Rep 2021, Flosdorf et al Stem Cell Rep 2023

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  - This has been described to occur very early in life (e.g. in utero or early childhood)
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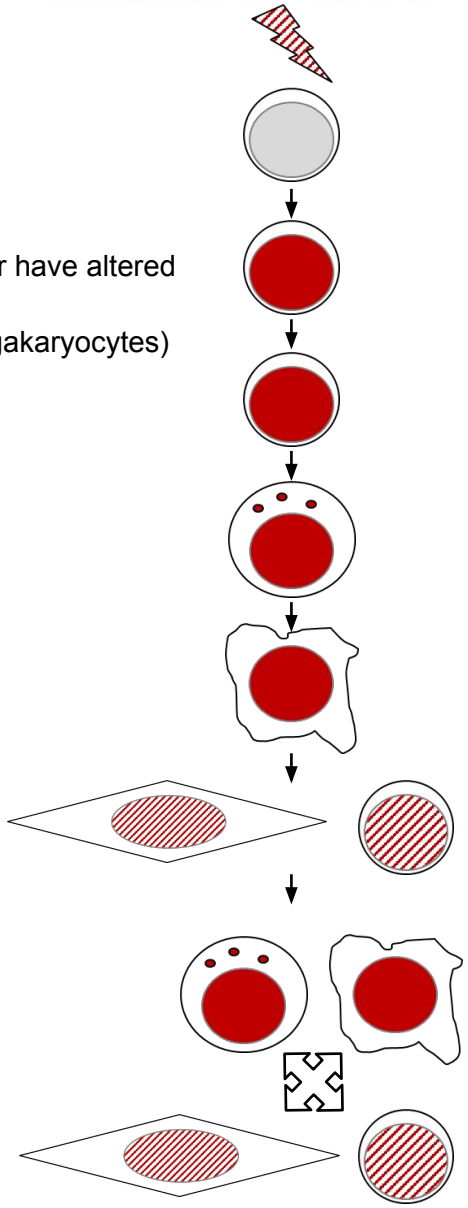
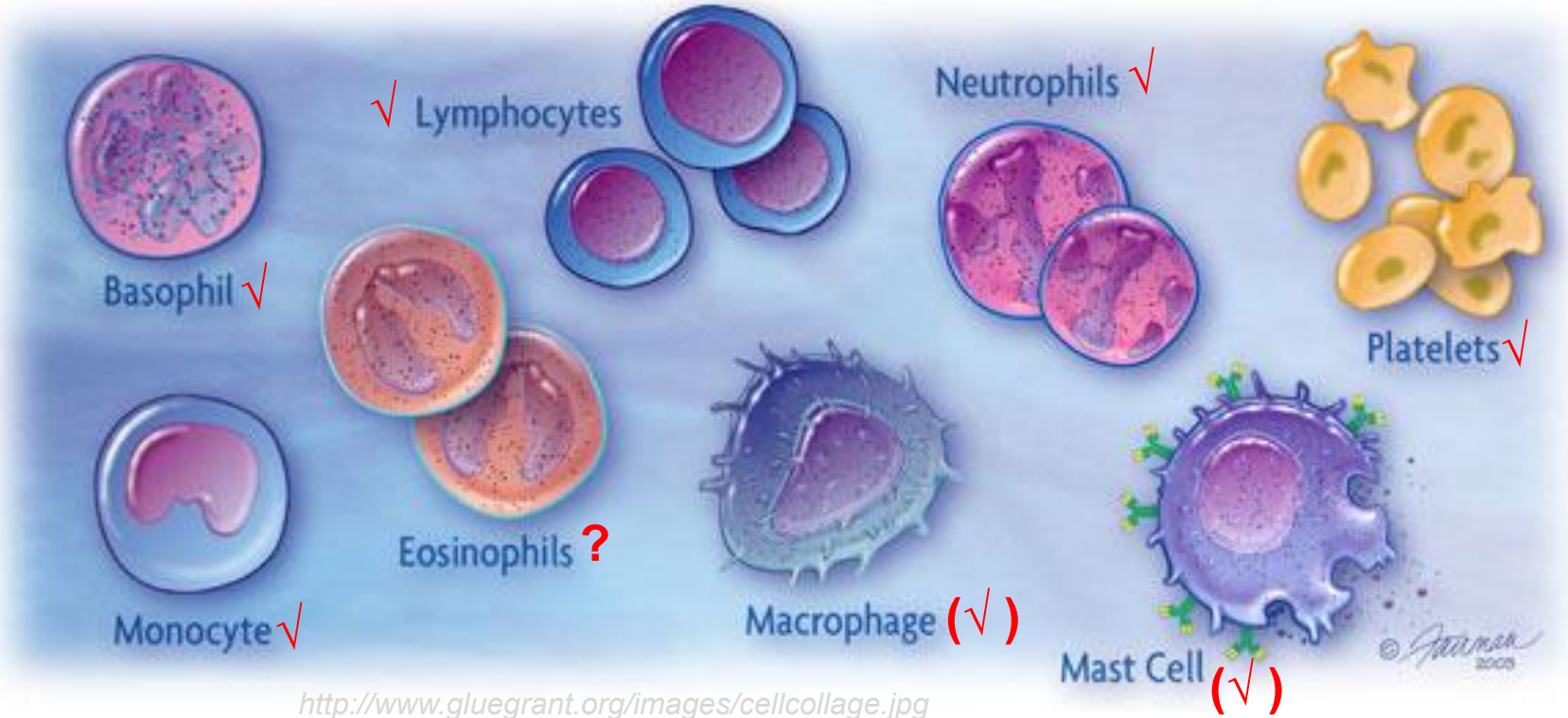
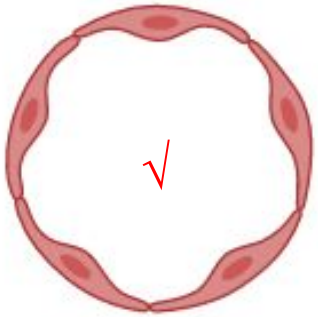
- JAK2V617F-mutant progenitors proliferate and further differentiate
  - Progenitor differentiation may be skewed (towards myeloid, away from lymphoid differentiation)



Inflammatory cells in MF: are they part of the JAK2V617F clone?



http://www.gluegrant.org/images/cellcollage.jpg



Endothelial cells (Blood vessel)

https://cdn.prod.website-files.com/621e95f9ac30687a56e4297e/64401622763e1e837b0490b9_vessel-cross-section-arteriole-endothelium.png

√ = JAK2 V617F mutation **shown at DNA level**

- But JAK2V617F protein expression unclear (=> single-cell proteomics)
- Biologic contribution of each cell subtype unclear

BM stromal cells are negative for JAK2V617F

Patient no.	Diagnosis	*JAK2*^{V617F} allele burden (%)	
		Granulocytes	MSCs
1	PMF	31	b.d. *(below detection limit)*
2	PMF	15	b.d.
3	PMF	23	b.d.
4	Post-PV MF	61	b.d.
5	Post-PV MF	98	b.d.
6	PV	100	b.d.
7	PV	66	b.d.

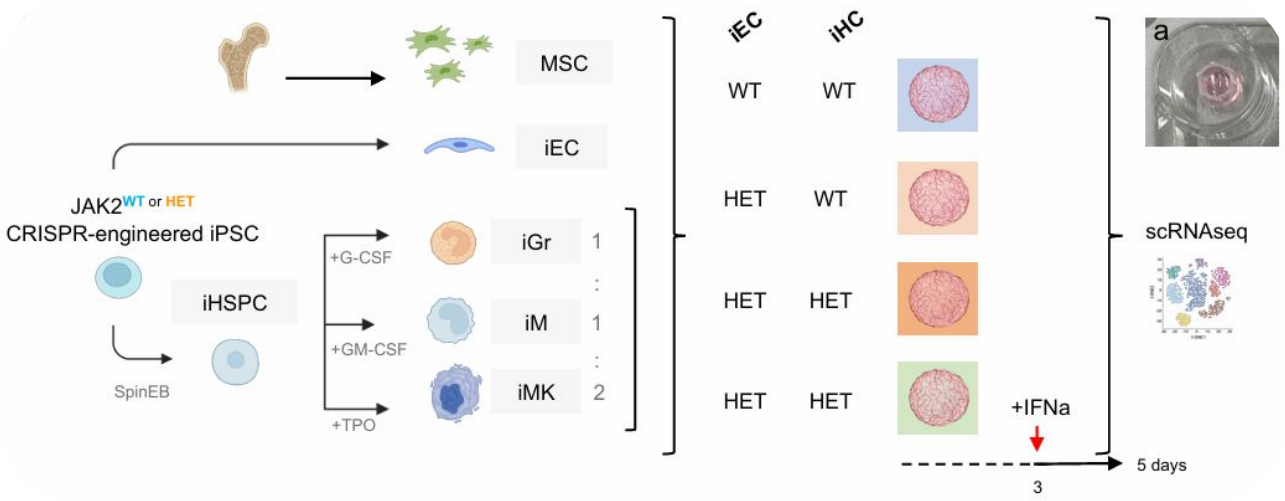
Pieri et al Leuk Res 2008

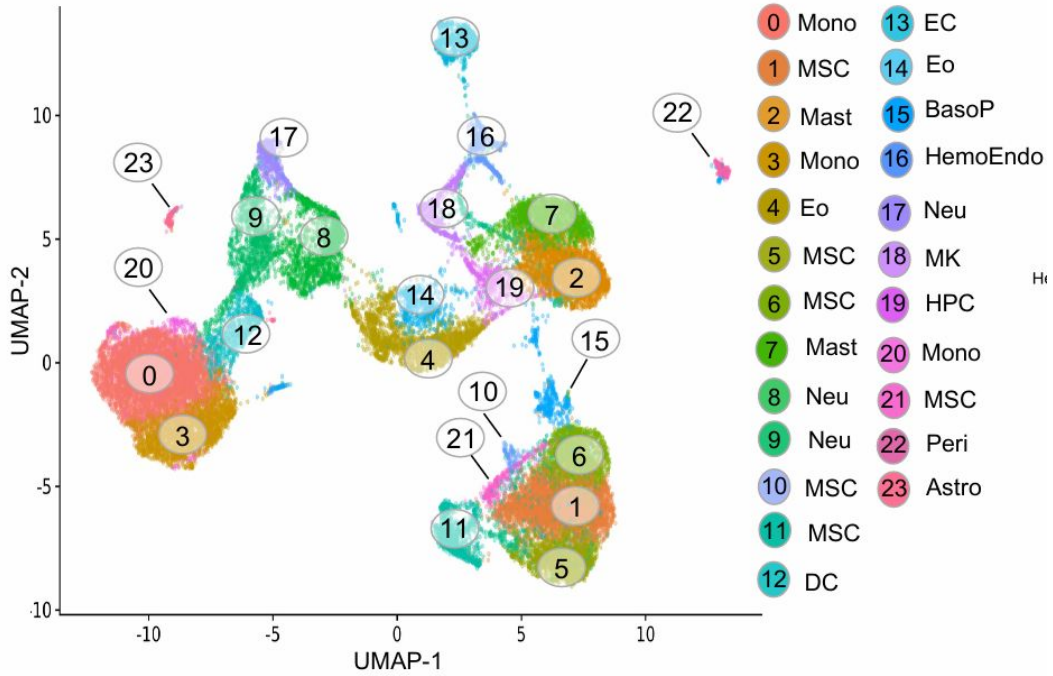
The JAK2 V617F vascular niche in MPN and its response to IFNa


M. Caduc


M. de Toledo

- Recapitulating the MPN BM niche with iPSC-derived 3D cocultures (JAK2V617F in iHC +/- iEC)





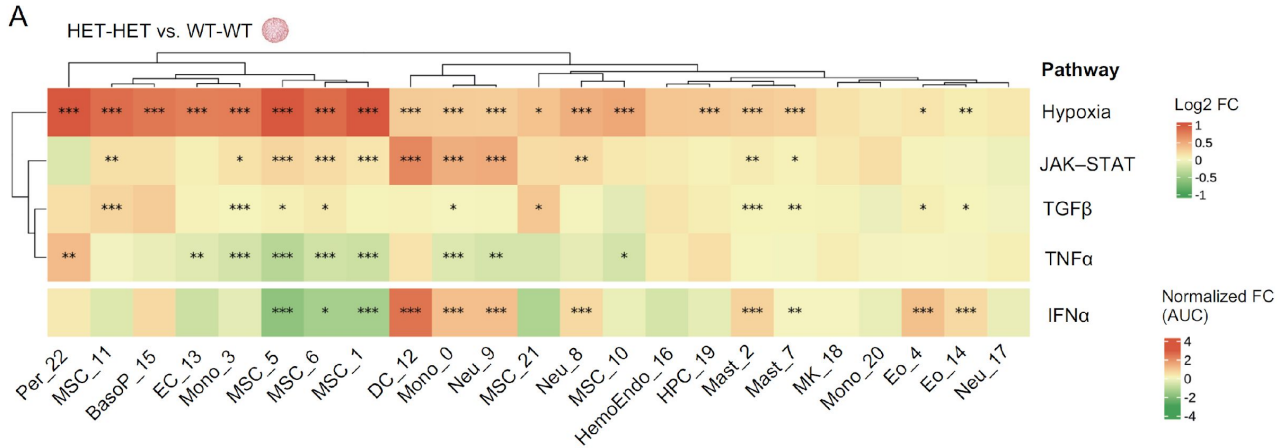
Caduc et al, bioRxiv 2024

The JAK2 V617F vascular niche in MPN and its response to IFNa

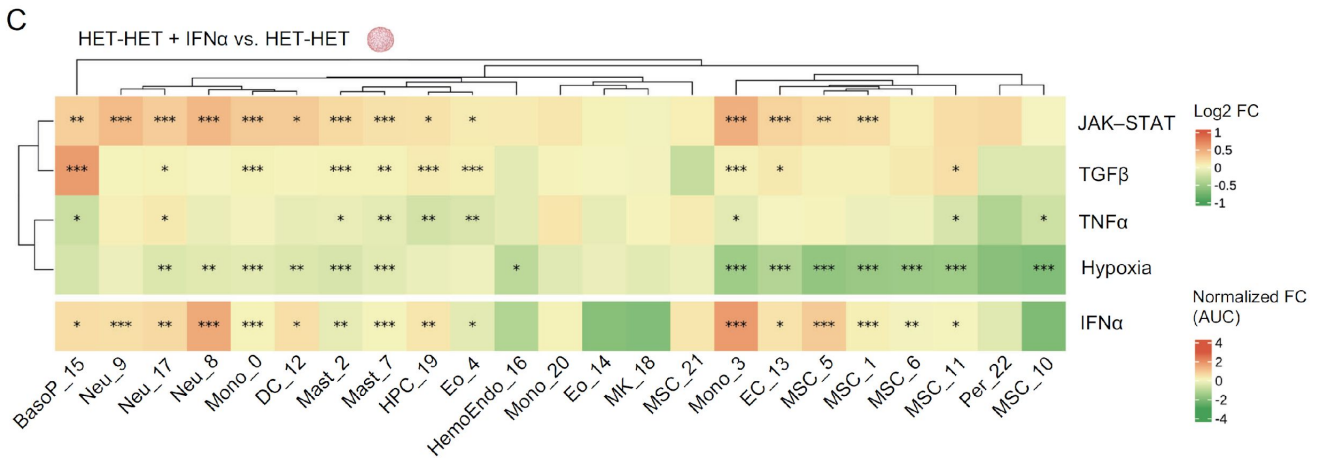

M. Caduc


M. de Toledo

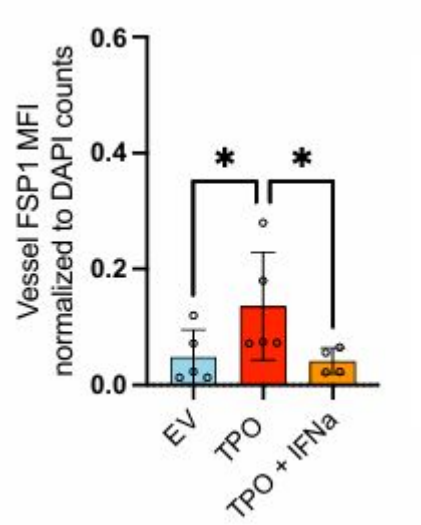
- Core MPN signatures such as hypoxia, JAK-STAT, and fibrosis (TGFß) recap. in 3D BM niches

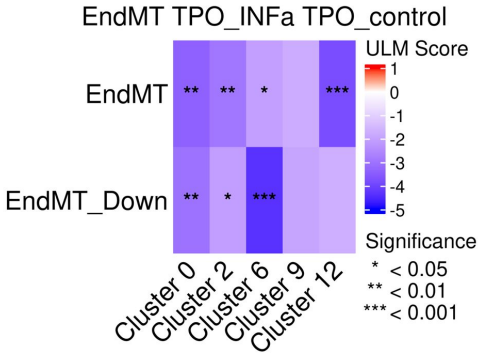


- IFNa reverts the hypoxic and profibrotic phenotype *in vitro* and *in vivo*



TPO mouse model





Caduc et al, bioRxiv 2024 and unpublished 2025

What is the evidence?

- HSC in the bone marrow (BM) acquires a somatic JAK2V617F (or CALR or MPL) driver mutation
  - This has been described to occur very early in life (e.g. in utero or early childhood)
  - JAK2V617F has been shown to induce cycling of HSCs
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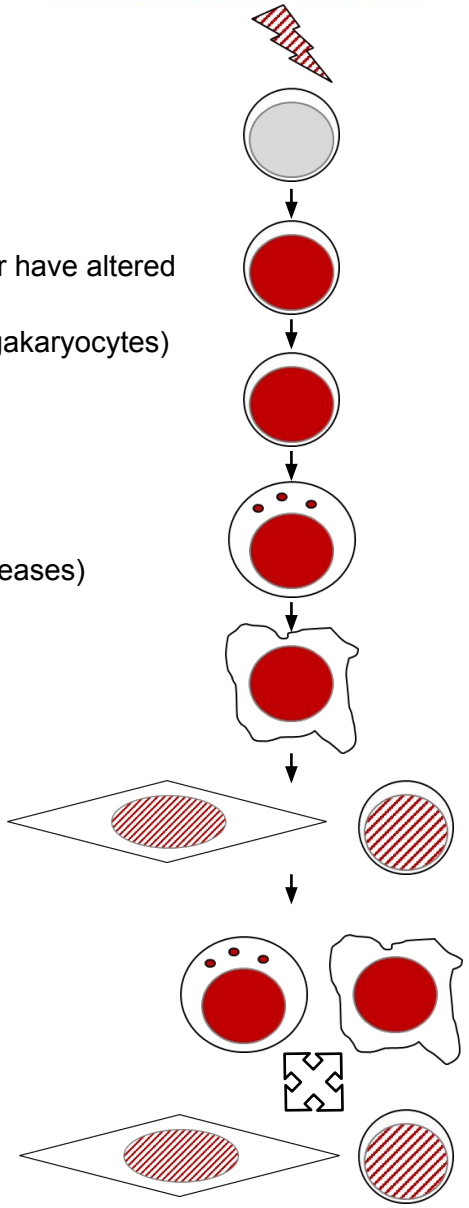
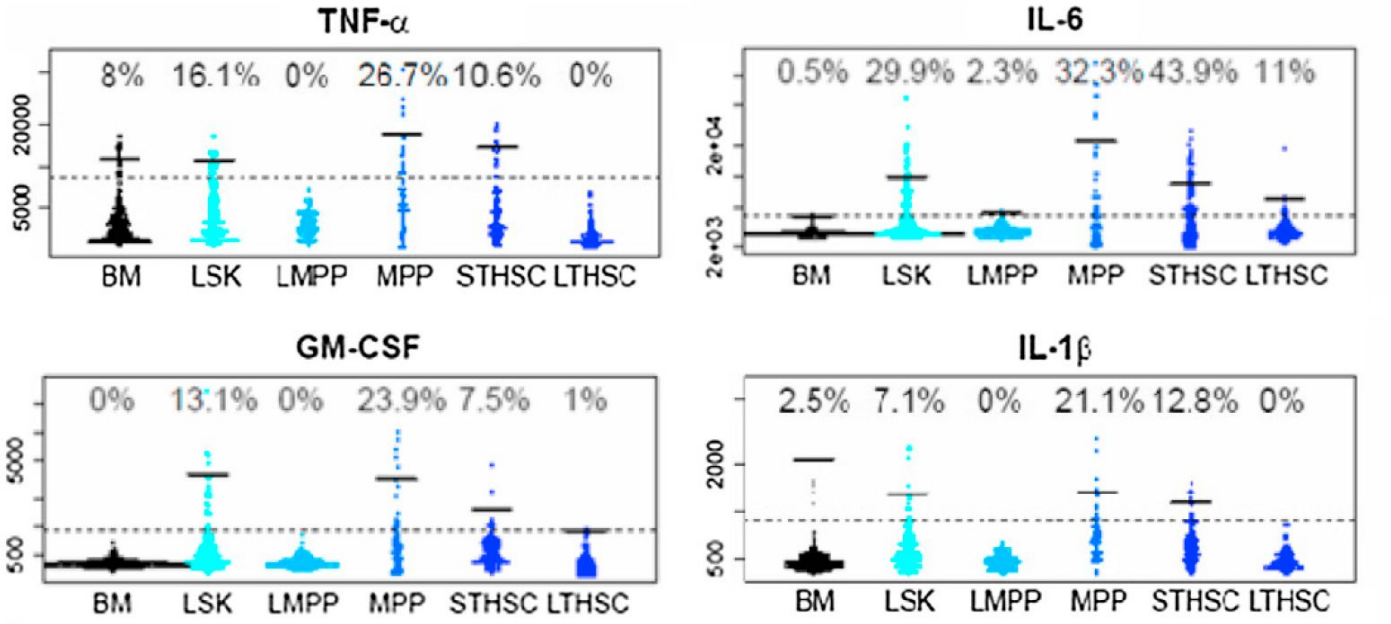
- JAK2V617F-mutant progeny produces local myeloid cytokines (e.g. IL-1beta, IL-6, TNF)
  - JAK2V617F-mutant HSC and progenitors may enhance their cell division activity (e.g. proliferation, differentiation)
  - Clonal hematopoiesis (CHIP) for JAK2V617F may be detectable by PCR/NGS diagnostics (Patient is at risk for MPN & cardiovascular diseases)



Single HSCs and MPPs produce inflammatory cytokines



Single-cell proteomics

Zhao et al Cell Stem Cell 2014

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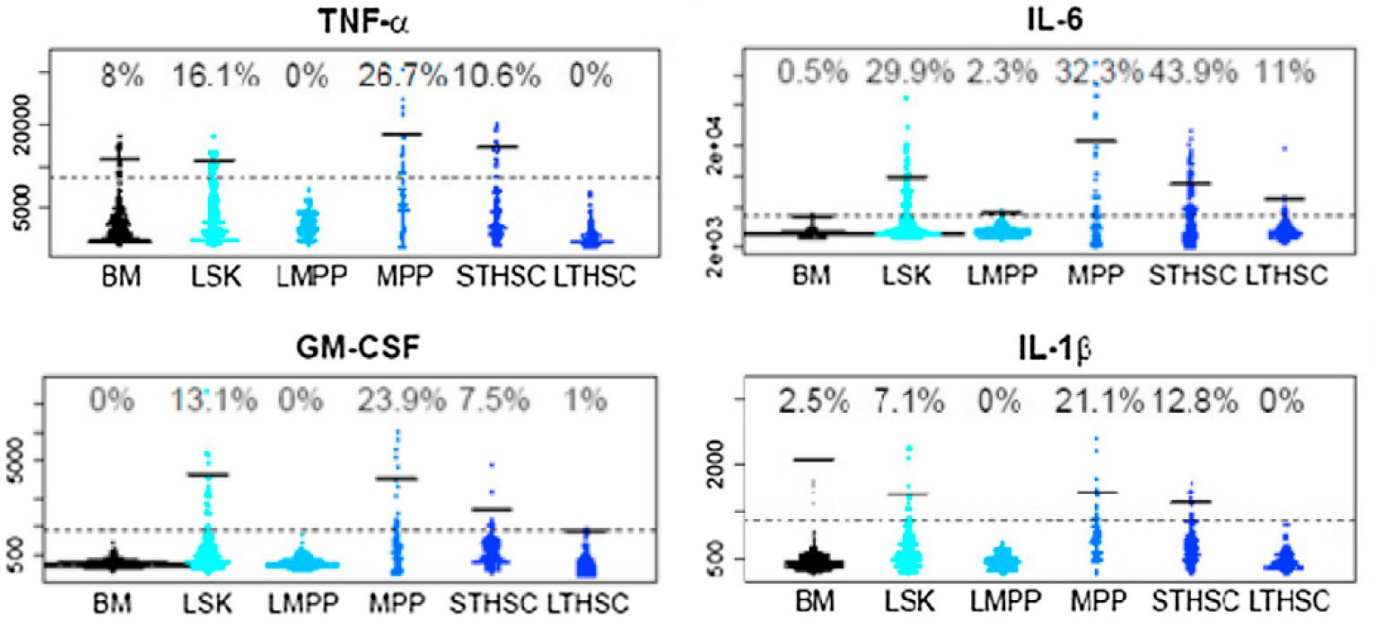

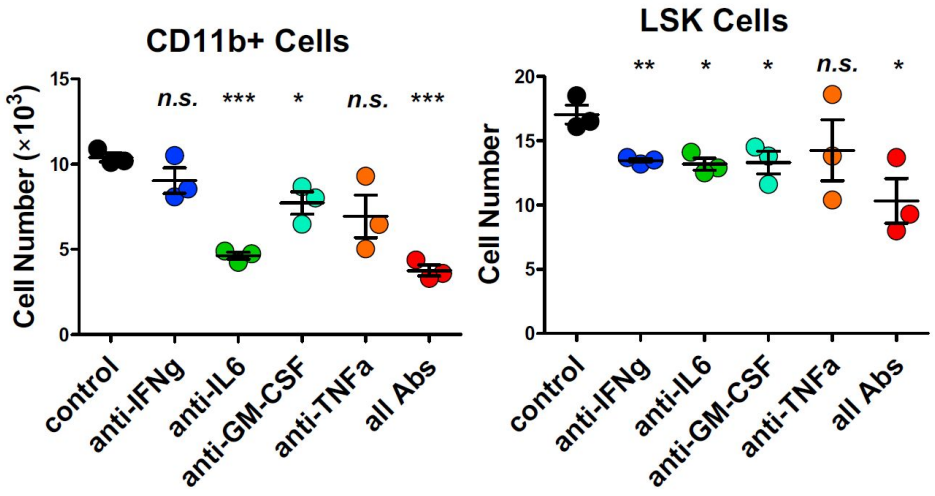

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Zhao et al Cell Stem Cell 2014

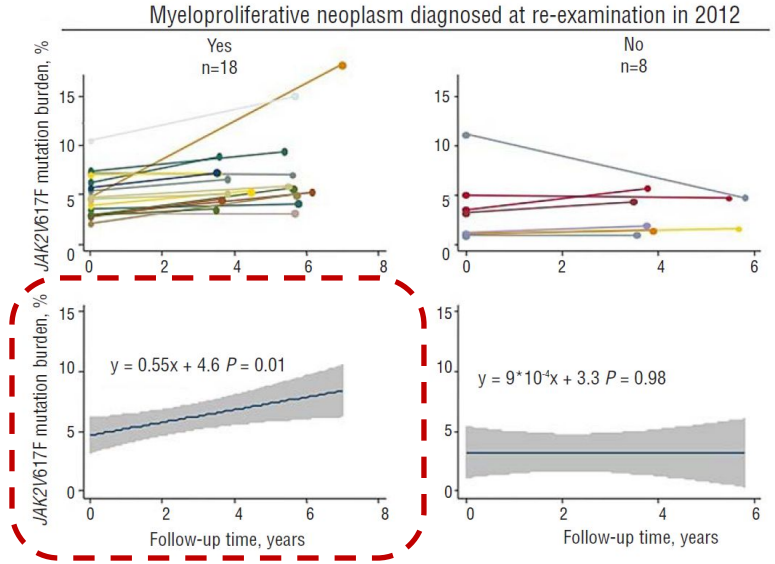
High risk of MPN in persons with clonal hematopoiesis (CHIP)

	JAK2 V617F (3.1%)	*CALR* (0.16%)	
		Type 1	Type 2
Number	613	24	8
Allele burden, %			
Mean (SE), range	2.1 (0.34), 0.010-96	6.2 (2.3), 0.020-44	11 (5.9), 0.013-38
<0.1, n (%)	255 (42)	5 (21)	1 (13)
0.1-0.99, n (%)	253 (41)	9 (38)	4 (50)
1-10, n (%)	75 (12)	4 (17)	0
>10, n (%)	30 (5)	6 (25)	3 (38)

Table III. Prevalent morbidity in the general population according to *JAK2* V617F somatic mutation status.

	JAK2 V617F somatic mutation status		
Endpoints	Negatives (n = 49 420) cases/controls	Positives (n = 68) cases/controls	Odds ratio (95% CI)
Any cancer	6969/42 451	23/45	2·7 (1·6–4·6)
Haematological cancer	139/49 281	10/58	44 (22–90)
Myeloproliferative cancer	32/49 388	10/58	221 (100–487)
Ischaemic heart disease	2689/46 731	11/57	2·2 (1·1–4·4)
Myocardial infarction	1091/48 329	6/62	2·6 (1·1–6·3)
Venous thromboembolism	989/48 431	5/63	3·1 (1·3–7·9)
Pulmonary embolism	344/49 076	0/68	–
Deep venous thrombosis	729/48 691	5/63	4·6 (1·7–10·9)

Odds ratios were adjusted for sex, age, tobacco consumption, alcohol consumption, and body mass index at the time of blood sampling. CI = confidence interval.



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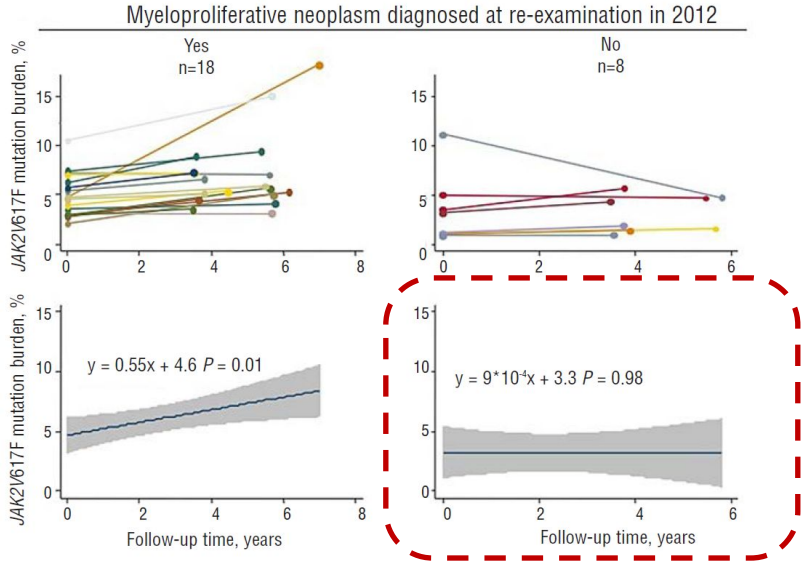

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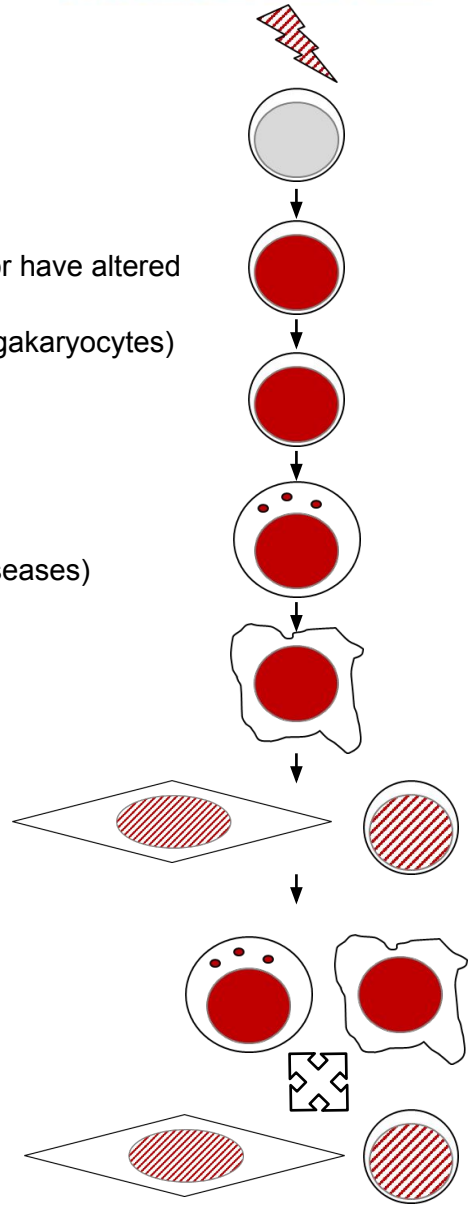
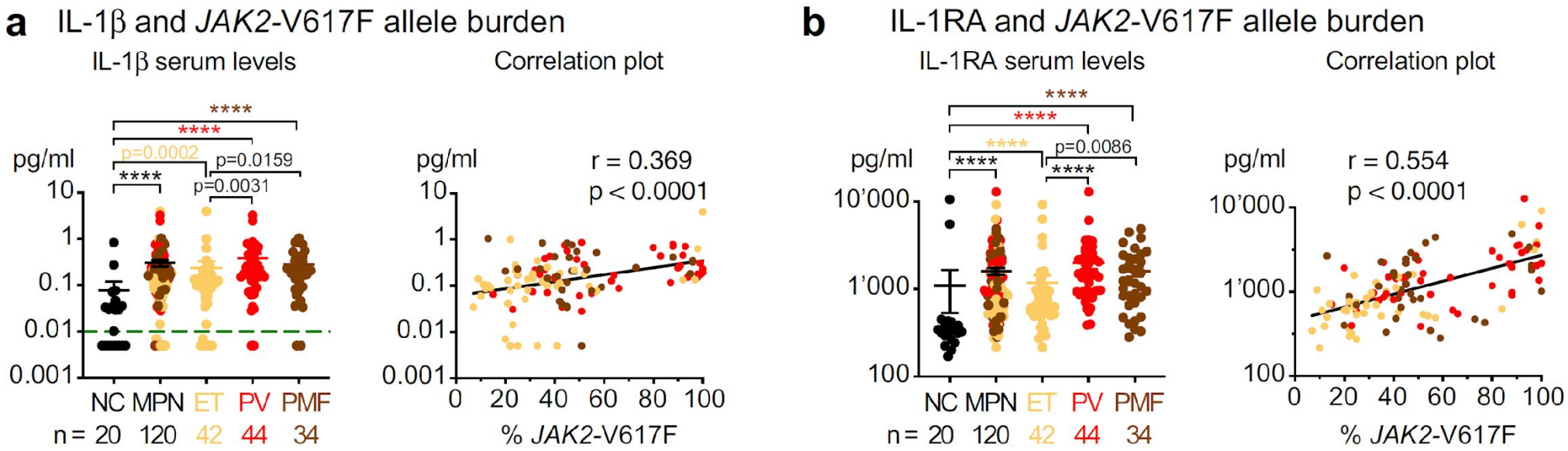
  - Clonal hematopoiesis (CHIP) for JAK2V617F may be detectable by PCR/NGS diagnostics (Patient is at risk for MPN & cardiovascular diseases)
- JAK2V617F-mutant differentiated cells accumulate in the peripheral blood and cause full-blown MPN
  - Systemic cytokines may cause chronic inflammatory symptoms (fever, night sweats, weight loss, fatigue, pruritus, …)
  - Thrombocytosis, erythrocytosis, leukocytosis (mostly neutrophilia, monocytosis), splenomegaly
  - Highly increased risk of cardiovascular complications (e.g. thrombosis, bleeding, organ damage)



IL-1beta is required for JAK2V617F-mediated MPN in mice



Rai et al Nature Immunol 2022

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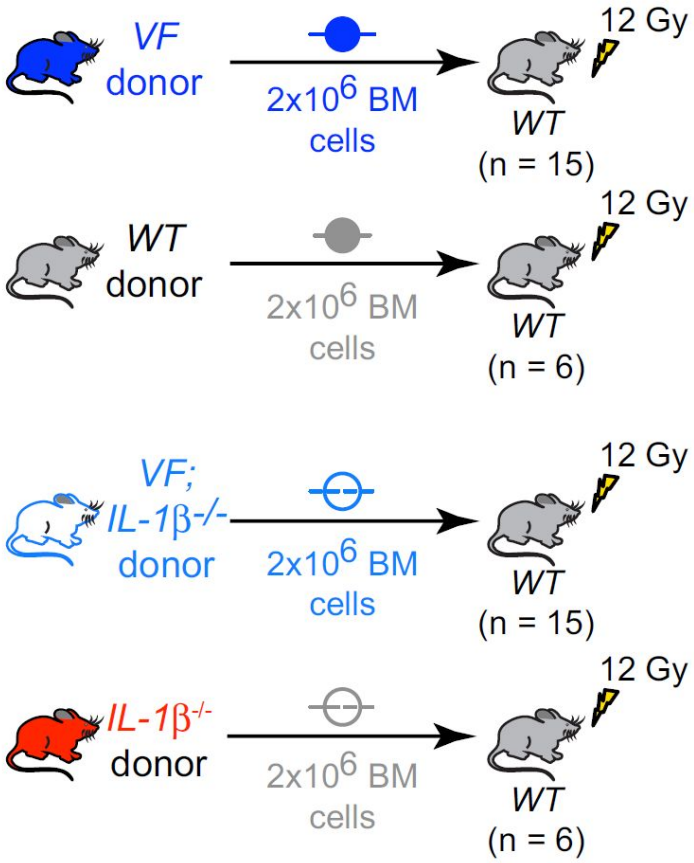

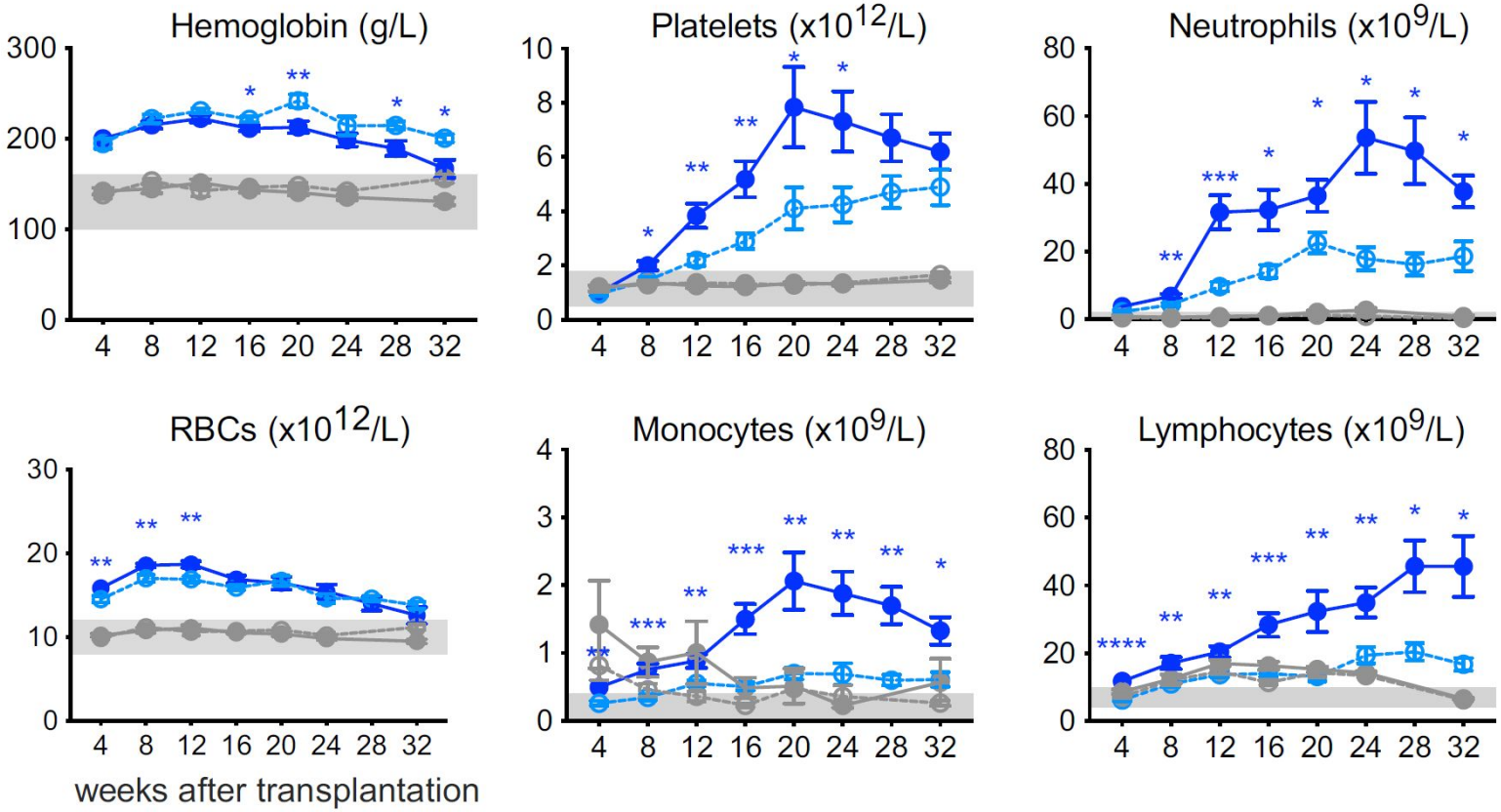

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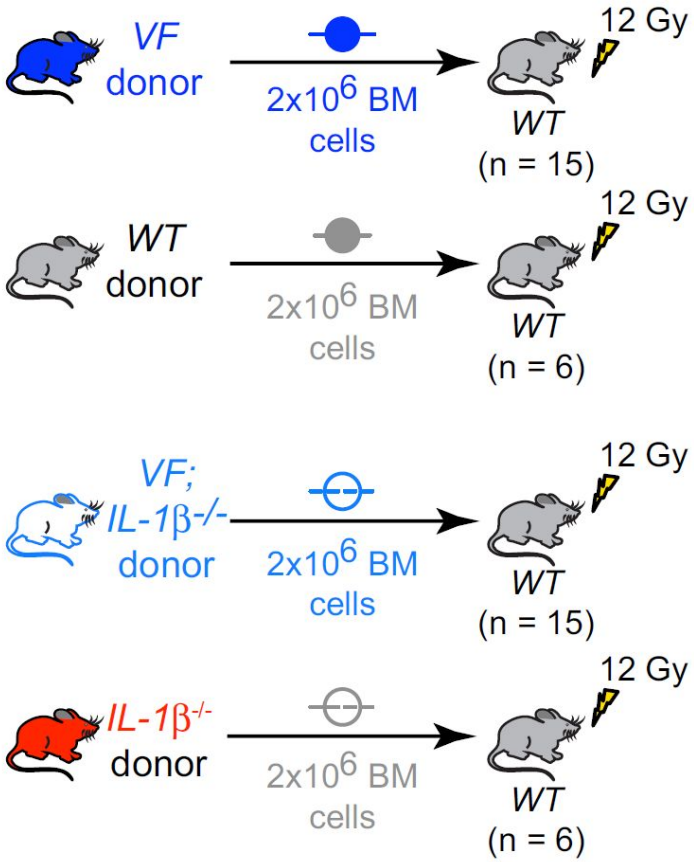
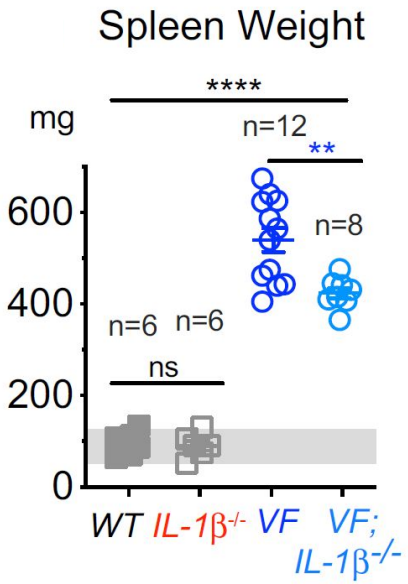
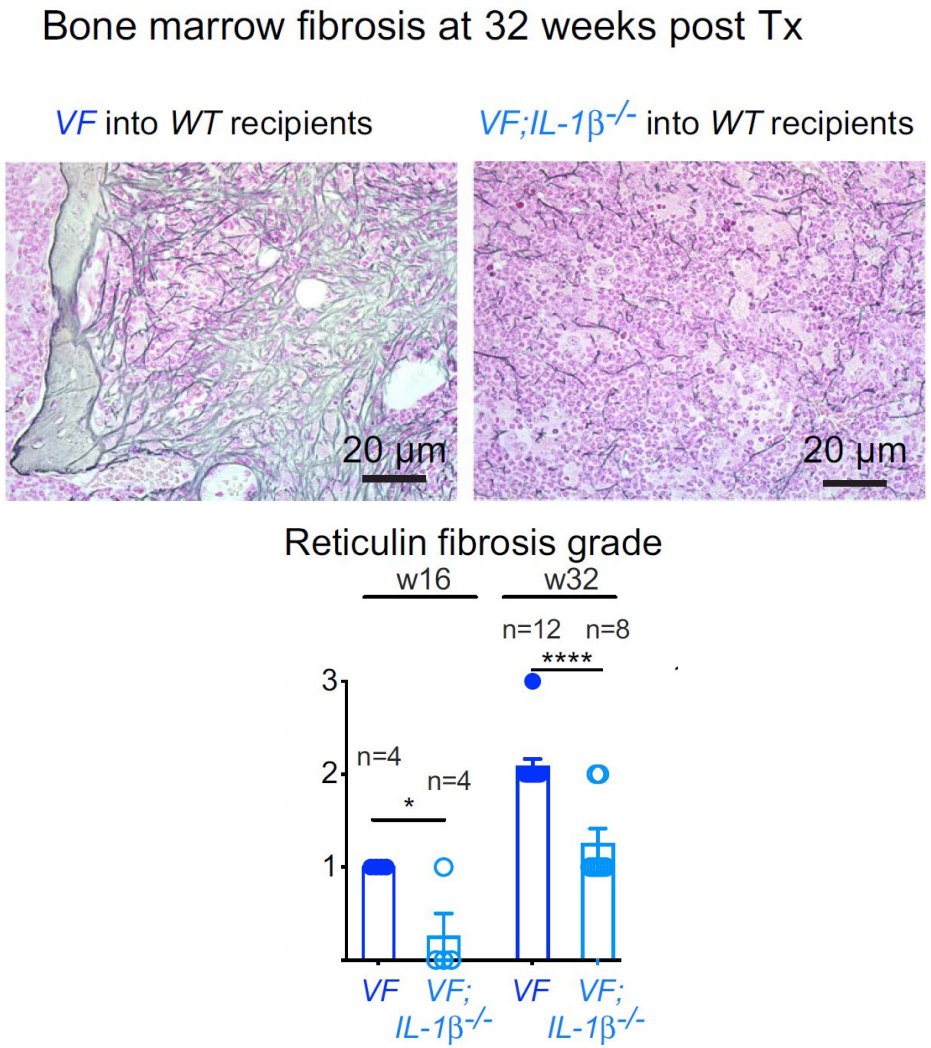
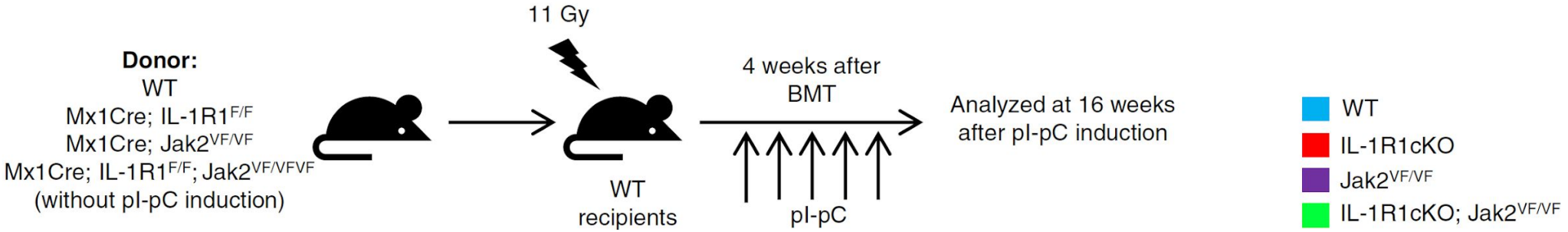


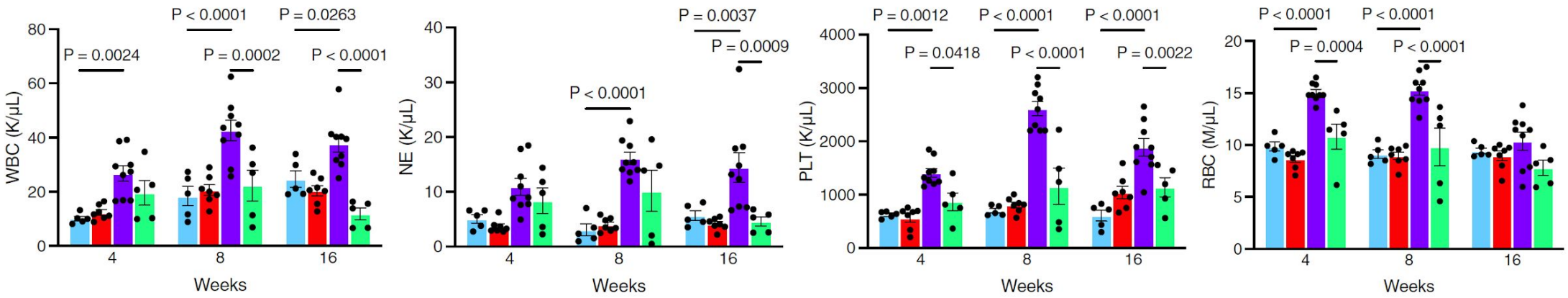


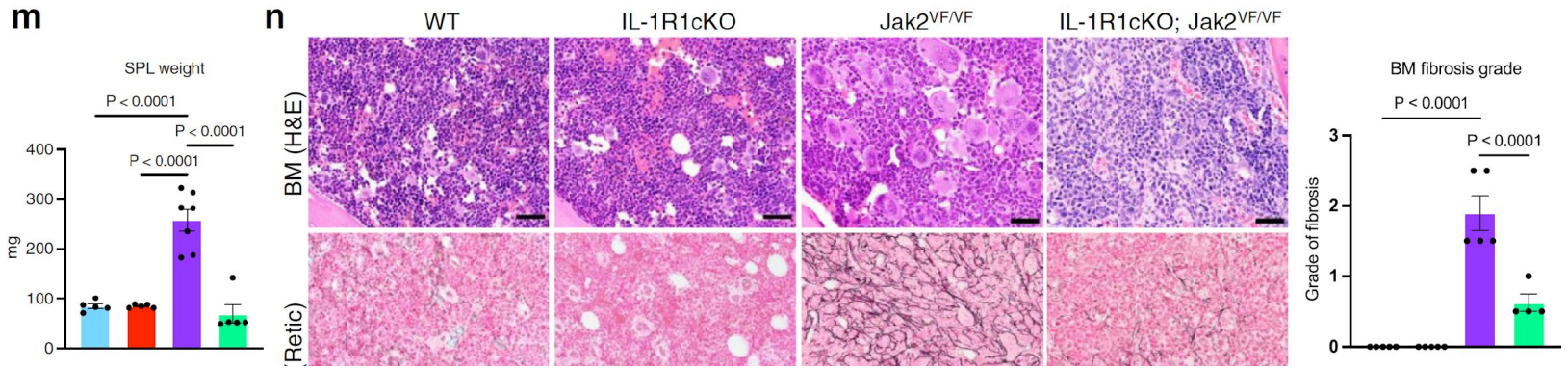


Rai et al Nature Immunol 2022

IL-1R1 is essential for JAK2V617F-mediated MPN in mice

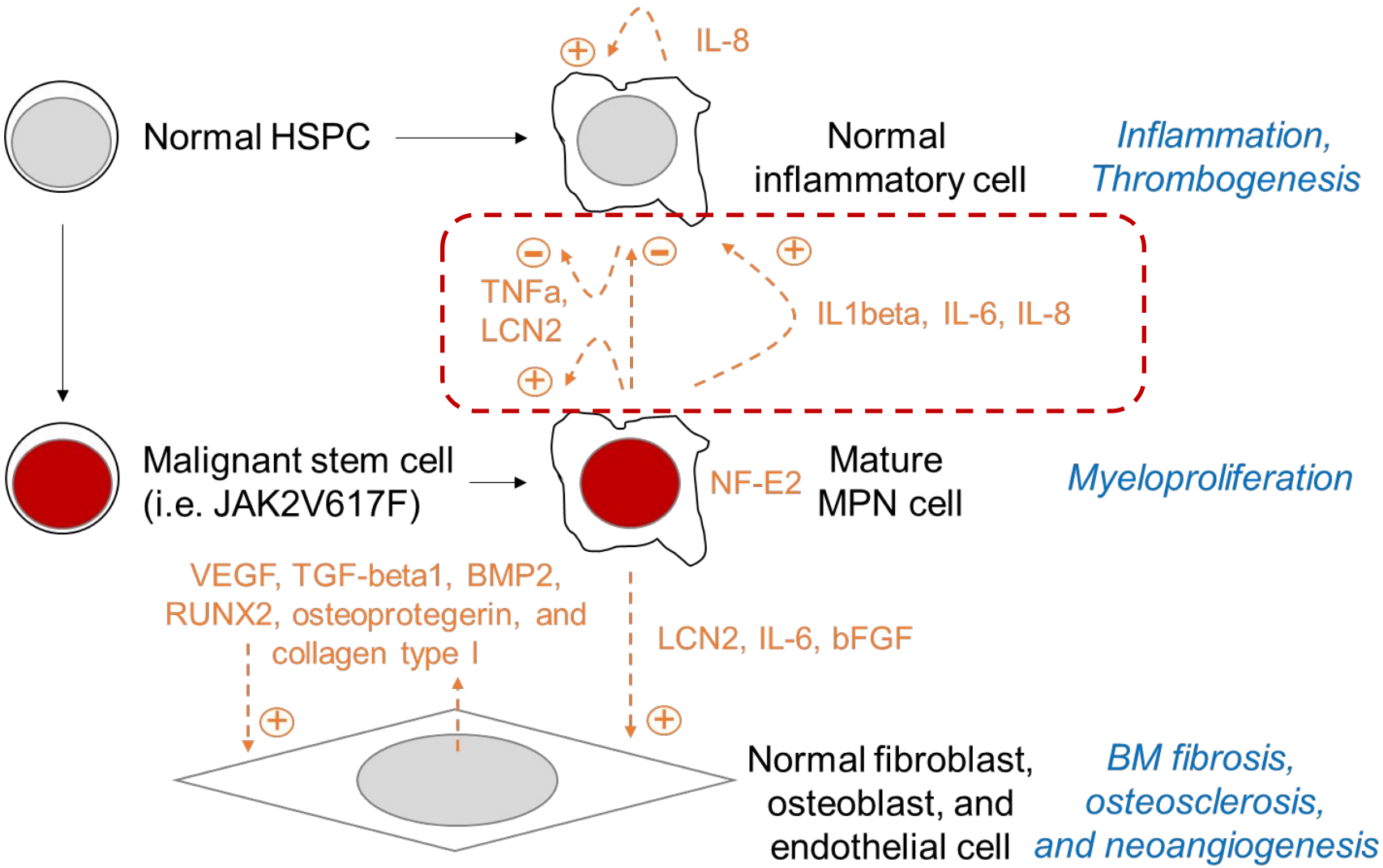






Rahman et al Nature Immunol 2022

Inflammation confers selective advantage to the malignant clone



Koschmieder et al Leukemia 2016

Inflammatory cytokine serum levels are increased in MF

Table 2. Cytokines Whose Plasma Levels Are Abnormally Increased (or decreased) in PMF and Their Relationship With Age, Sex, and Clinically Relevant Disease Features at Time of First Referral at the Mayo Clinic

Cytokines (pg/mL)	Controls (n = 35) Median	Controls (n = 35) Range	All Patients With PMF (N = 127) Median	All Patients With PMF (N = 127) Range	P	P: Constitutional Symptoms	P: RBC Transfusion Dependency	P: Spleen > 10 cm	P: WBC > 10 × 10^9/L	P: Platelets > 450 × 10^9/L	P: Platelets < 100 × 10^9/L	P: *JAK2*V617F Positivity	P: Age	P: Sex
IL-1β	4	0-49	10.8	0-3,576	.02	.81	.68	.21	.87	.64	.3	.35	.12	.05
IL-1RA	203	2-419	552	37-9,991	< .001	.84	.62	.07	.68	.27	.47	< .001	.14	.26
IL-2R	217	0-507	556	91-3,956	< .001	.24	.001	.17	.006	.76	.68	.008	.06	.01†
IL-6	0.6	0-9	6.3	0-186	< .001	.03	.05	.09	.34	.13	.35	.007	.05	.12
IL-8	3.3	0-18	14.3	0-1,156	< .001	.004	.03	.35	.07	.58	.26	.63	.1	.04†
IL-10	4.8	2.3-51	12.5	2-2,009	< .001	.48	.02	.34	.73	.23	.31	.61	.55	.22
IL-12	100	35-182	192	18-1,883	<.001	.55	.14	.28	.80	.99	.04*	.02	.34	.43
IL-13	0	0-0	0	0-4,909	.001	.9	.06	.46	.46	.87	.97	.48	.09	.11
IL-15	0	0-38	0	0-2,671	.03	.8	.61	.46	.86	.95	.90	.85	.16	.02†
TNF-α	0	0-15	0	0-400	.02	.97	.13	.09	.60	.48	.95	.58	.97	.08
G-CSF	33	0-373	45	0-888	.007	.1	.91	.99	.72	.23	.08	.66	.34	.38
IFN-α	27.6	0-96	42	0-1,021	.02	.4	.11	.96	.33	.59	.95	.83	.99	.06
IFN-γ	5.5	0-23	0	0-683	.02*	.55	.8	.55	.5	.21	.53	.12	.91	.52
MIP-1α	0	0-112	25.4	0-1,305	< .001	.55	.03	.05	.21	.87	.74	.98	.14	.001†
MIP-1β	21.8	4.4-91	65.7	0-1,935	< .001	.67	.3	.16	.69	.12	.03	.05	.07	.74
HGF	129	0-433	391	0-11,572	< .001	.14	.9	.02	.02	.27	.39	.003	.54	.76
IP-10	22	4-97	72	5.3-755	< .001	.08	.2	.19	.02	.11	.006	< .001	< .001	.73
MIG	19.4	0-86	49	0-971	< .001	.48	.3	.08	.76	.44	.28	.01	.12	.04†
MCP-1	173	61-342	222	62-1,705	.001	.19	.009	.77	.87	.20	.07	.27	.68	.24
VEGF	1	0-2.7	2.3	0-47	< .001	.42	.42	.23	.72	.87	.27	.89	.31	.32

Tefferi et al JCO 2011

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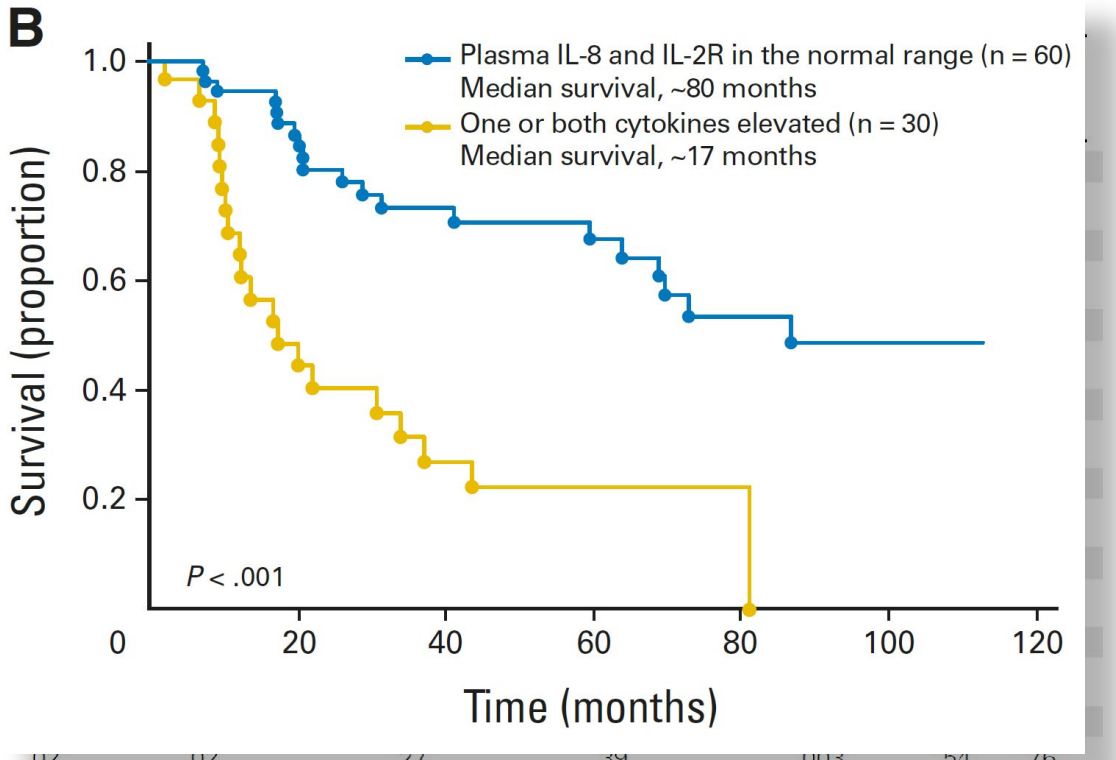
IL-8	3.3	0-18	14.3	0-1,156	< .001	.004	.03
IL-10	4.8	2.3-51	12.5	2-2,009	< .001	.48	.02
IL-12	100	35-182	192	18-1,883	< .001	.55	.14
IL-13	0	0-0	0	0-4,909	.001	.9	.06
IL-15	0	0-38	0	0-2,671	.03	.8	.61
TNF-α	0	0-15	0	0-400	.02	.97	.13
G-CSF	33	0-373	45	0-888	.007	.1	.91
IFN-α	27.6	0-96	42	0-1,021	.02	.4	.11
IFN-γ	5.5	0-23	0	0-683	.02*	.55	.8
MIP-1α	0	0-112	25.4	0-1,305	< .001	.55	.03
MIP-1β	21.8	4.4-91	65.7	0-1,935	< .001	.67	.3
HGF	129	0-433	391	0-11,572	< .001	.14	.9
IP-10	22	4-97	72	5.3-755	< .001	.08	.2
MIG	19.4	0-86	49	0-971	< .001	.48	.3
MCP-1	173	61-342	222	62-1,705	.001	.19	.009
VEGF	1	0-2.7	2.3	0-47	< .001	.42	.42



	.02	.02	.27	.39	.003	.54	.76					
	.19	.02	.11	.006	< .001	< .001	.73					
	.08	.76	.44	.28	.01	.12	.04†					
	.77	.87	.20	.07	.27	.68	.24					
	.23	.72	.87	.27	.89	.31	.32					

Tefferi et al JCO 2011

Inflammatory cytokine serum levels are increased in MF

Table 2. Cytokines Whose Plasma Levels Are Abnormally Increased (or decreased) in PMF and Their Relationship With Age, Sex, and Clinically Relevant Disease Features at Time of First Referral at the Mayo Clinic

Cytokines (pg/mL)	Controls (n = 35) Median	Controls (n = 35) Range	All Patients With PMF (N = 127) Median	All Patients With PMF (N = 127) Range	P	P: Constitutional Symptoms	P: RBC Transfusion Dependency	P: Spleen > 10 cm	P: WBC > 10 × 10^9/L	P: Platelets > 450 × 10^9/L	P: Platelets < 100 × 10^9/L	P: *JAK2*V617F Positivity	P: Age	P: Sex
IL-1β	4	0-49	10.8	0-3,576	.02	.81	.68	.21	.87	.64	.3	.35	.12	.05
IL-1RA	203	2-419	552	37-9,991	< .001	.84	.62	.07	.68	.27	.47	< .001	.14	.26
IL-2R	217	0-507	556	91-3,956	< .001	.24	.001	.17	.006	.76	.68	.008	.06	.01†
IL-6	0.6	0-9	6.3	0-186	< .001	.03	.05	.09	.34	.13	.35	.007	.05	.12
IL-8	3.3	0-18	14.3	0-1,156	< .001	.004	.03	.35	.07	.58	.26	.63	.1	.04†
IL-10	4.8	2.3-51	12.5	2-2,009	< .001	.48	.02	.34	.73	.23	.31	.61	.55	.22
IL-12	100	35-182	192	18-1,883	<.001	.55	.14	.28	.80	.99	.04*	.02	.34	.43
IL-13	0	0-0	0	0-4,909	.001	.9	.06	.46	.46	.87	.97	.48	.09	.11
IL-15	0	0-38	0	0-2,671	.03	.8	.61	.46	.86	.95	.90	.85	.16	.02†
TNF-α	0	0-15	0	0-400	.02	.97	.13	.09	.60	.48	.95	.58	.97	.08
G-CSF	33	0-373	45	0-888	.007	.1	.91	.99	.72	.23	.08	.66	.34	.38
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IFN-γ	5.5	0-23	0	0-683	.02*	.55	.8	.55	.5	.21	.53	.12	.91	.52
MIP-1α	0	0-112	25.4	0-1,305	< .001	.55	.03	.05	.21	.87	.74	.98	.14	.001†
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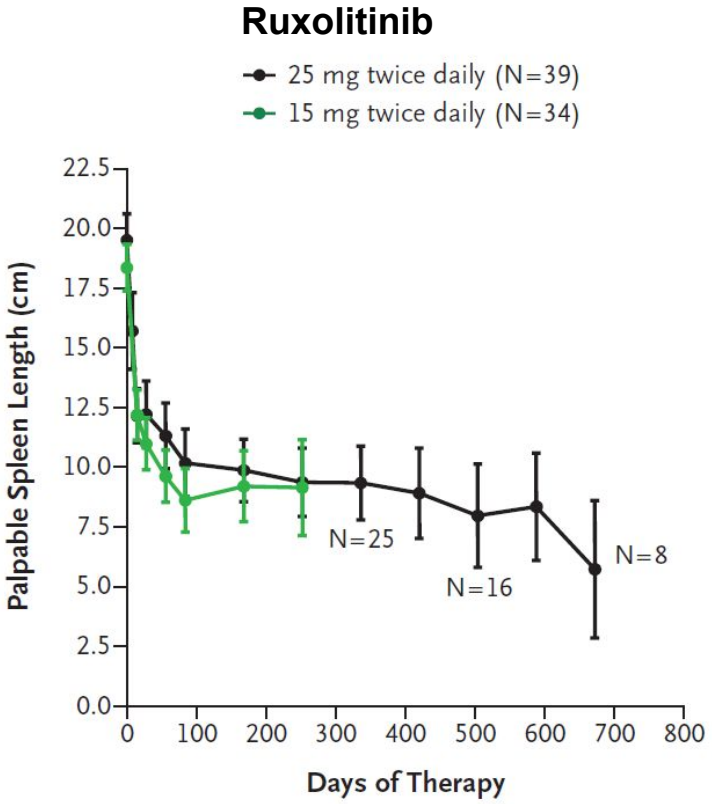
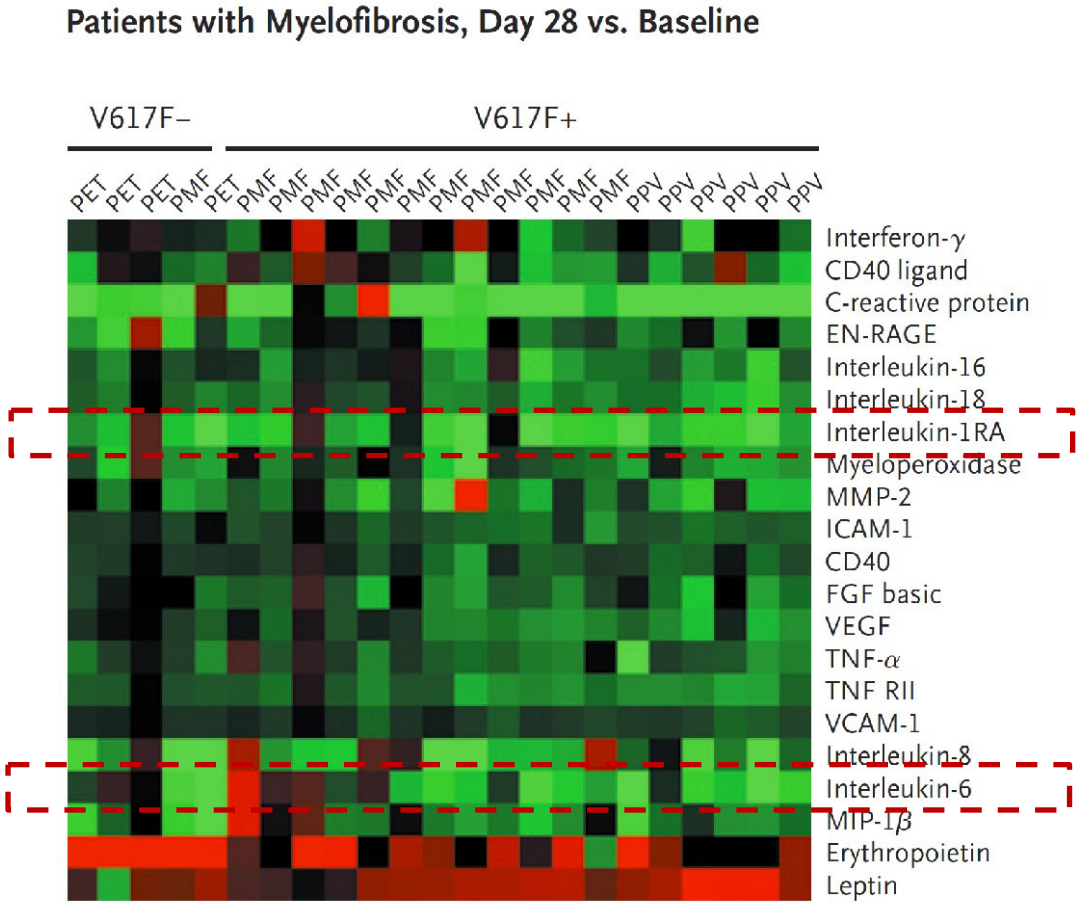
JAK inhibitors may ameliorate MPN (in part via IL-6 decrease?)





Modified from Verstovsek et al NEJM 2010

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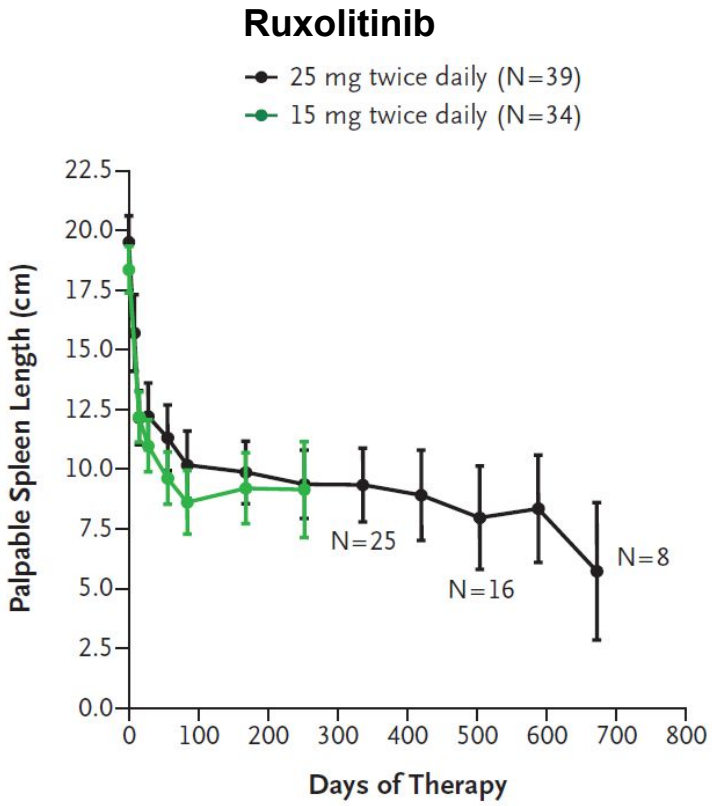

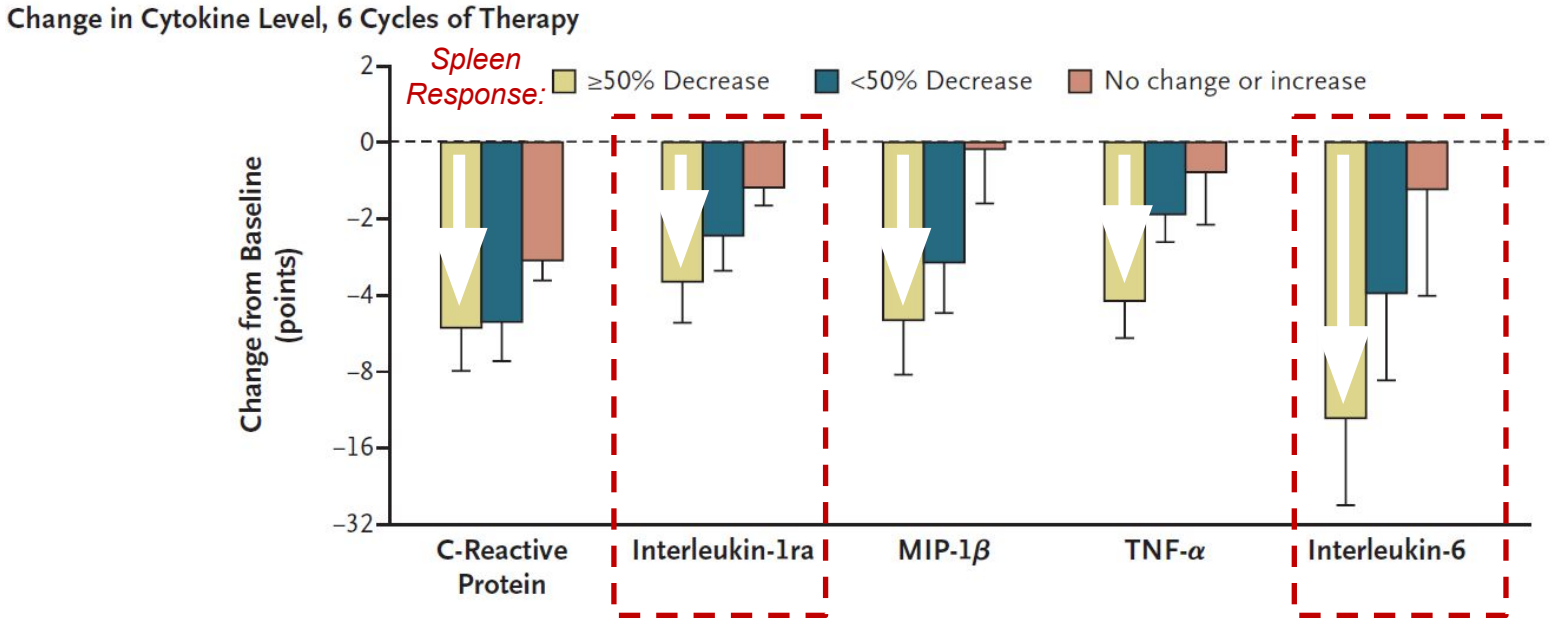

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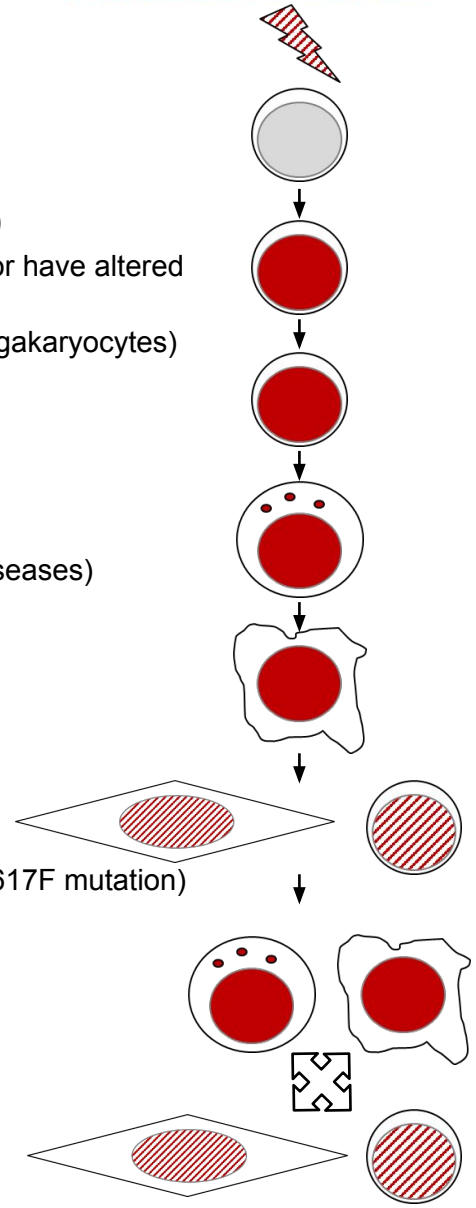
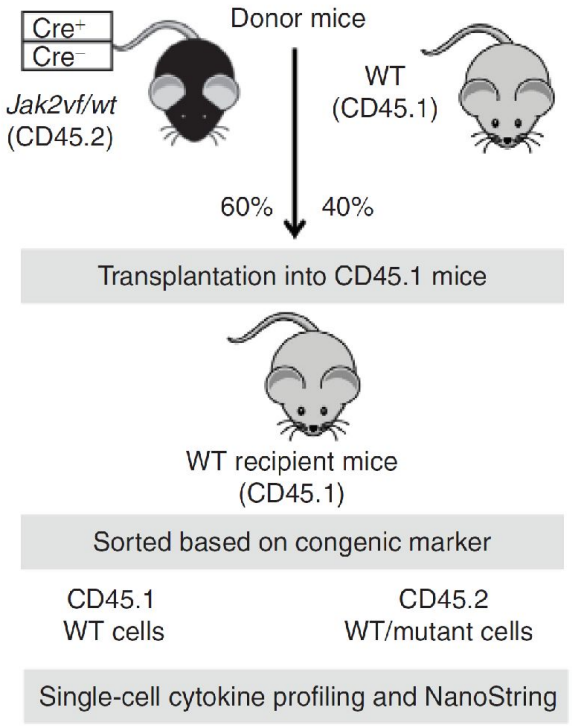
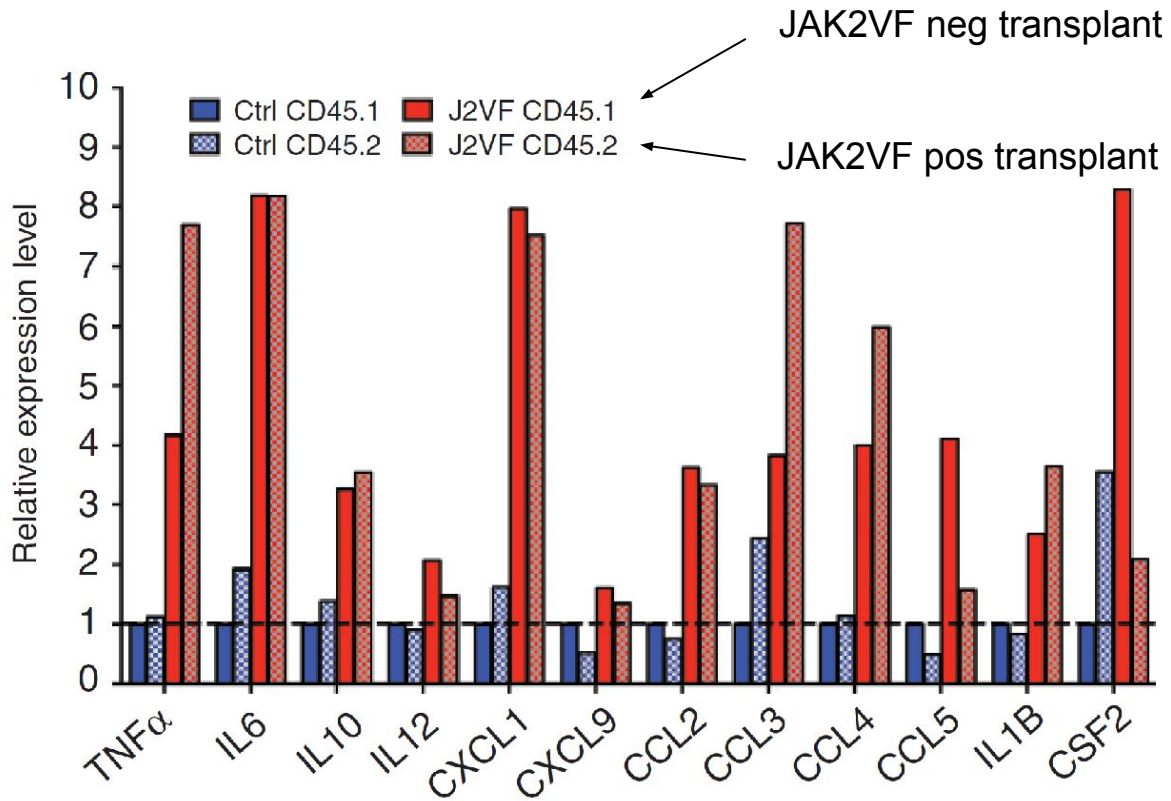


JAK2V617F clone alters normal hematopoiesis





Kleppe et al Cancer Discov 2015

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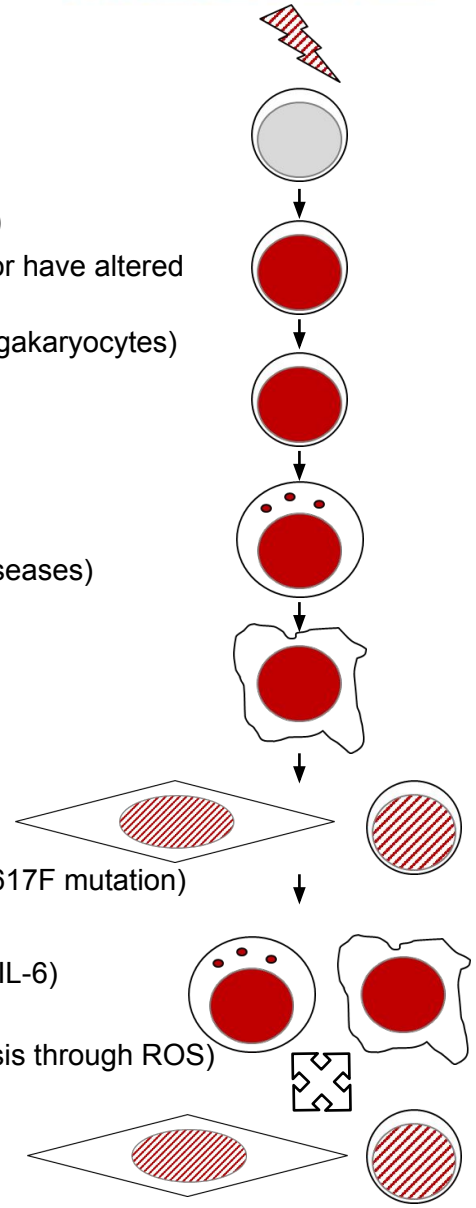


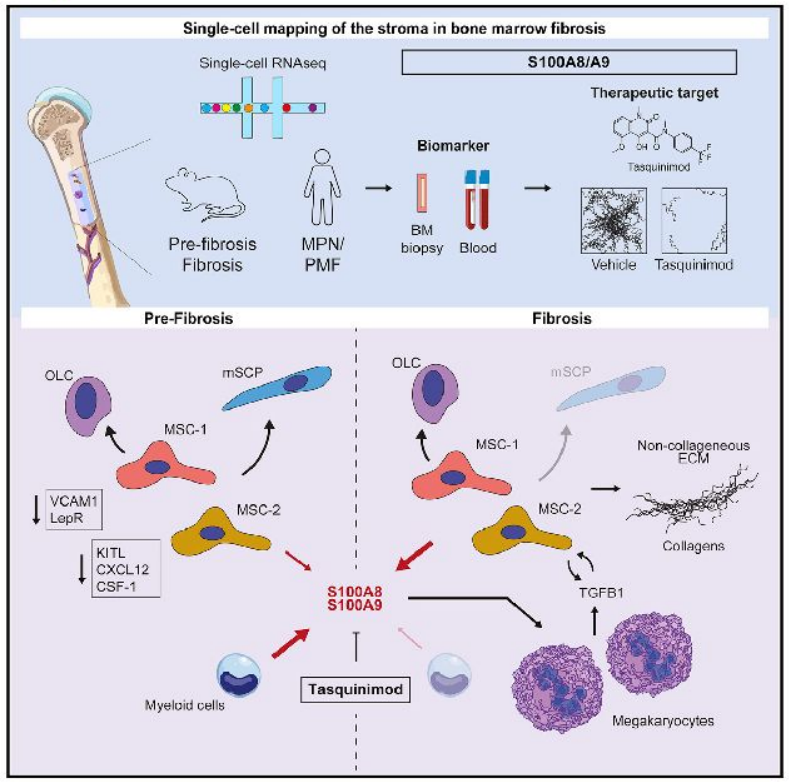
scRNAseq defines separate subgroups of BM stromal cells in MPN

Article

Cell Stem Cell

Heterogeneous bone-marrow stromal progenitors drive myelofibrosis via a druggable alarmin axis

Graphical Abstract



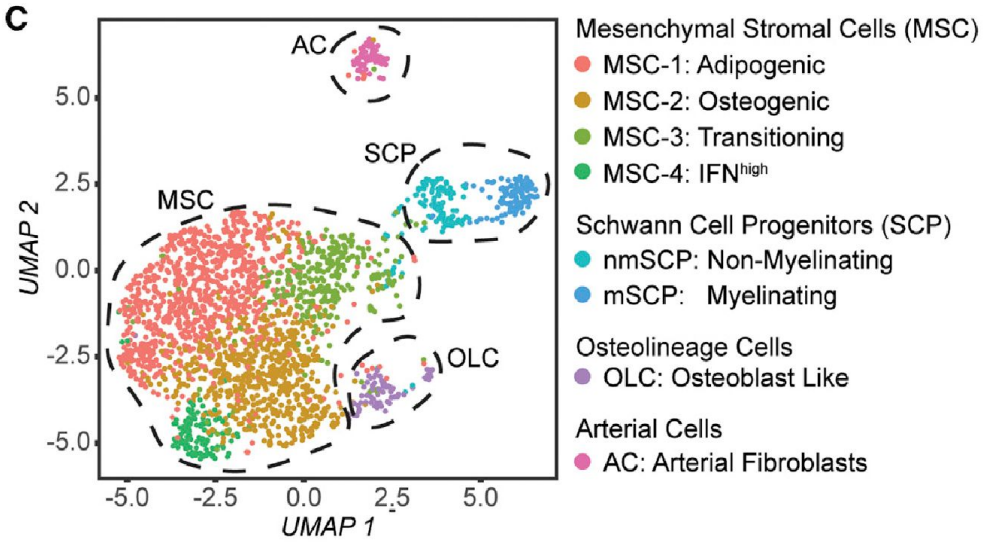
Nils B. Leimkühler,[1,14] Hélène F.E. Gleitz,[1,14] Li Ronghui,[2,14] Inge A.M. Snoeren,[1] Stijn N.R. Fuchs,[1] James S. Nagai,[2] Bella Banjanin,[1] King H. Lam,[3] Thomas Vogl,[4] Christoph Kuppe,[5] Ursula S.A. Stalmann,[1] Guntram Büsche,[6] Hans Kreipe,[6] Ines Gütgemann,[7] Philippe Krebs,[8] Yara Banz,[8] Peter Boor,[9] Evelyn Wing-Ying Tai,[9] Tim H. Brümmendorf,[10] Steffen Koschmieder,[10] Martina Crysandt,[10] Eric Bindels,[1] Rafael Kramann,[5,13,15] Ivan G. Costa,[2,15] and Rebekka K. Schneider[1,11,12,15,16,*]

Correspondence

reschneider@ukaachen.de

In Brief

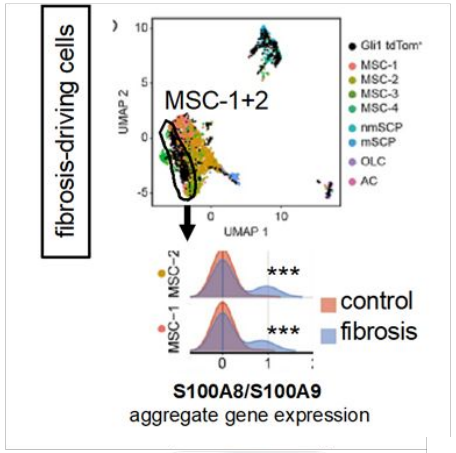
Leimkühler and colleagues demonstrate that mesenchymal stromal progenitor cells are fibrosis-driving cells in mice and patients, that inflammation in the bone-marrow stroma precedes TGF-β signaling-driven fibrosis, and that the alarmin heterocomplex S100A8/S100A9 holds promise as MPN progression marker and therapeutic target.

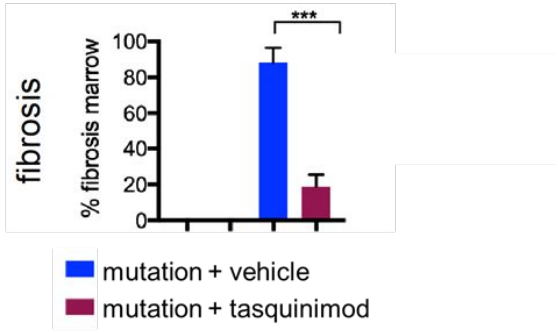


Leimkühler, Gleitz, Ronghui et al Cancer Stem Cell 2021

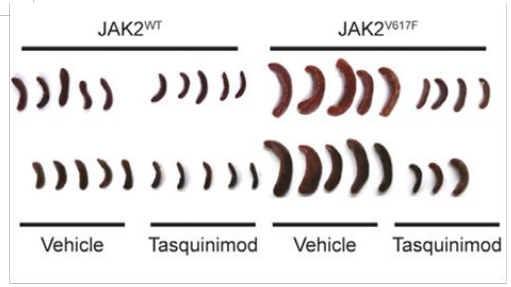
Early interventions: Role of alarmins S100A8/A9 in MPN initiation

Target Identification (S100A8/A9) and Target Validation (Tasquinimod)[1]





Rebekka Schneider
Aachen



Tasquinimod is disease-modifying

- anti-fibrotic,
- anti-cytopenic,
- splenomegaly-reducing

[1]Leimkühler, Gleitz, Ronghui et al Cell Stem Cell 2021

Early interventions: Role of alarmins S100A8/A9 in MPN initiation

UNIKLINIK RWTH AACHEN

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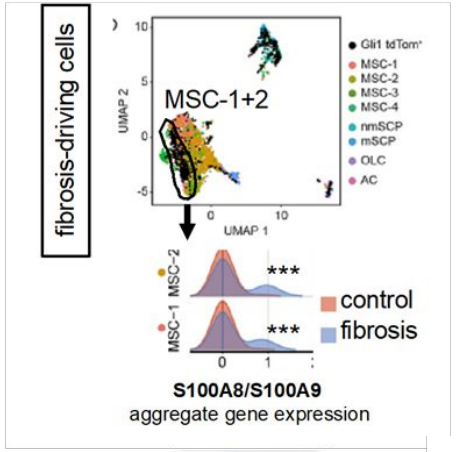

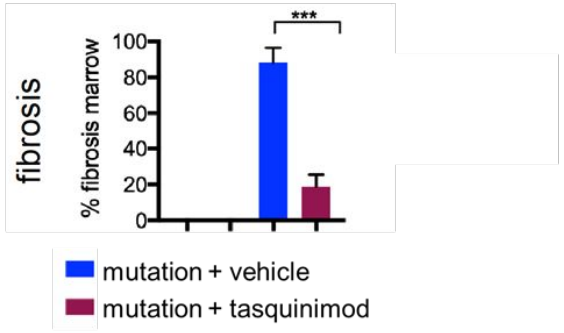

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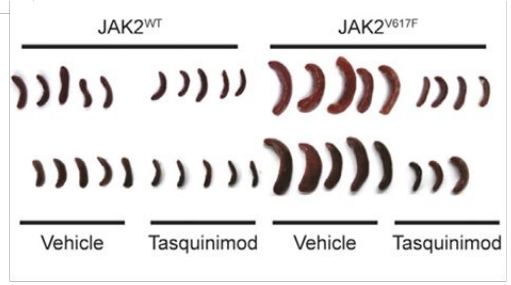

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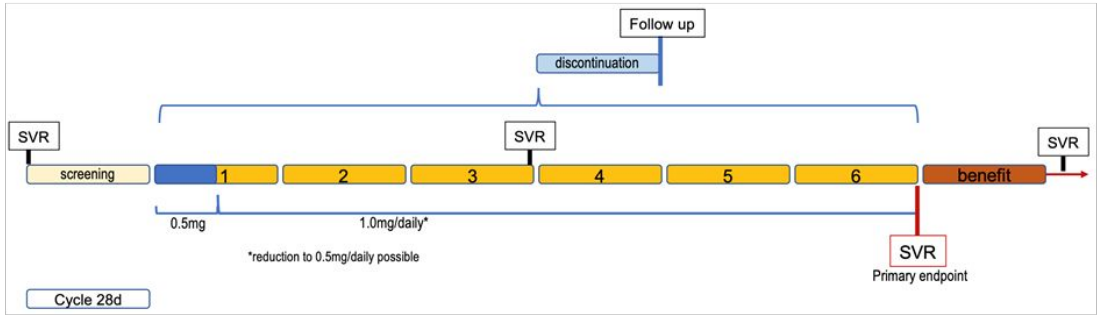
Proof-of-concept Phase II Clinical Trial – TasquForce MPN

Patient cohort: heavily pretreated patients with MPN and bone marrow fibrosis



Peter te Boekhorst
Rotterdam

Martina Crysandt
Aachen

Funding: Oncode Institute

Sponsor: Erasmus MC University Medical Center Rotterdam

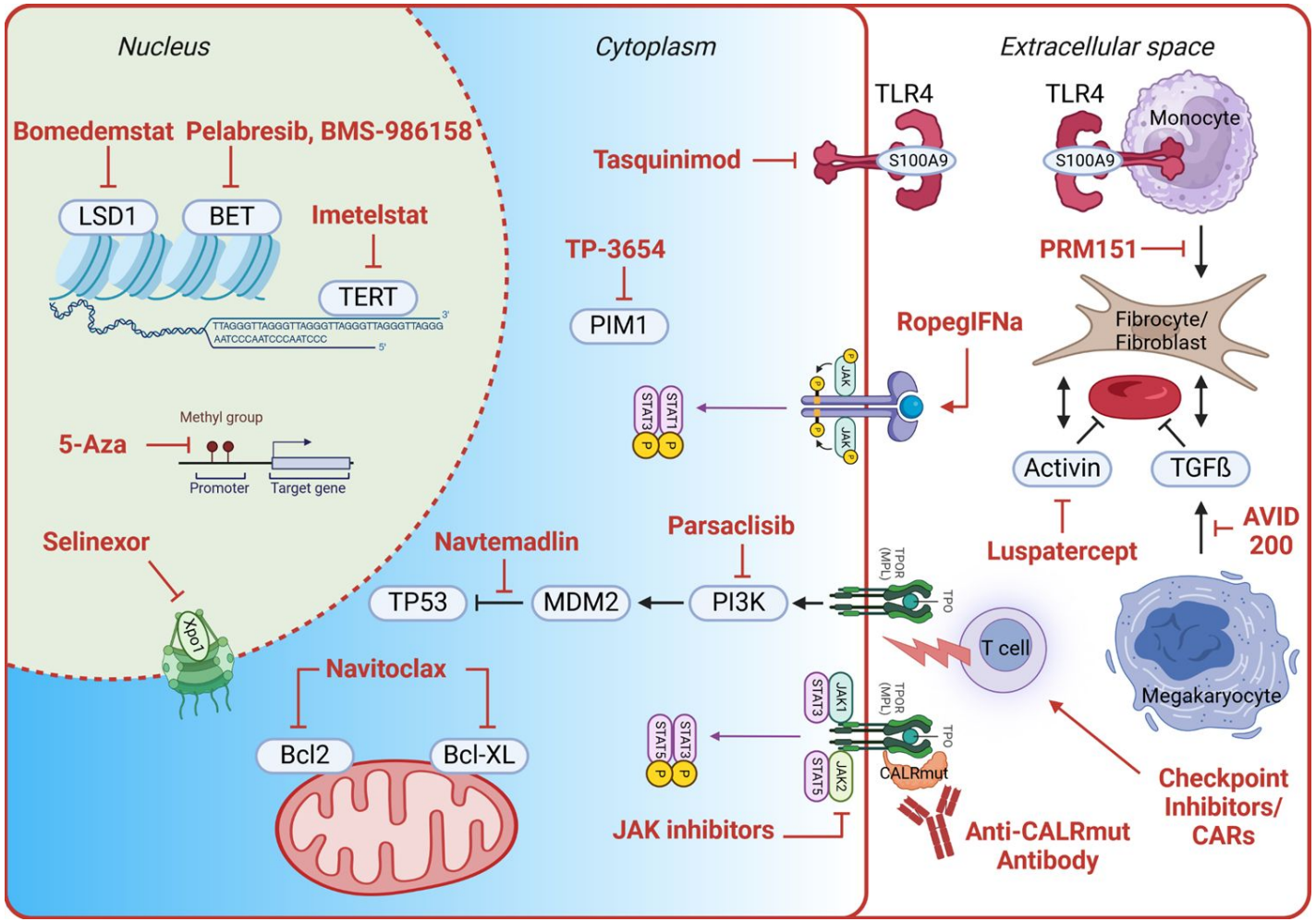
Clinical has recently started…

[1]Leimkühler, Gleitz, Ronghui et al Cell Stem Cell 2021

Summary and Outlook

Aspects of Inflammation in MPN

Pathogenesis	Diagnosis	Therapy
• Inflammatory cytokines • Other soluble factors • Cellular interactions • Prothrombotic state • Fibrotic stimuli • Contribution by clonal cells (i.e. granulocytes, monocytes, platelets) • Contribution by non-clonal cells (i.e. T and NK cells, MDSC, residual non-clonal cells)	• Serum markers of inflammation • Clonal markers („Driver and passenger mutations“) • Diagnosis in the absence of a clonal marker (i.e. Triple-neg. MF, Triple-neg. ET, MPN-U) • Physiologic clonal hematopoiesis	• JAK inhibitors • (Peg-)Interferon alpha • Corticosteroids • Immunomodulating drugs (IMIDs) • Imetelstat • Pentraxin-2 • Other drugs



Koschmieder et al Leukemia 2016

Koschmieder Hemasphere 2024

Acknowledgments

Our Department, Aachen University:

Dept. of Hematology, Oncology, Hemostaseology, and SCT:
Nicolas Chatain, Marcelo Szymanski de Toledo, Julian Baumeister, Jimena Rodriguez, Milena Kalmer, Kathrin Olschok, Stefan Tillmann, Mithuoshni Arullmoli, Kim Kricheldorf, Joelle Schifflers, Manuela Klever, Mirle Schemionek, Deniz Gezer, Julia Stomper, Madeline Caduc, Rosa Cho, Rebecca Lemanzyk, Chiara Wirths, Martina Crysandt, Gerda Silling, Tim Brümmendorf (and more)

Our collaborators:

RWTH Aachen University: Rafael Kramann, Sikander Hayat, Mirle Schemionek, Gerhard Müller-Newen, Rebekka Schneider, Martina Crysandt, Martin Zenke, Nicolas Chatain, Alexandros Sofias, Wolfgang Wagner, Hélène Gleitz, Natalia Torow, Mathias Hornef, Tim Brümmendorf, Ivan Costa, all other CRU344 members

GSG-MPN Germany: Konstanze Döhner, Martin Griesshammer, Tim Brümmendorf, Florian Heidel, Susanne Isfort, Frank Stegelmann, Haifa K. Al-Ali, Heiko Becker, Nikolas v. Bubnoff, Thomas Ernst, Thomas Fischer, Norbert Gattermann, Joachim Göthert, Madlen Jentzsch, Philipp Jost, Nicolaus Kröger, Eva Lengfelder, Heike Pahl, Markus Radsak, Andreas Reiter, Christoph Scheid, Lino Teichmann, Dominik Wolf, and other GSG-MPN members

MPN Patient Advocacy Groups: mpn-netzwerk e.V. (Germany), MPN Research Foundation (USA), MPN Advocates Network (Switzerland)

International: Alexandre Theocharides, Radek Skoda, Claire Harrison, Ruben Mesa, Jean-Jacques Kiladjian, John Mascarenhas, Naveen Pemmaraju, Raajit Rampal, Jyoti Nangalia, Tiziano Barbui, Alberto Alvarez-Larran, Simon Mendez-Ferrer, Hans Hasselbalch, Tomasz Skorski, Shannon Elf, and many others

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DFG Deutsche Forschungsgemeinschaft

MRC Medical Research Council

josé CARRERAS LEUKÄMIE-STIFTUNG

Deutsche Krebshilfe
HELFEN. FORSCHEN. INFORMIEREN.

Fritz Thyssen Stiftung für Wissenschaftsförderung

IZKF AACHEN

Stiftung Universitätsmedizin Aachen

MPN RESEARCH FOUNDATION

Thank you for your attention!

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E-Mail: skoschmieder@ukaachen.de

Personal view on MPN pathogenesis and the role of inflammation

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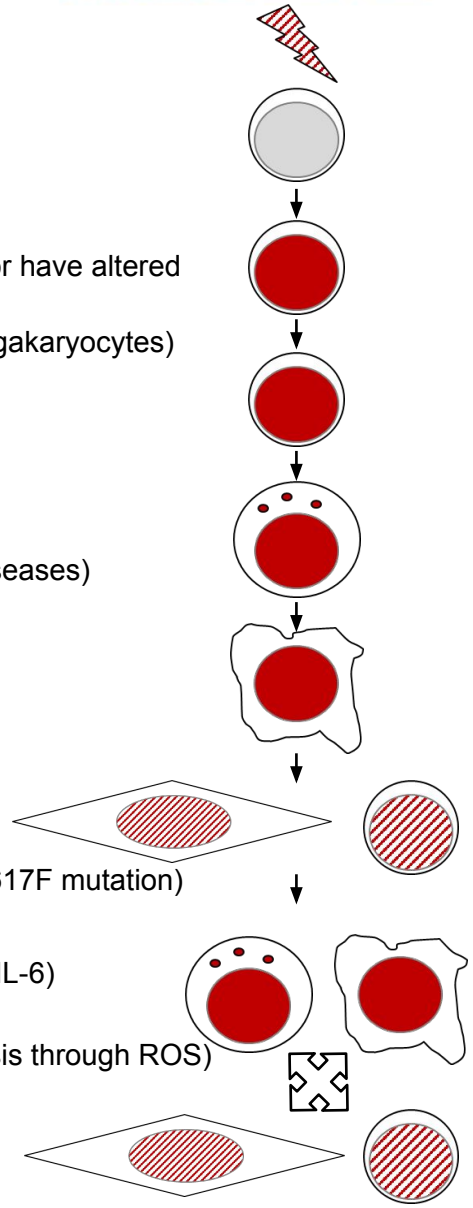
  - These processes induce selection against TP53 WT in the hematopoietic compartment, favoring emergence of TP53 mutations (mutagenesis through ROS)
- Eventually, disease progression occurs



Koschmieder 2025 (unpublished)