SFGM-TC Scientific Day
October 19, 2023
10h00-16h00
Amphi Milian – Hôpital Saint Louis – PARIS

« Hematopoietic stem cell aging »

The Microbiome-IL-1 Axis drives HSC Inflamm-Ageing and *Tet2*$^{+/-}$ Clonal Hematopoiesis

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Comprehensive Cancer Center Zurich
Switzerland

Conflict of interest M.G. Manz

- No conflict of interest in relation to this presentation

Inflamm-Ageing

- driver of (hematopoietic) ageing via the «microbiome»
- driver of clonal hematopoietic expansion
- potential target to attenuate / reverse hematopoietic ageing and clonal expansion

Ageing – a Success of Economy / Lifestyle / Healthcare

<u>Expected scenario:</u>

growth of population > 65y in CH

https://www.sciencemag.org/topic/aging

Zukünftige Bevölkerungsentwicklung – Daten, Indikatoren - Schweiz Szenarien

Geschlechts- und Altersstruktur

Ständige Wohnbevölkerung nach Alter gemäss dem mittleren Szenario

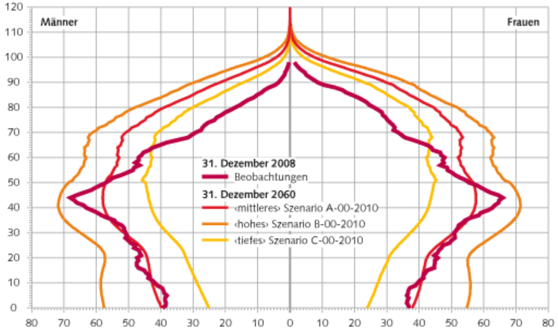
am Jahresende, in Tausend

	2010	2015	2020	2030	2040	2050	2060
Total	7856.6	8155.1	8401.9	8738.5	8906.5	8983.0	8987.2
0-19 Jahre	1635.1	1638.3	1664.8	1705.7	1657.8	1638.6	1652.1
20-39 Jahre	2081.7	2110.9	2105.9	2024.7	2021.8	2054.4	2016.3
40-64 Jahre	2796.5	2884.4	2944.2	2893.2	2835.9	2798.9	2775.7
65-79 Jahre	961.6	1087.9	1199.7	1429.5	1526.9	1430.4	1472.2
80 Jahre und älter	381.7	433.6	487.5	685.4	864.1	1060.6	1071.0

Quelle: SCENARIO

Alterspyramide

Nach den 3 Grundszenarien, in Tausend



Quelle: SCENARIO © BFS

http://www.bfs.admin.ch/bfs/portal/de/index/themen/01/03/blank/key/ind_erw.html

Positive Correlation between Ageing and Cancer Incidence

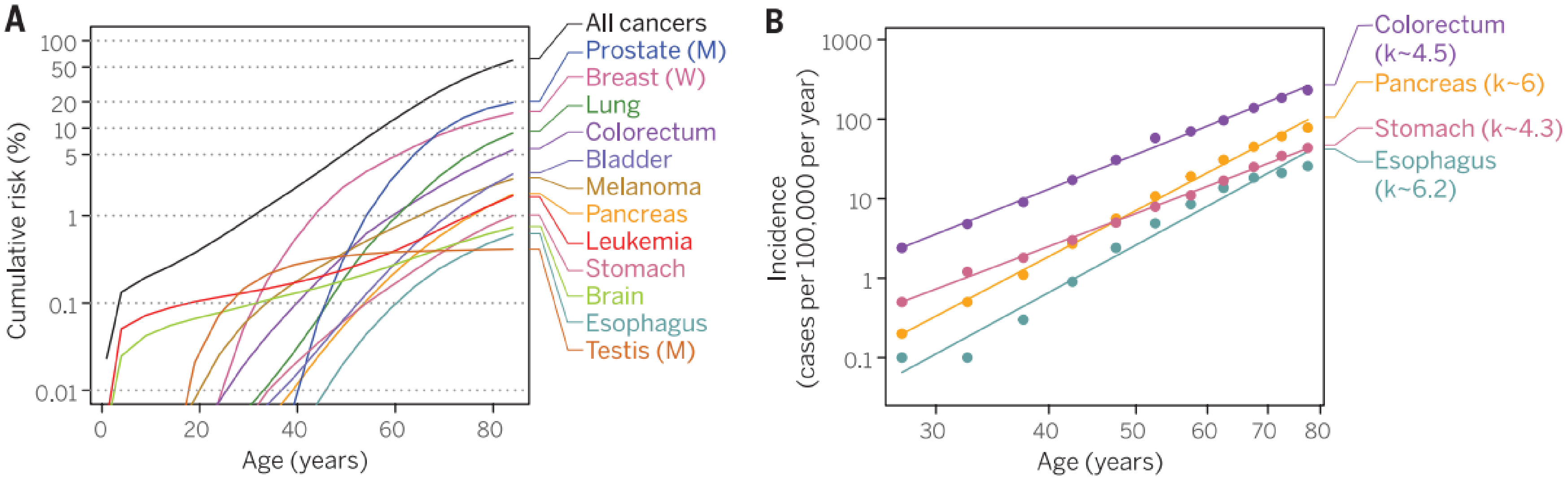


Fig. 4. Age incidence of cancer. (**A**) Cumulative risk of cancer versus age. This plot shows the risk of suffering a given cancer before a particular age. (**B**) Log-log representation of the incidence of different cancers (cases per year per 100,000 people) versus age. The regression lines highlight the approximately geometrical increase of cancer incidence with age, although the association is imperfect and only correlative for some cancer types (*54*). k denotes line slope. U.S. cancer-incidence data are from the SEER (Surveillance, Epidemiology, and End Results Program) Cancer Statistics Review (data are from 2008 to 2012 and include any race and both genders, unless otherwise specified; M, men; W, women).

REVIEW

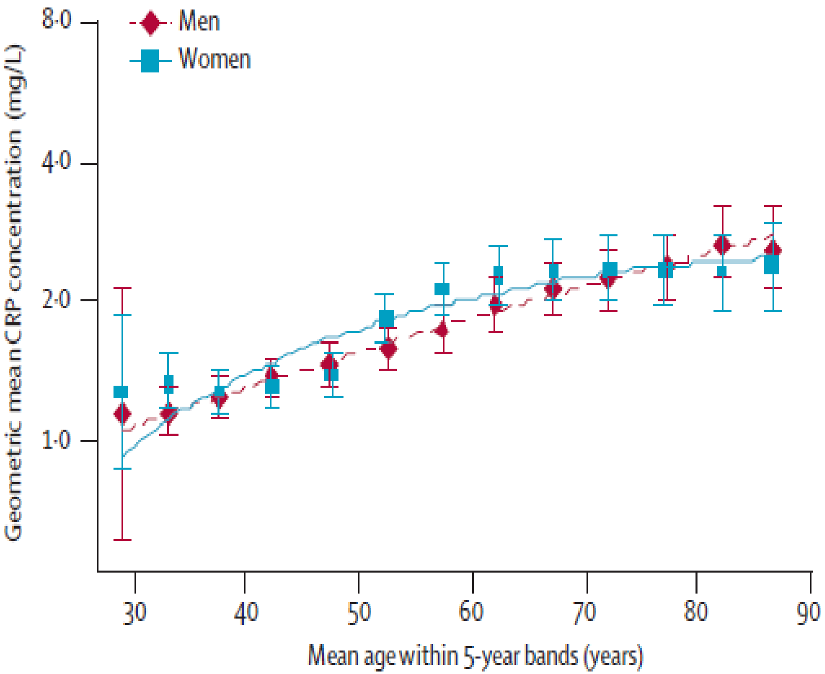
Somatic mutation in cancer and normal cells

Iñigo Martincorena[1] and Peter J. Campbell[1,2]*

SCIENCE sciencemag.org 25 SEPTEMBER 2015 • VOL 349 ISSUE 6255

Positive Correlation between Ageing and Markers of Inflammation

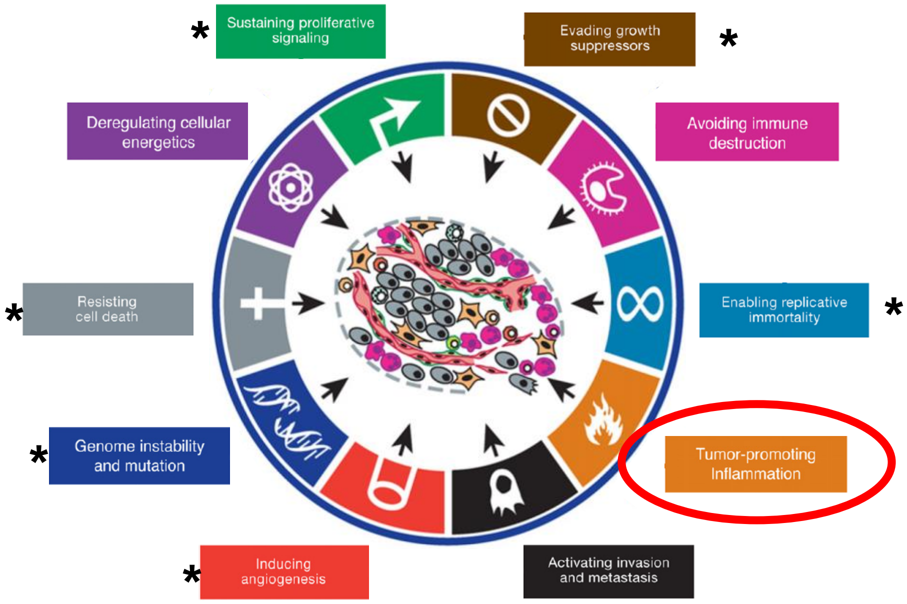
CRP increase with age



C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis.

The emerging risk factors collaboration, Lancet, 2010

Hallmarks of Cancer



Adapted from Hanahan und Weinberg, Cell 2011

→ Contribution of «Inflamm*Ageing*» to cancer hallmarks?

Ageing is associated with clonal dominance in hematopoiesis

Clonal **H**ematopoiesis of **i**ndeterminate **P**otential **(CHiP)**
(also termed Ageing **R**elated **Clonal H**ematopoeisis**, ARCH)**

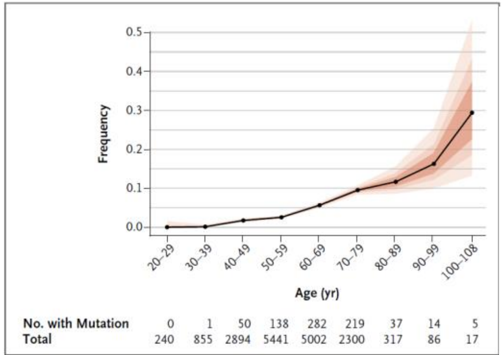
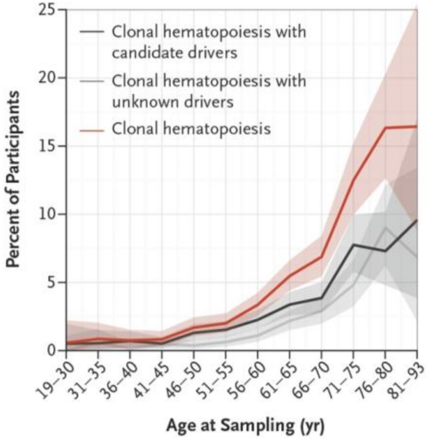
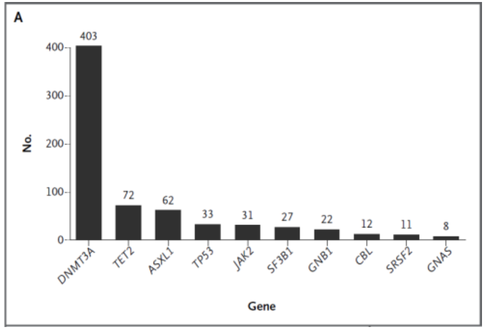


Figure 1. Prevalence of Somatic Mutations, According to Age.
Colored bands, in increasingly lighter shades, represent the 50th, 75th, and 95th percentiles.

Jaiswal et al., N Engl J Med 2014



Genovese et al.; N Engl J Med. 2014



Jaiswal et al., N Engl J Med 2014

CHiP (def. > 2% VAF)
increases with age:

- 70-79y: **9.5%**
- 80-89y: **11.7%**
- 90-108y: **18.4%**

→ **Clonal dominance is driven (in part) by oncogenic (leukemia) mutations**

→ **only 1% per year develop hem. cancer** (leukemia; corr. VAF, type of mut. comb. of mut.)

Ageing is associated with clonal Dominance in multiple (most?) Tissues

Tissue-specific mutation accumulation in human adult stem cells during life

Francis Blokzijl[1,2], Joep de Ligt[1,2*], Myrthe Jager[1,2*], Valentina Sasselli[2*], Sophie Roerink[3*], Nobuo Sasaki[2], Meritxell Huch[2], Sander Boymans[1,2], Ewart Kuijk[1,2], Pjotr Prins[2], Isaac J. Nijman[2], Inigo Martincorena[3], Michal Mokry[4], Caroline L. Wiegerinck[4], Sabine Middendorp[4], Toshiro Sato[2], Gerald Schwank[2], Edward E. S. Nieuwenhuis[4], Monique M. A. Verstegen[5], Luc J. W. van der Laan[5], Jeroen de Jonge[5], Jan N. M. IJzermans[5], Robert G. Vries[6], Marc van de Wetering[2], Michael R. Stratton[3], Hans Clevers[2], Edwin Cuppen[1,2] & Ruben van Boxtel[1,2]

260 | NATURE | VOL 538 | 13 OCTOBER 2016

Genome-wide quantification of rare somatic mutations in normal human tissues using massively parallel sequencing

Margaret L. Hoang[a,b,1], Isaac Kinde[a,b,2], Cristian Tomasetti[c,d], K. Wyatt McMahon[a,b], Thomas A. Rosenquist[e], Arthur P. Grollman[e,f], Kenneth W. Kinzler[a,3], Bert Vogelstein[a,b,g,3], and Nickolas Papadopoulos[a,g]

9846–9851 | PNAS | August 30, 2016 | vol. 113 | no. 35

Somatic mutant clones colonize the human esophagus with age

Iñigo Martincorena[1*†], Joanna C. Fowler[1*], Agnieszka Wabik[1], Andrew R. J. Lawson[1], Federico Abascal[1], Michael W. J. Hall[1,2], Alex Cagan[1], Kasumi Murai[1], Krishnaa Mahbubani[3], Michael R. Stratton[1], Rebecca C. Fitzgerald[2], Penny A. Handford[4], Peter J. Campbell[1,5], Kourosh Saeb-Parsy[3], Philip H. Jones[1†]

Martincorena *et al.*, *Science* **362**, 911–917 (2018) 23 November 2018

Article

The landscape of somatic mutation in normal colorectal epithelial cells

https://doi.org/10.1038/s41586-019-1672-7
Received: 11 September 2018
Accepted: 11 September 2019
Published online: 23 October 2019

Henry Lee-Six[1], Sigurgeir Olafsson[1], Peter Ellis[1], Robert J. Osborne[1], Mathijs A. Sanders[1,2], Luiza Moore[1], Nikitas Georgakopoulos[3,4], Franco Torrente[5], Ayesha Noorani[6,7], Martin Goddard[8], Philip Robinson[1], Tim H. H. Coorens[1], Laura O'Neill[1], Christopher Alder[1], Jingwei Wang[1], Rebecca C. Fitzgerald[6,7], Matthias Zilbauer[5,9], Nicholas Coleman[7,10], Kourosh Saeb-Parsy[3,4], Inigo Martincorena[1], Peter J. Campbell[1] & Michael R. Stratton[1*]

532 | Nature | Vol 574 | 24 OCTOBER 2019

Article

Somatic mutations and clonal dynamics in healthy and cirrhotic human liver

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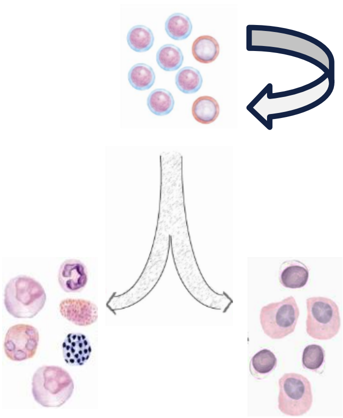
Published online: 23 October 2019

Simon F. Brunner[1], Nicola D. Roberts[1], Luke A. Wylie[1], Luiza Moore[1], Sarah J. Aitken[2,3], Susan E. Davies[3], Mathijs A. Sanders[1,4], Pete Ellis[1], Chris Alder[1], Yvette Hooks[1], Federico Abascal[1], Michael R. Stratton[1], Inigo Martincorena[1], Matthew Hoare[2,5*] & Peter J. Campbell[1,6*]

538 | Nature | Vol 574 | 24 OCTOBER 2019

→ **Clonal dominance in other tissues is also prevalent with ageing**

Young Hematopoiesis



Aged Hematopoiesis

- **Increase in anemia, shift towards mature myeloid cells, increased platelets (in mice)**
- **Myeloid shift in HSC hematopoietic lineage-output**
- **Increase in HSC numbers, but**
  - **Decrease in self-renewal capacity of HSCs**
  - **Decrease in HSC homing efficiency**
- **Increased incidence of malignant transformation / outgrowth of HSCs (→ myeloid malignancies)**

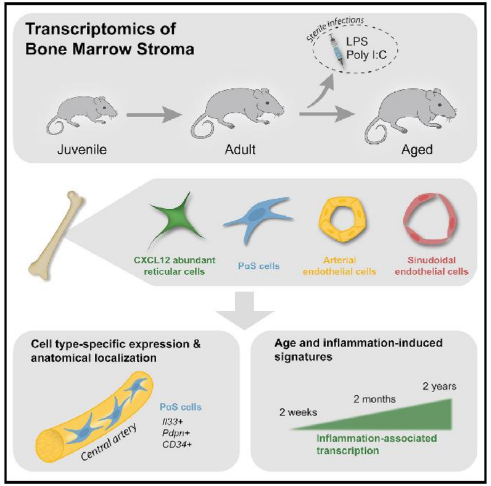
e.g. Morrison et al., Nat Med 1996; Sudo et al., JEM 2000; Dykstra et al., JEM 2011; Beerman et al., PNAS 2010; Challen et al., CSC 2010; Pang et al., PNAS 2011

Causes for ageing-related changes of the hematopoietic system / of HSCs:

- Hematopoietic System **Intrinsic** (e.g. genetic, epigenetic, metabolic changes)
- Hematopoietic System **Extrinsic** (e.g. nutrition/niche support, pathogens)
    - **Combination of both** (?)

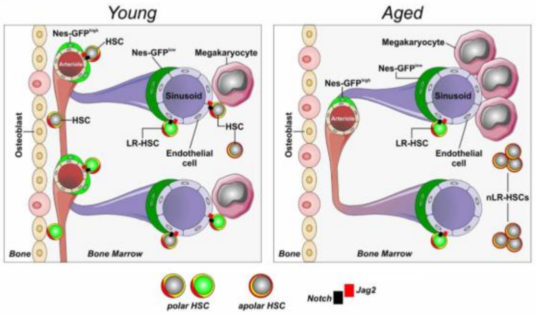
Examples for «Extrinsic» Changes in mouse BM

Global Transcriptomic Profiling of the Bone Marrow Stromal Microenvironment during Postnatal Development, Ageing, and Inflammation
Patrick M. Helbling et al.
Cell Rep, 2019



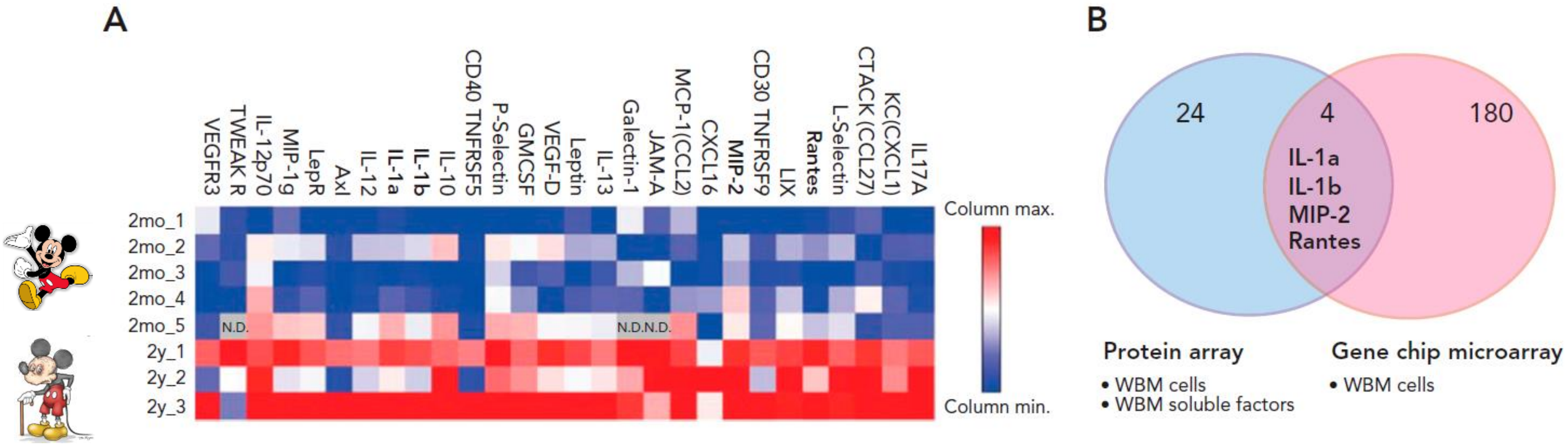
- Transcriptional profiling of BM stromal cells throughout postnatal lifespan.
- **Dynamic remodeling of stromal transcriptome in transition from juvenile to adult stages.**
- **Ageing induces prototypical inflammatory transcriptional programs in BM stromal cells** (with high similarity to what is observed upon pattern recognition receptor stimulation in young mice).

Haematopoietic stem cells in perisinusoidal niches are protected from ageing
Mehmet Saçma et al.;
Nat Cell Biol, 2020



- Most quiescent HSC subpopulation with the highest regenerative capacity and cellular polarity, reside predominantly in perisinusoidal niches.
- **Perisinusoidal niches are uniquely preserved and thereby protect HSCs from ageing.**

Global inflammatory molecule analysis in young vs. aged bone marrow

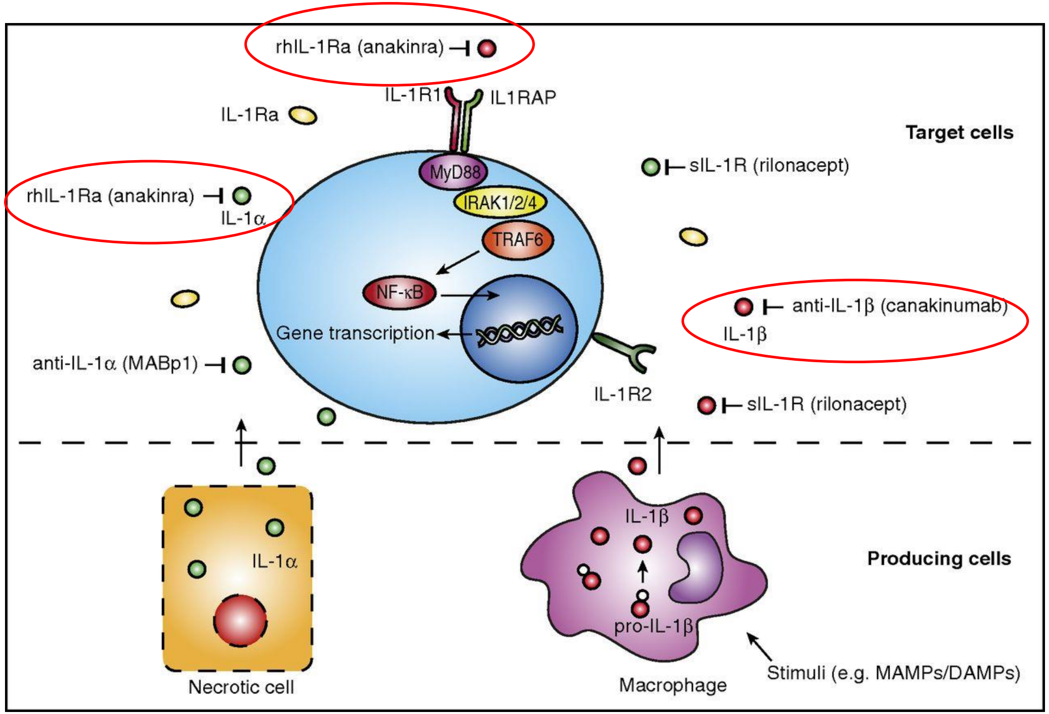


Inflammatory protein expression array

→ IL-1a/b is upregulated in aged bone marrow (transcripts and protein)

Kovtonyuk et al., Blood 2022

IL-1a and IL-1b: Production and Receptors



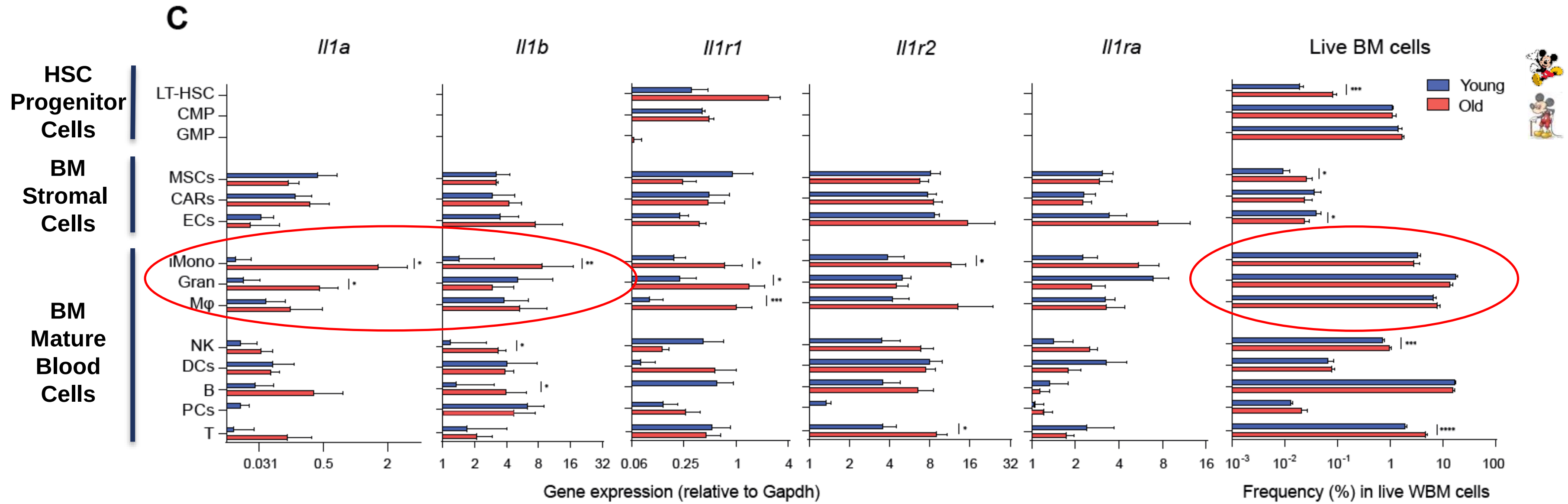
Functions:

- Inflammatory response
- Infection control
- Tissue repair
- Hemato-/Myelopoiesis
- Anti-cancer immunity(?)
- ……

de Mooij, CEM *et al.* Blood 2017

Potential therapeutic targets on the IL-1 pathway and available IL-1–targeting therapies. Production of IL-1β, mainly by monocytes, macrophages, and dendritic cells, requires a stimulus such as MAMPs or DAMPs. IL-1α does not require a stimulus, and is released upon cell necrosis (bottom panel). IL-1α and IL-1β bind to the IL-1R1 and induce further intracellular signaling pathways, whereas IL-1R2 functions as a **decoy** receptor for IL-1. Various agents are available that target specific components of the IL-1 pathway. **rhIL-1Ra anakinra targets both IL-1α and IL-1β**, as does the sIL-1R rilonacept. Specific antibodies targeting IL-1α or IL-1β are MABp1 and canakinumab, respectively. Both IL1RAP, a coreceptor of the IL-1R1, and IRAK1, a kinase downstream of the IL-1R1, have also been suggested potential targets for treatment of hematological malignancies. MyD88, myeloid differentiation primary response 88; rhIL-1Ra, recombinant human IL-1Ra; sIL-1R, soluble IL-1R; TRAF6, TNF receptor–associated factor 6.

Global IL-1a/b and receptor analysis in young vs. old BM cells



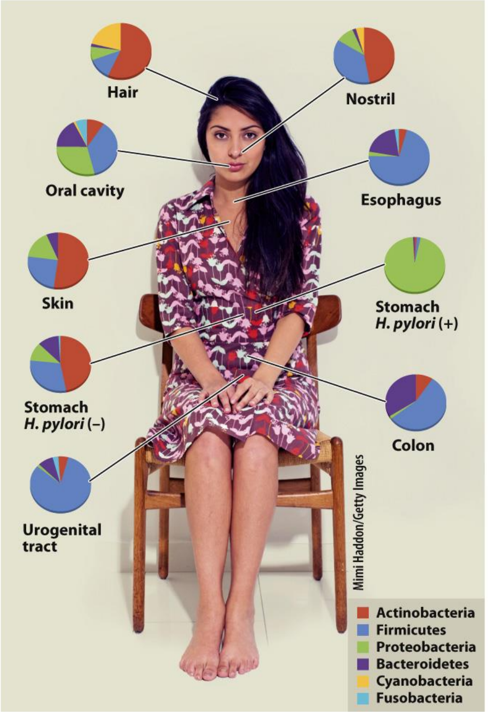
→ **IL-1a/b transcription is significantly increased in BM myeloid cells in aged mice**

→ **BM myeloid cells are quantitatively the dominant cell fraction BM**

→ **Myeloid cells are not the only, but possibly the major producers of IL-1 in BM**

Kovtonyuk et al., Blood 2022

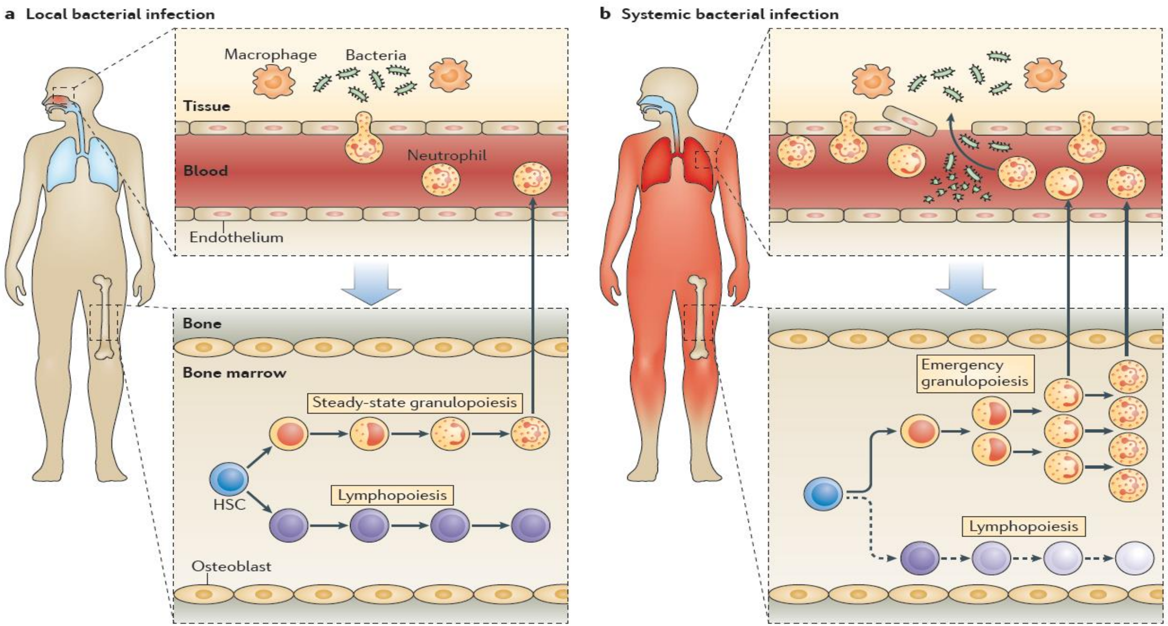
Some Background on the Human Microbiome

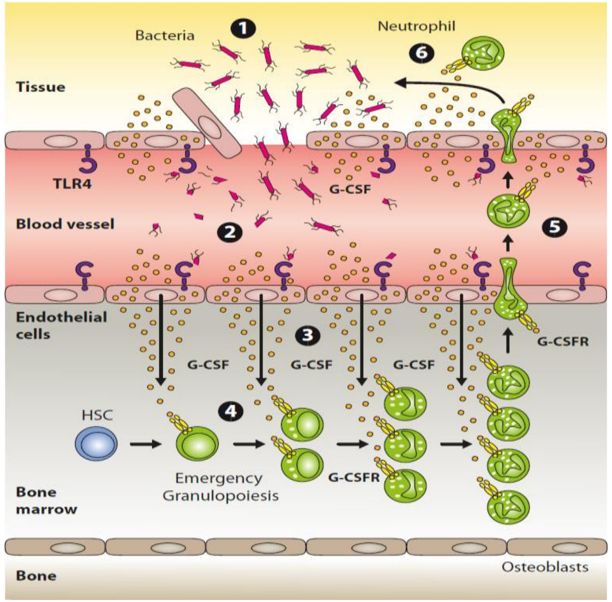


Different groups of bacteria reside in or on each part of the body (macmillanhighered.com)

- "To our **30 trillion human cells**, we have on average about **39 trillion microbial cells**. By that measure, we're only about **43% human**" Rob Knight, University of California San Diego Center for Microbiome Innovation
- About **0.2 kg of bacteria in the body**, primarily in the gut
- **The microbiome is not static**. People with larger social networks tend to have a more diverse microbiome - social interactions shape the microbial community of the gut.
- The **diversity among the microbiome** of individuals **is immense** compared to genomic variation: individual humans are about 99.9% identical to one another in terms of their genome, but can be 80-90% different from one another in terms of the microbiome.

Acute demand-adapted inflammatory response: Emergency Granulo-/ Myelopoiesis





- No systemic alterations

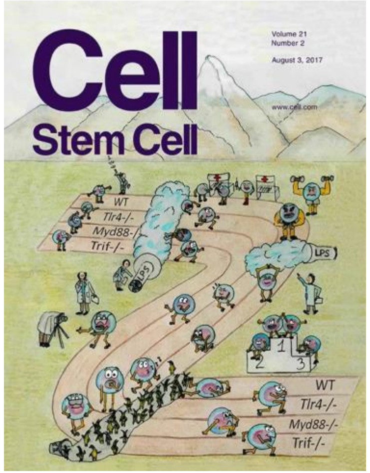
- Neutrophilia "Left-shift"
- BM myelopoiesis ↑

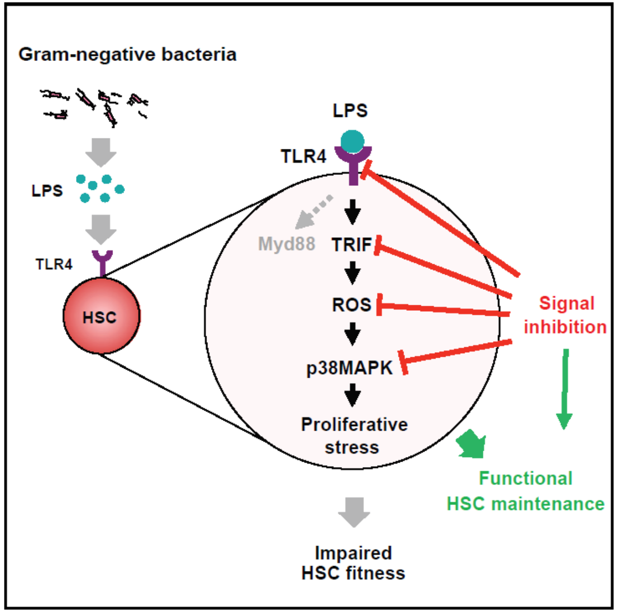
- ECs catalyze the detection of systemic infection into demand-adapted granulopoiesis

Human neutrophile production about 0.6-1.2 x 10E11 per day, can increase upon demand 3-4x

Boettcher et al., **J Immunol 2012**; Boettcher et al. **Blood 2014**
Manz and Boettcher, **Nature Rev. Immunology 2014**

Pathogen-Induced TLR4-TRIF Innate Immune Signaling in Hematopoietic Stem Cells Promotes Proliferation but Reduces Competitive Fitness





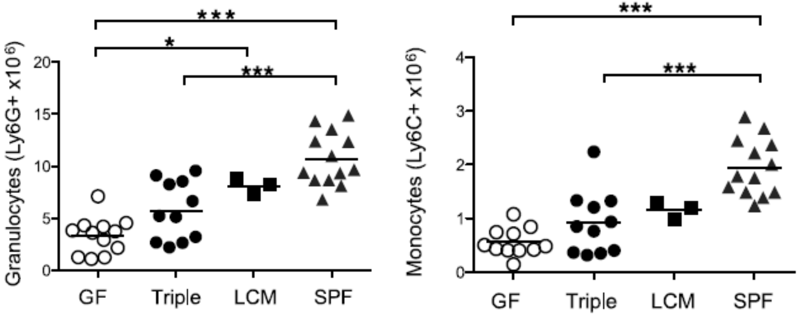
- Direct TLR4 activation in HSCs induces HSC cycling and inflammatory responses
- Sustained TLR4 activation in HSCs impairs their competitive repopulating ability
- **LPS and S. Typhimurium cause proliferative stress in HSCs via TLR4-TRIF signals**
- **Inhibition of TLR4-TRIF-ROS-p38 signaling prevents LPS induced HSC dysfunction**

→ Microbial-derived compounds can directly act on HSCs

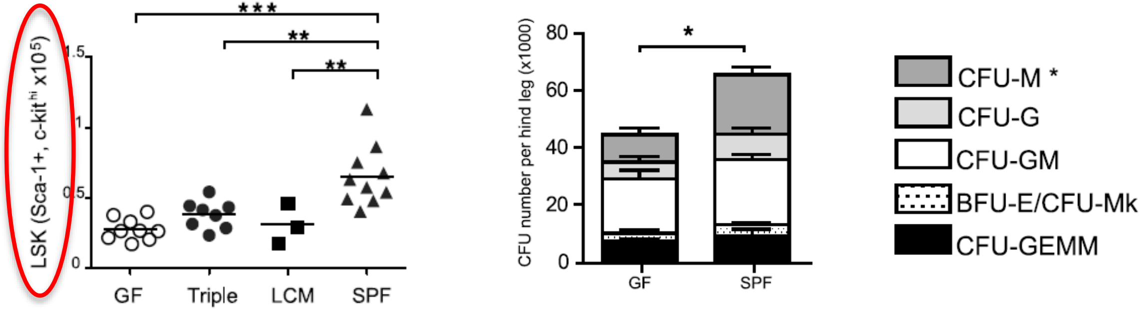
Takizawa et al.; Cell Stem Cell, 2017

Does the Microbiome in *steady-state* matter for Hematopoiesis?

Myeloid Cells



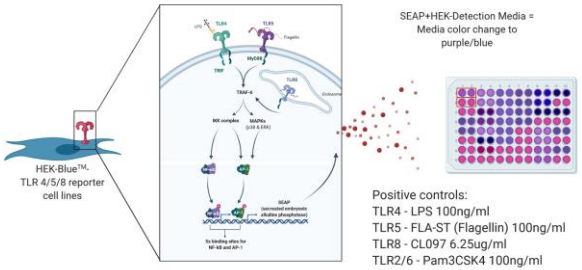
HSPCs

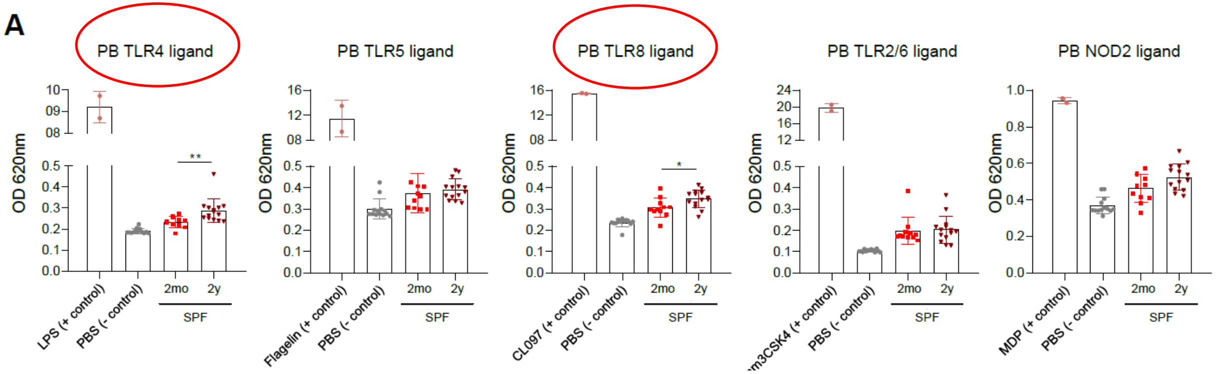


→ **Reduction in** mature peripheral blood cell and **BM HSPC numbers in germ-free (GF) mice**
(mediated via MyD88/TRIF and rescued via heat-stable microbiome compounds)

Balmer et al., J Immunol 2014

Microbial-derived compounds (PAMPs) in blood of young and old mice

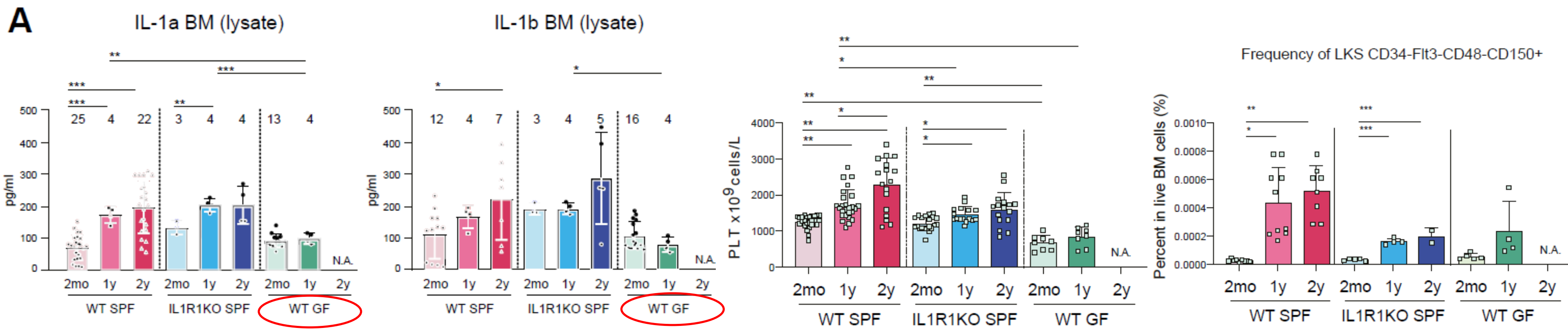




→ Microbial-derived compounds are *increased* in blood of aged mice, likely due to a less tight gut mucosal barrier

Kovtonyuk et al., Blood 2022

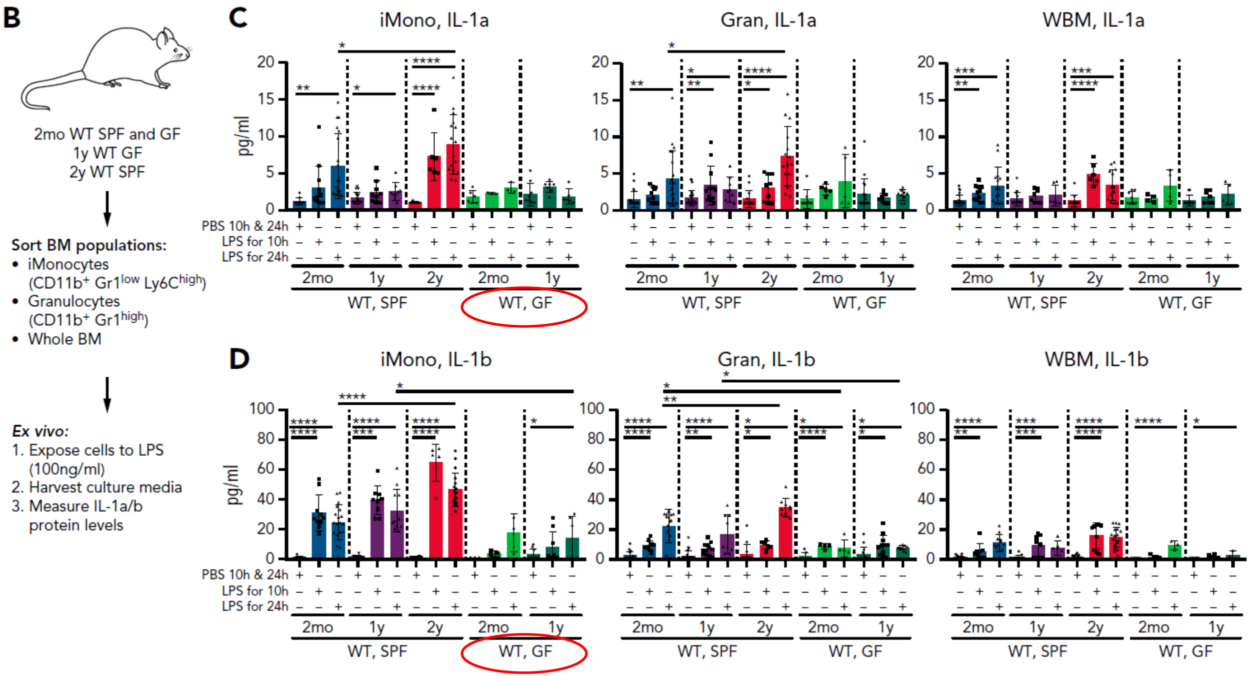
Is the Microbiome / are PAMPs “driving” IL-1 levels and hematopoietic ageing phenotypes?



- **IL-1a/b is not increased in BM of aged germ-free (GF) mice**
- **Ageing-associated neutrophil-, platelet- and HSC-increase is reduced in GF mice** (similar as in IL-1R1KO mice)

Kovtonyuk et al., Blood 2022

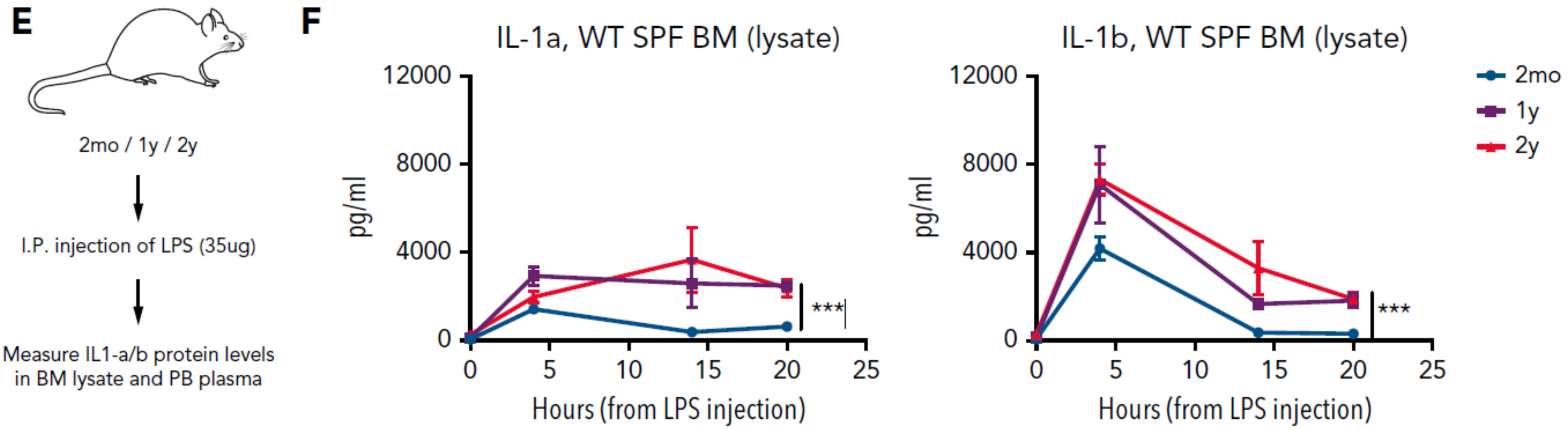
Older mice BM cells respond *in vitro* with increased IL-1 secretion upon LPS Stimulation in WT but less so in germ-free (GF) mice



→ **Myeloid "Innate Memory Reaction"** (measured by IL-1 release) **reduced in aged GF mice**

Kovtonyuk et al., Blood 2022

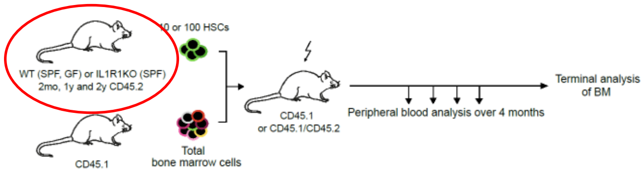
Older Mice respond with increased and sustained IL-1 secretion upon LPS stimulation *in vivo*

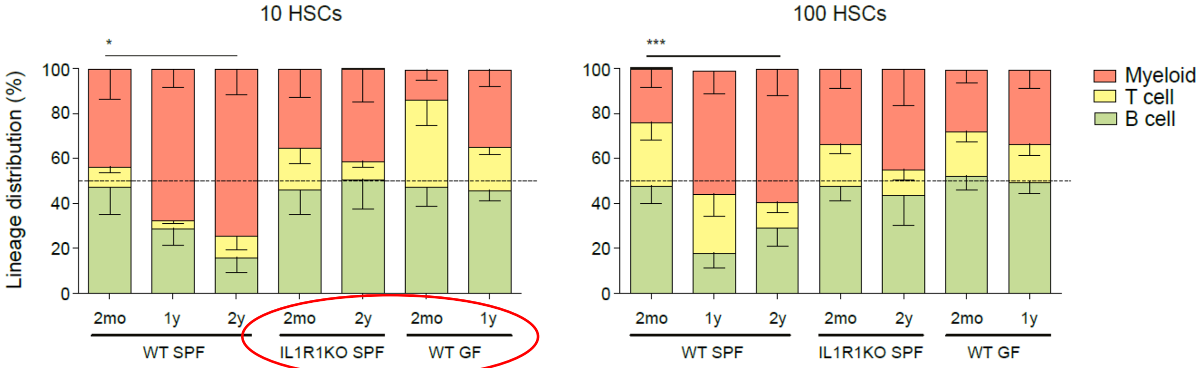


→ **Innate "Trained Memory" Reaction**

Kovtonyuk et al., Blood 2022

Functional behavior of aged HSC populations from IL1R1KO SPF and WT GF mice





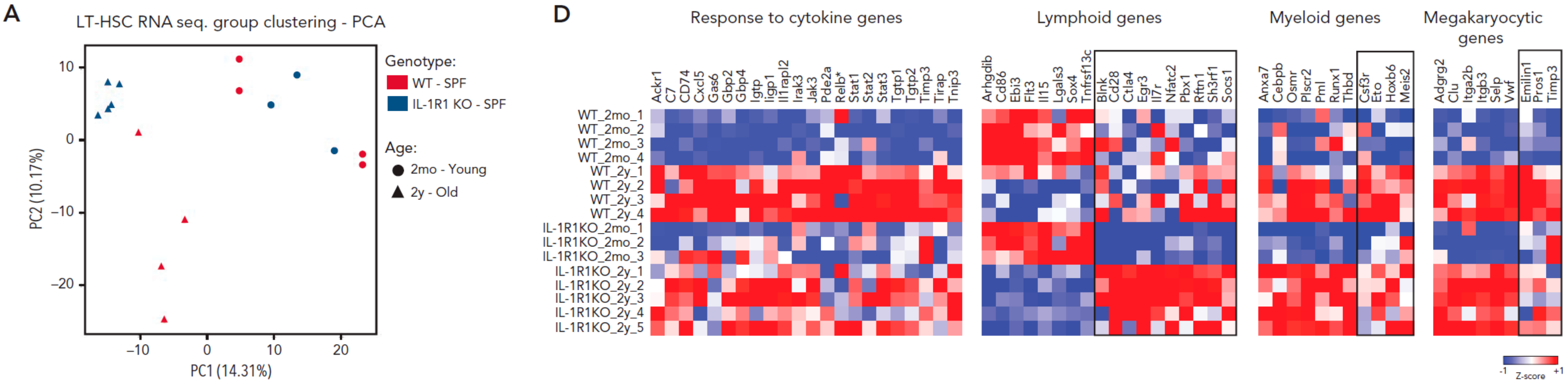
→ Aged HSCs from IL1R1KO SPF and WT GF mice

are not producing myeloid-biased output upon transplantation

Kovtonyuk et al., Blood 2022

RNA-seq of 2mo young and 2y old SPF WT and SPF IL-1R1KO

LT-HSCs (LKS CD34–Flt3–CD48–CD150+)

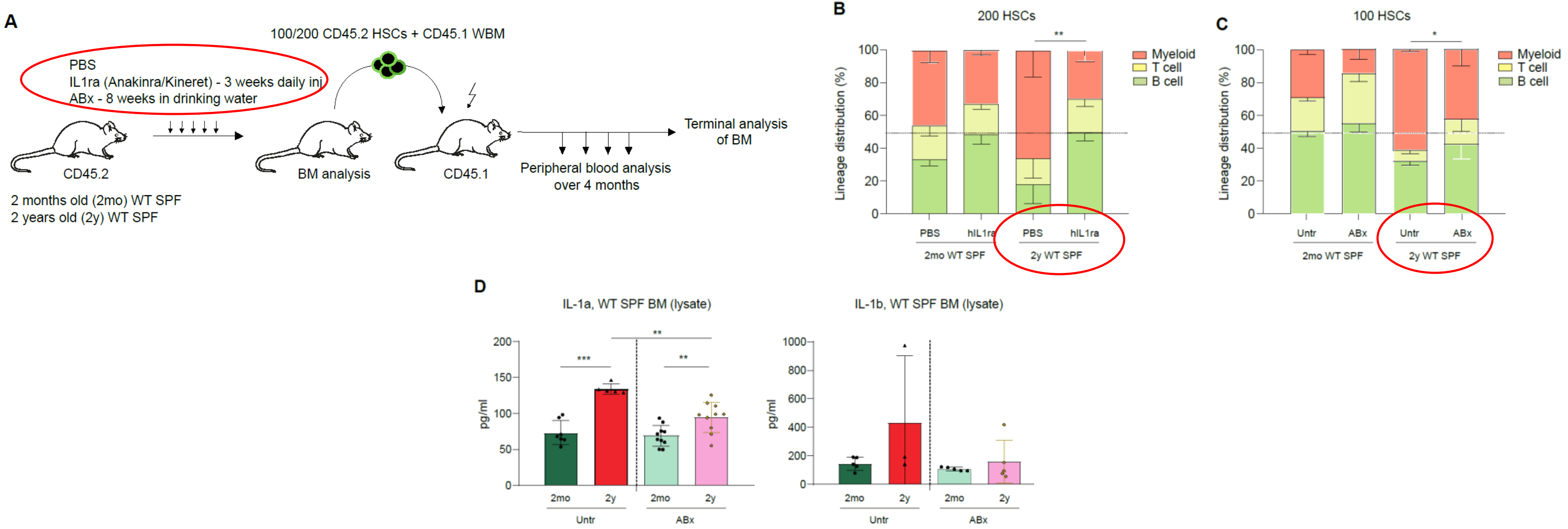


→ Older HSCs develop an IL-1R1–dependent immune-inflammatory transcriptional signature

(**in old IL-1R1KO mice:** lower response to cytokine gene increase, **maintenance of lymphoid gene tanscription, less myeloid and megakaryocyte gene transcription**)

Kovtonyuk et al., Blood 2022

Partial “therapeutic” reversal of HSC Inflamm-Ageing

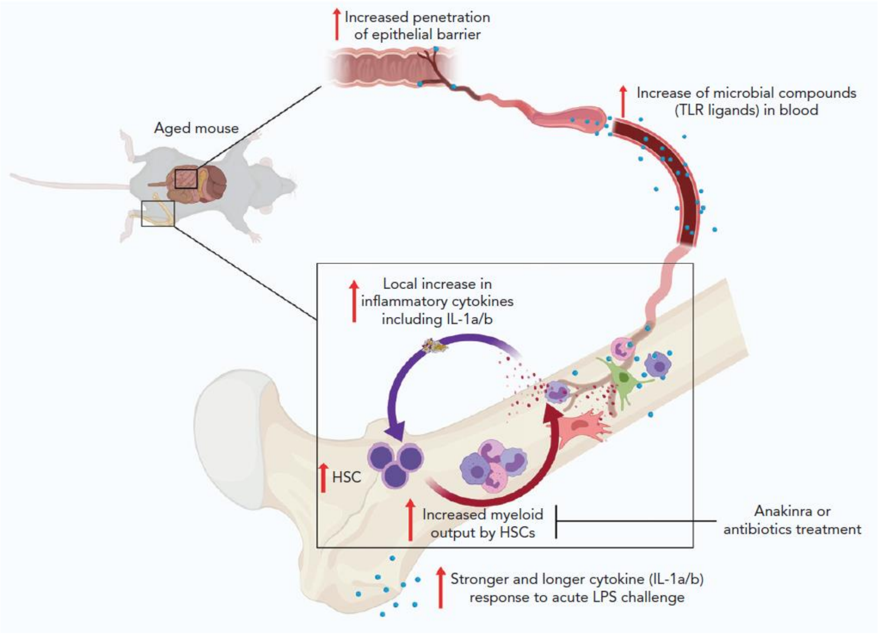


→ IL-1 receptor antagonist (anakinra) or antibiotic treatment of WT SPF mice restores balanced differentiation of aged HSCs populations upon transplantation

→ Antibiotic treatment reduces IL-1a (and b) in aged mouse BM

Kovtonyuk et al., Blood 2022

Model for extrinsic-driven Inflamm-Ageing “Loop” of HSCs and Hematopoiesis



1. **Microbial compounds**/conserved pattern recognition-ligands are **increased in blood of aged mice**
2. **BM IL-1** levels are **elevated during ageing** as a response to increased blood microbial compounds
3. **Multiple cells contribute to increased IL-1 in BM** of aged mice. Importantly, BM resident Ly-6C^{high} monocytes of aged mice produce more IL-1 upon stimulation with LPS as compared to their young counterparts
4. **Aged IL1R1KO mice** as well as **germ-free mice** are substantially **protected from “inflamm-ageing”**-associated phenotypic and functional HSC- and subsequent hematopoiesis-alterations
5. **Ageing-associated alterations** of HSCs can be in part **reverted by antibiotic reduction** of the intestinal microbiome **or**, alternatively, **by IL-1 antagonists**

Kovtonyuk et al., Blood 2022

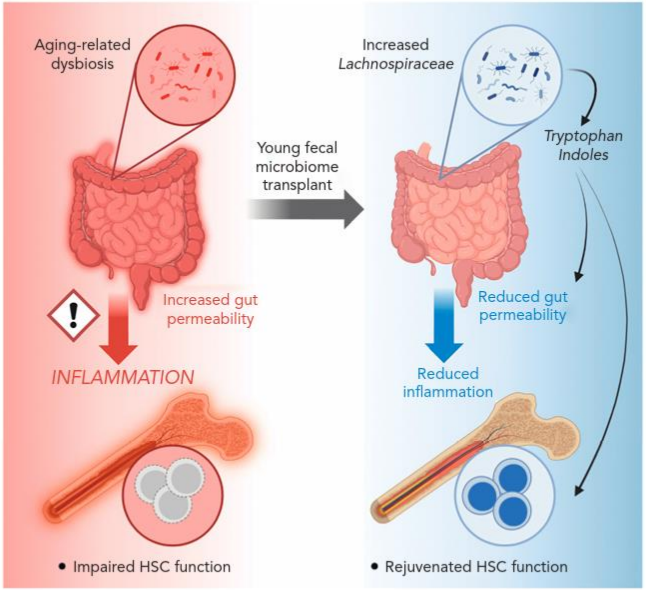
Extended Context/Confirmation: “Young bugs rejuvenate old blood”

Fecal microbiota transplantation from young mice rejuvenates aged hematopoietic stem cells by suppressing inflammation

Xiangjun Zeng,[1-4,*] Xiaoqing Li,[1-4,*] Xia Li,[1-4,*] Cong Wei,[1-4,*] Ce Shi,[1-4,*] Kejia Hu,[1-4] Delin Kong,[1-4] Qian Luo,[1-4] Yulin Xu,[1-4] Wei Shan,[1-4] Meng Zhang,[1-4] Jimin Shi,[1-4] Jingjing Feng,[1-4] Yingli Han,[1-4] He Huang,[1-4] and Pengxu Qian[1-5]

- FMT from young mice restored lymphoid differentiative potential and improved the number and engraftment ability of aged HSCs.
- Lachnospiraceae and tryptophan-associated metabolites could improve both the phenotype and the reconstitution capacity of HSCs in aged mice.

blood® 6 APRIL 2023 | VOLUME 141, NUMBER 14



Aging-related dysbiosis is associated with increased intestinal permeability and systemic overproduction of proinflammatory cytokines that drive numerous “inflamm-aging” phenotypes.
Comment on Zeng et al. by Eric Pietras

Extended Context/Confirmation:

nature cell biology

Article https://doi.org/10.1038/s41556-022-01053-0

Stromal niche inflammation mediated by IL-1 signalling is a targetable driver of haematopoietic ageing

Received: 9 November 2021

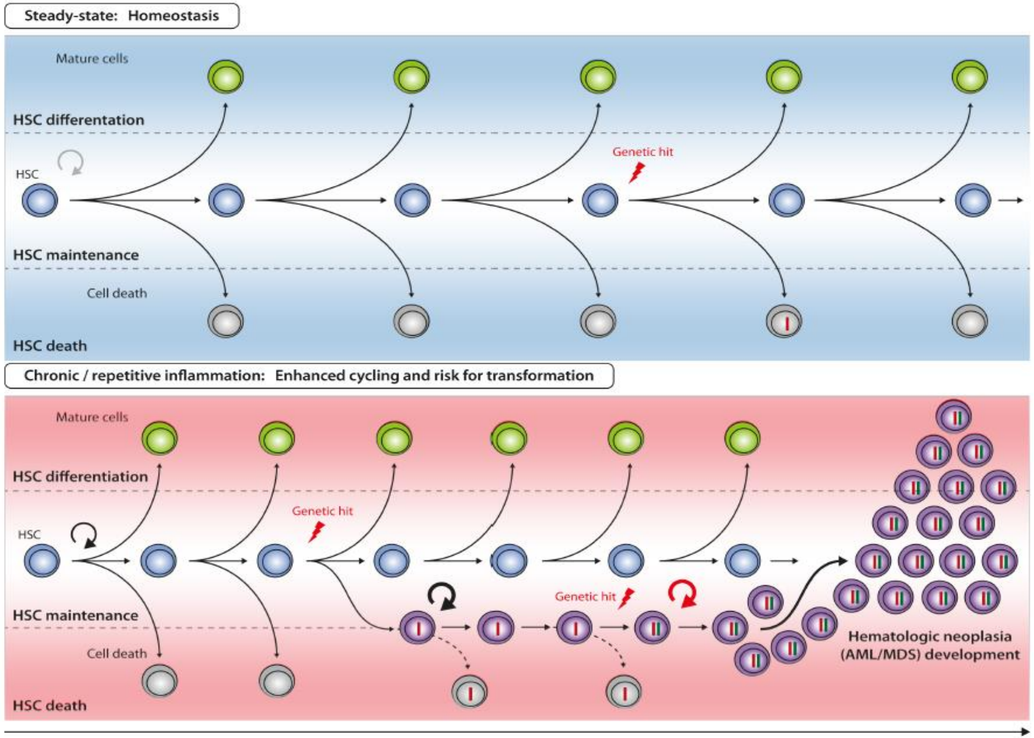
Accepted: 15 November 2022

Published online: 17 January 2023

Check for updates

Carl A. Mitchell[1], Evgenia V. Verovskaya[1,2], Fernando J. Calero-Nieto[3], Oakley C. Olson[1], James W. Swann[1], Xiaonan Wang[3], Aurélie Hérault[2], Paul V. Dellorusso[1], Si Yi Zhang[2], Arthur Flohr Svendsen[2], Eric M. Pietras[2], Sietske T. Bakker[2], Theodore T. Ho[2], Berthold Göttgens[3] & Emmanuelle Passegué[1,2]

Model for Ageing / Inflammation and Promotion of Clonality



time

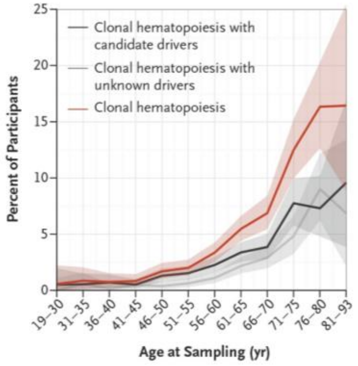
Takizawa H, Boettcher S and Manz MG; **Blood 2012**

Model how chronic/repetitive
- Infection
- Inflammation

Might promote development of
- Clonal Hematopoiesis
- MDS
- MPN
- AML

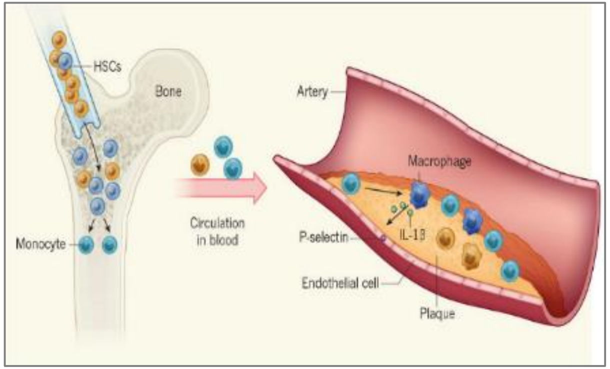
Clonal Hematopoiesis of Indeterminate Potential (CHIP) – Ageing and Inflammation

1) Ageing: strongest predictor of CHIP and correlates positively with low-level chronic inflammation - **Inflamm-ageing**



Genovese *et al. N Engl J Med*. 2014

2) *Tet2* and *DNMT3a* mutant myeloid cells show **pro-inflammatory** phenotypes, including **IL-1 increase**



Fuster, J.J. *et al.* Science 2017
Zhang *et al. Nature* 2015
Sano,S *et al. CircResearch* 2018
Abegunde,SO *et al. Exp.Hematol* 2018
Philipp Rauch, unpublished ASH 2018

Hypothesis:

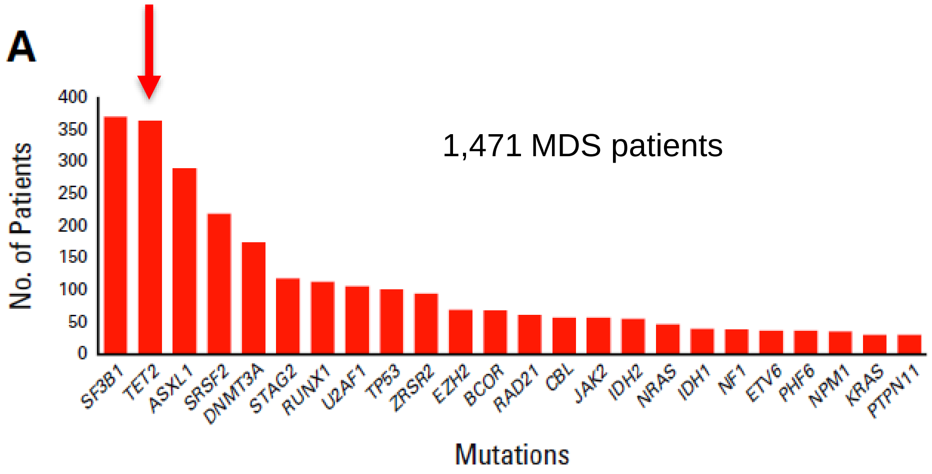
Inflamm-Ageing is a direct driver of *Tet2* mutant HSC clonal expansion, possibly via IL-1

3) *Tet2* mutant HSPCs show **increased fitness** in pro-inflammatory conditions (Cai, Z et al. Cell Stem Cell 2018; Meisel, M et al. Nature 2018, reviewed in Caiado et al. JEM 2021)

Potential Clinical Relevance in Myelodysplastic Syndromes (Neoplasia)

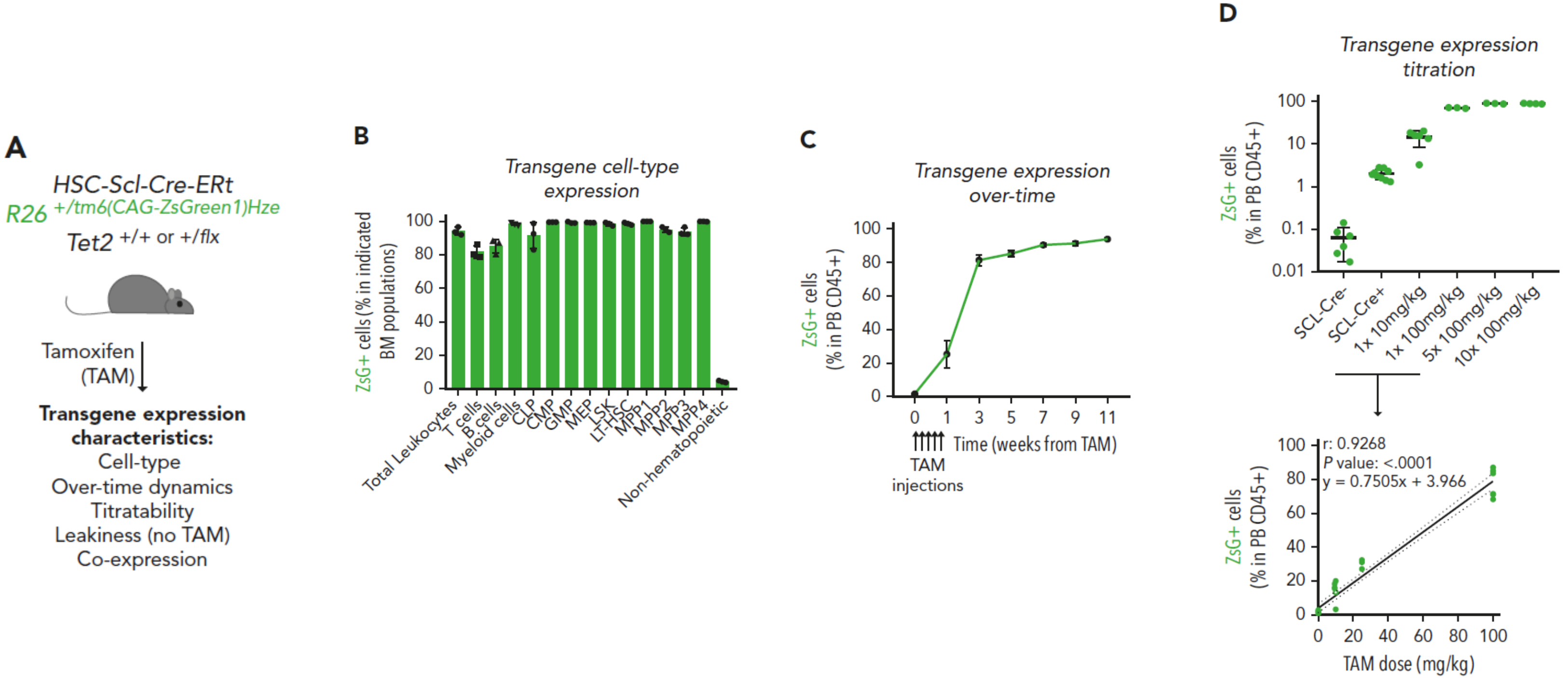
Personalized Prediction Model to Risk Stratify Patients With **Myelodysplastic Syndromes**
Aziz Nazha et al.

Journal of Clinical Oncology®
Volume 39, Issue 33 **3737**



→ *TET2* is one of the most frequently mutated genes in MDS

Generation of an inducible hematopoietic genetic mosaicism mouse model of Tet2+/−-driven clonal hematopoiesis

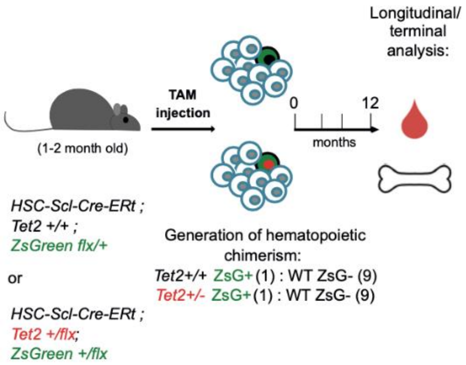


Caiado et al., Blood 2023

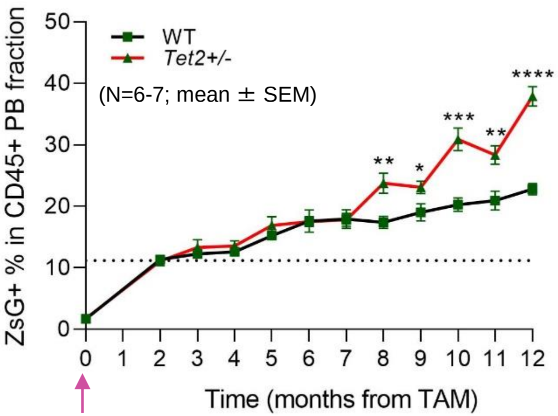
Generation of an Inducible Hematopoietic *Tet2+/-* Mouse Model

A

Inducible BM chimera model:

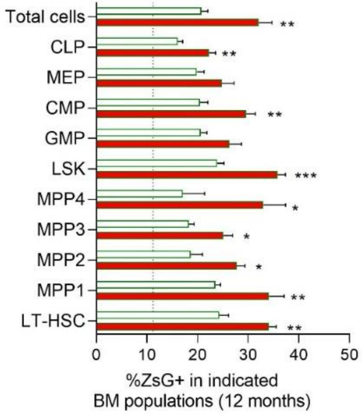


B



single TAM injection

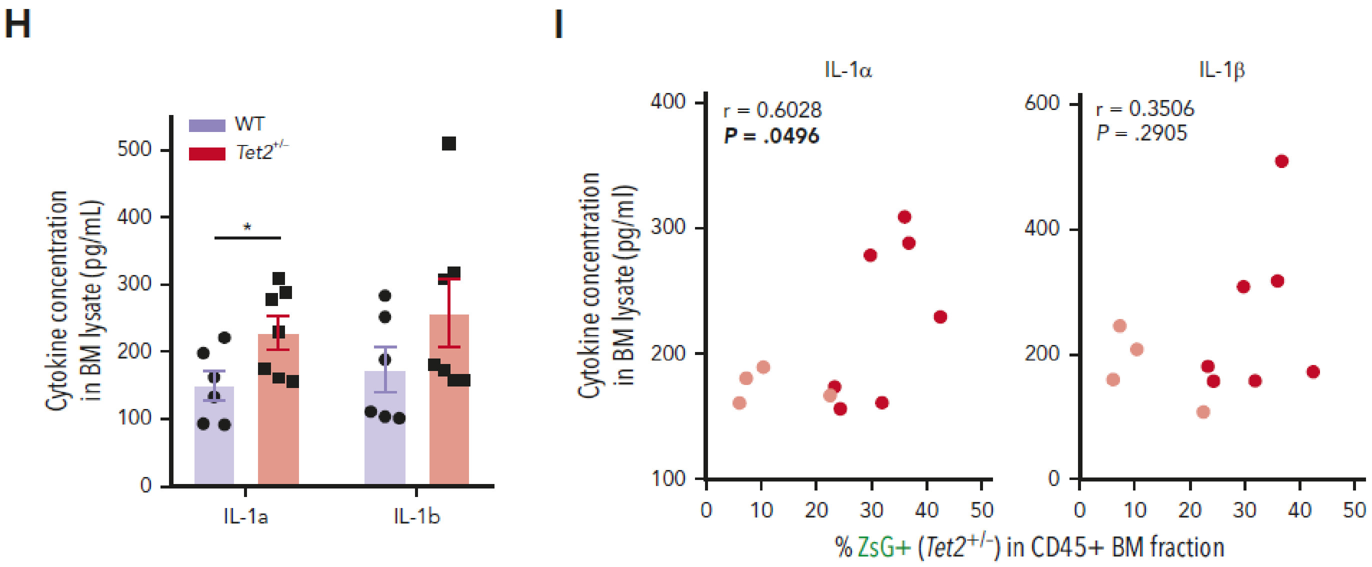
C



Hematopoietic *Tet2+/-* clonal expansion rate increases in aged mice

Caiado et al., Blood 2023

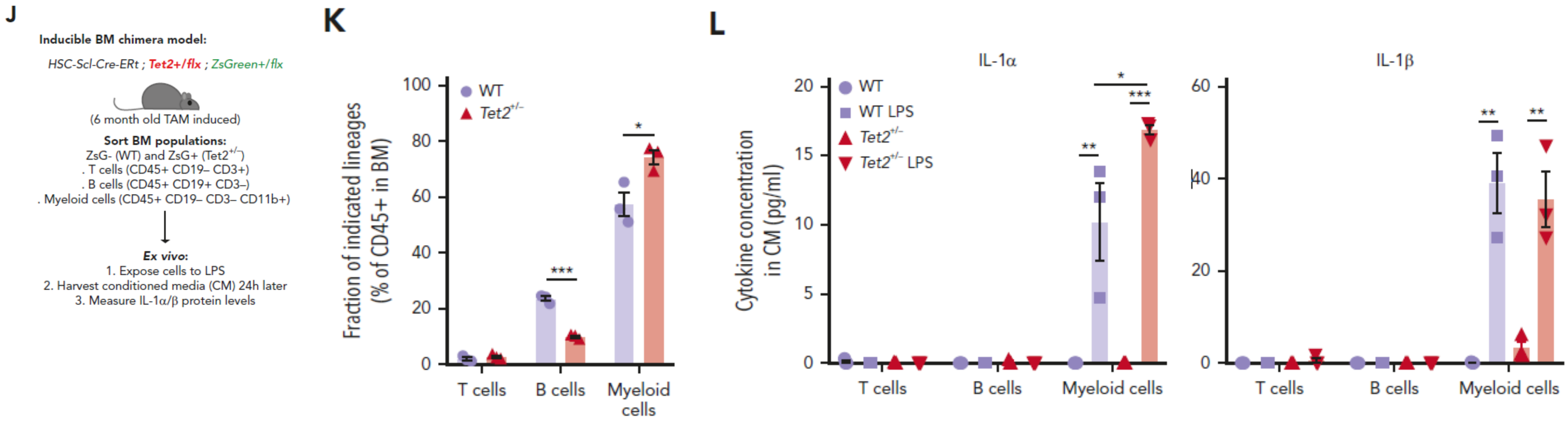
Generation of an Inducible Hematopoietic *Tet2+/-* Mouse Model



Hematopoietic *Tet2+/-* clonal expansion rate associates with increased IL-1 BM levels

Caiado et al., Blood 2023

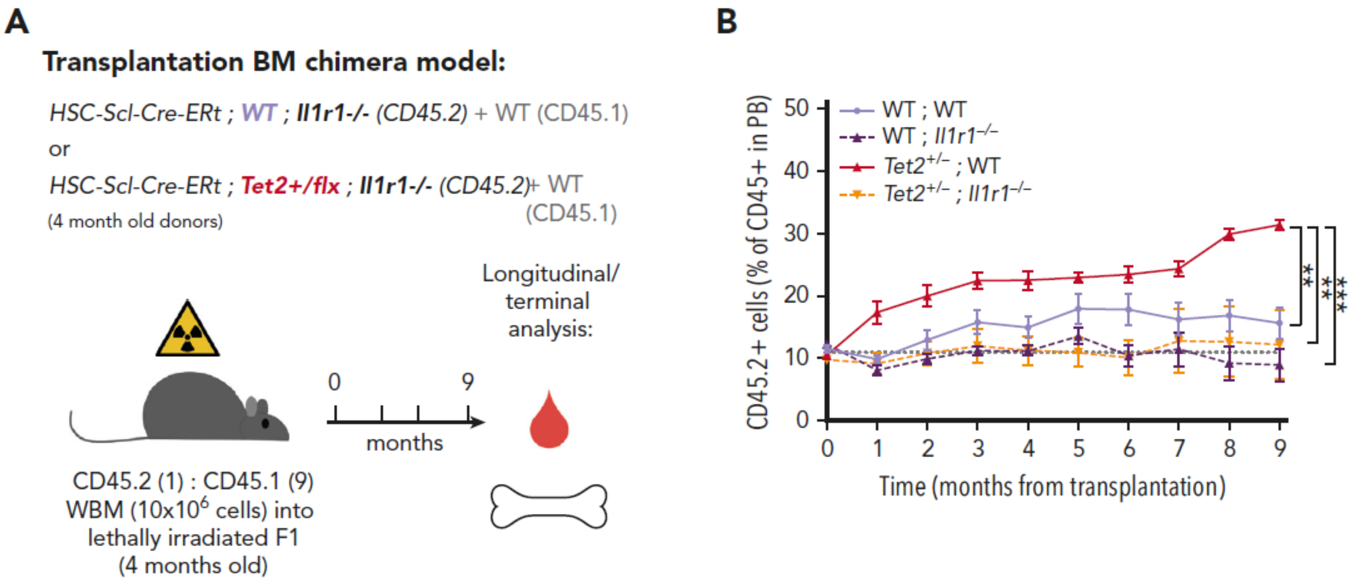
Generation of an Inducible Hematopoietic *Tet2+/-* Mouse Model



Hematopoietic *Tet2+/-* myeloid cells produce/release more IL-1(a) upon TLR4 agonist stimulation

Caiado et al., Blood 2023

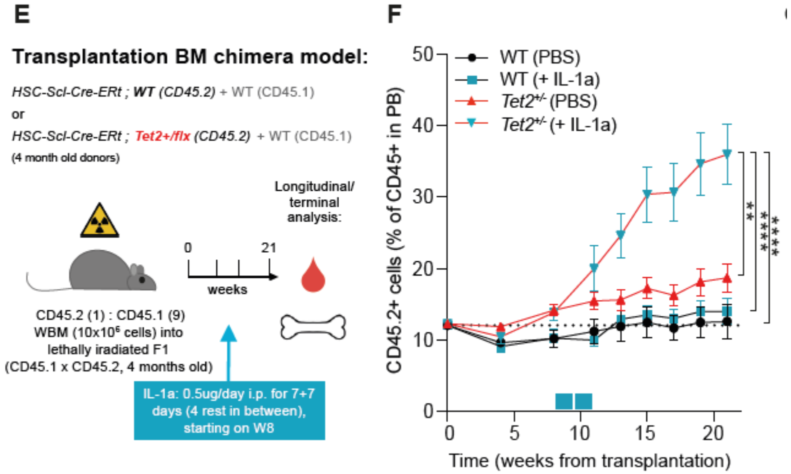
Hematopoietic *Tet2+/-* Mouse Model Findings

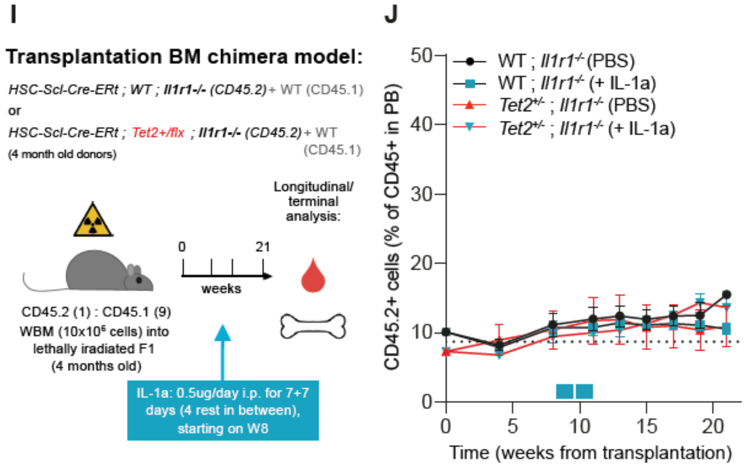


Genetic deletion of IL-1R1 signaling prevents Tet2+/− clonal expansion

Caiado et al., Blood 2023

Hematopoietic *Tet2+/-* Mouse Model Findings



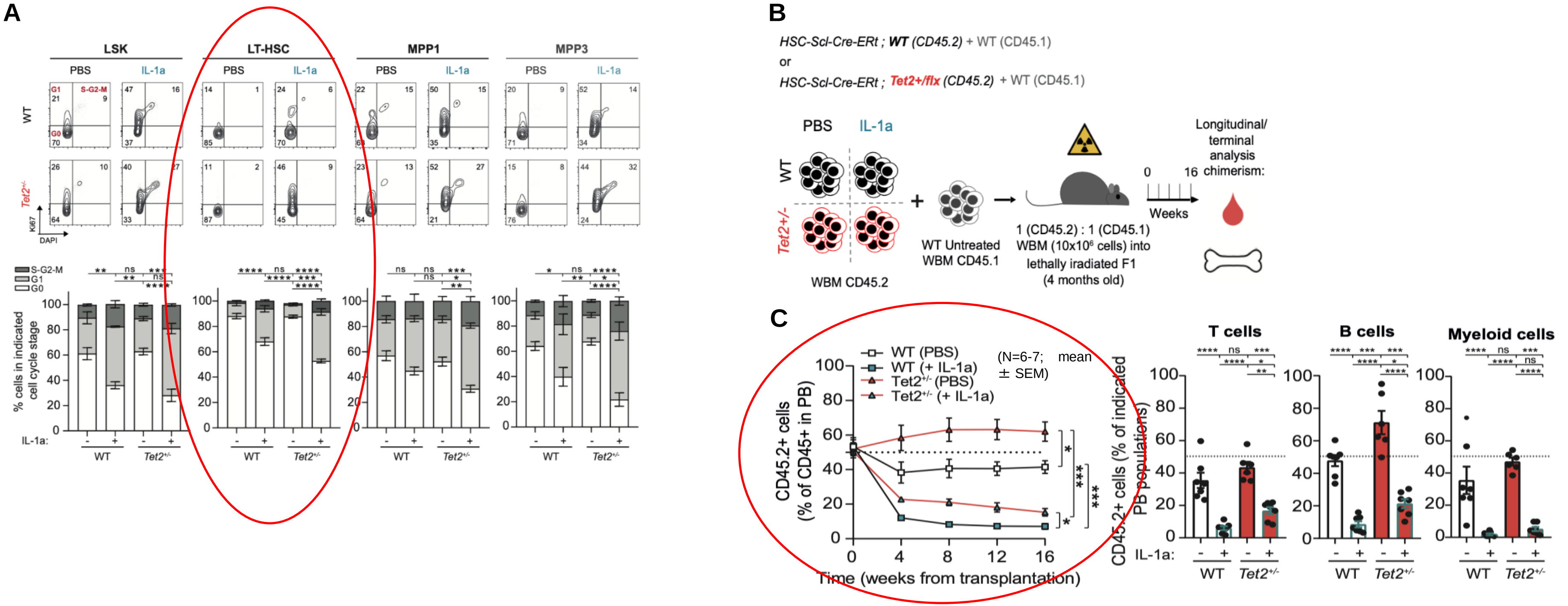


External IL-1a/b addition enhances *Tet2+/-* clonal hematopoiesis

Enhancement effects are blocked in *Tet2+/-* IL-1R1KO hematopoietic cells

Caiado et al., Blood 2023

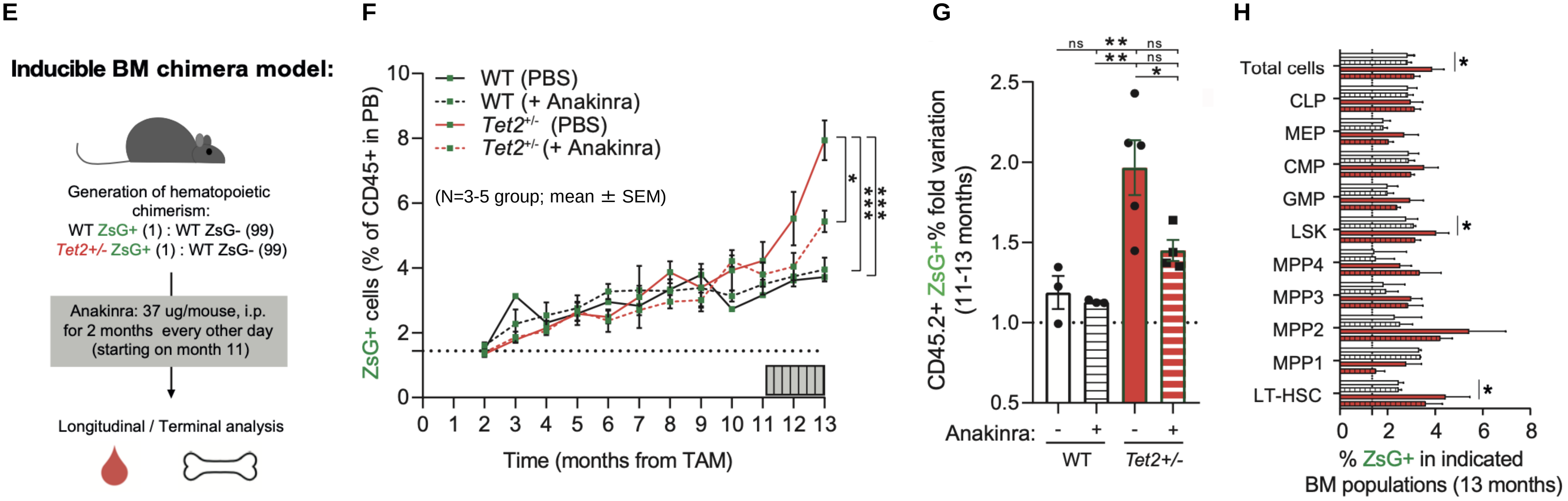
Hematopoietic *Tet2+/-* Mouse Model Findings



$Tet2^{+/-}$ HSPCs maintain higher proliferation and repopulation-capacity than WT HSPCs in response to chronic IL-1a exposure

Caiado et al., Blood 2023

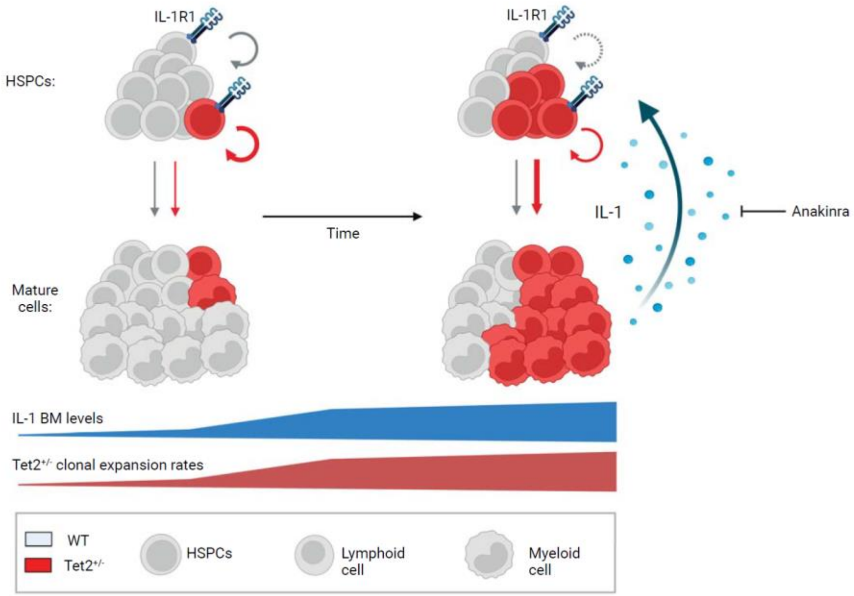
Hematopoietic *Tet2+/-* Mouse Model Findings



***Tet2+/-* clonal hematopoiesis can be targeted therapeutically by IL-1 antagonists**

Caiado et al., Blood 2023

Aging Derived IL-1 Promotes *Tet2+/-* Clonal Expansion via a targetable IL1-IL1R1 autocrine loop – working model



- **Increased BM IL-1 levels during aging drive *Tet2*$^{+/-}$ clonal expansion** via increased HSPC proliferative activity and multi-lineage hematopoietic differentiation.
- ***Tet2*$^{+/-}$ cells produce more IL-1**, acting in a self-sustaining cycle
- IL-1a-treated *Tet2*$^{+/-}$ HSPC show increased DNA replication and repair and reduced down-regulation of self-renewal transcriptomic signatures
- **Genetic deletion of IL-1R1 abolishes and pharmacological inhibition of IL-1-IL-1R1 signaling impairs *Tet2*$^{+/-}$ clonal expansion** during aging.
- Targeting IL-1/IL1R1 (or the inflammasome?) might open **new avenues of intervention in *Tet2*$^{+/-}$ hematopoiesis** / pre-malignancy / MDS.

Caiado et al., Blood 2023

Extended Context/Confirmation: Homozygeous *Tet2-/-* Mouse Model

LETTER OPEN

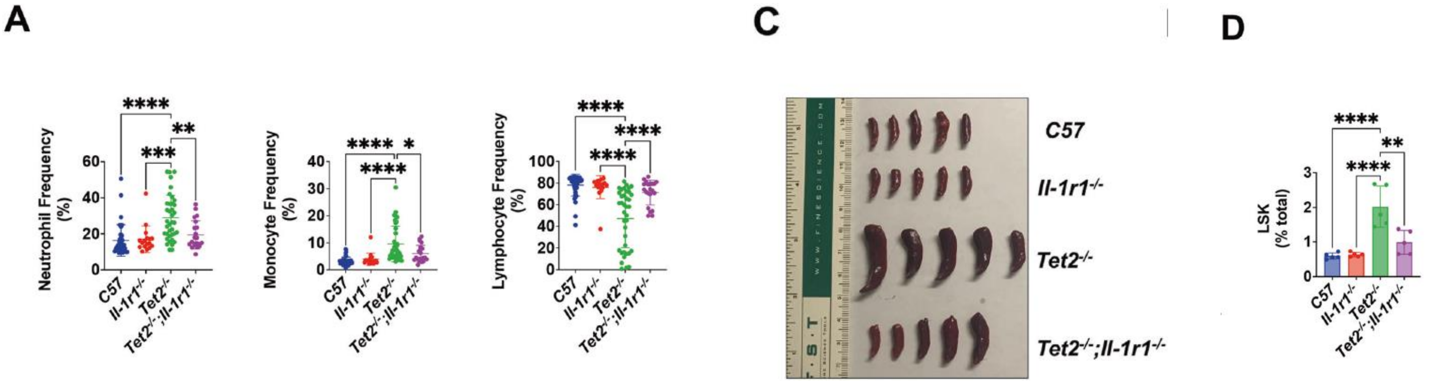
Check for upda

ANIMAL MODELS

Il-1r1 drives leukemogenesis induced by *Tet2* loss

Sarah S. Burns[1,2,3], Ramesh Kumar[3,4], Santhosh Kumar Pasupuleti[3,4], Kaman So[5], Chi Zhang[2,6] and Reuben Kapur[2,3,4,7,8,9]

Leukemia (2022) 36:2531–2534; https://doi.org/10.1038/s41375-022-01665-3



→ Tet2-/-;Il-1r1-/- mice demonstrated a correction of myeloid cell elevation, lymphocyte suppression, spleen size, and HSPC levels.

Extended Context: MPN JAK2-V617F mouse model findings

nature communications

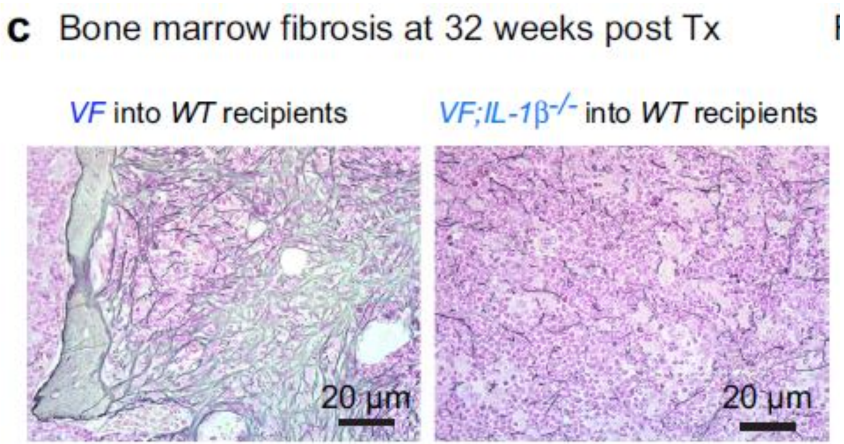
Article https://doi.org/10.1038/s41467-022-32927-4

Inhibition of interleukin-1β reduces myelofibrosis and osteosclerosis in mice with *JAK2*-V617F driven myeloproliferative neoplasm

Received: 8 July 2021

Accepted: 24 August 2022

Shivam Rai[1], Elodie Grockowiak[2,3,4], Nils Hansen[1], Damien Luque Paz[1], Cedric B. Stoll[1], Hui Hao-Shen[1], Gabriele Mild-Schneider[1], Stefan Dirnhofer[5], Christopher J. Farady[6], Simón Méndez-Ferrer[2,3,4] & Radek C. Skoda[1]



Loss of IL-1β in JAK2-V617F mutant cells reduces MPN symptom burden and myelofibrosis

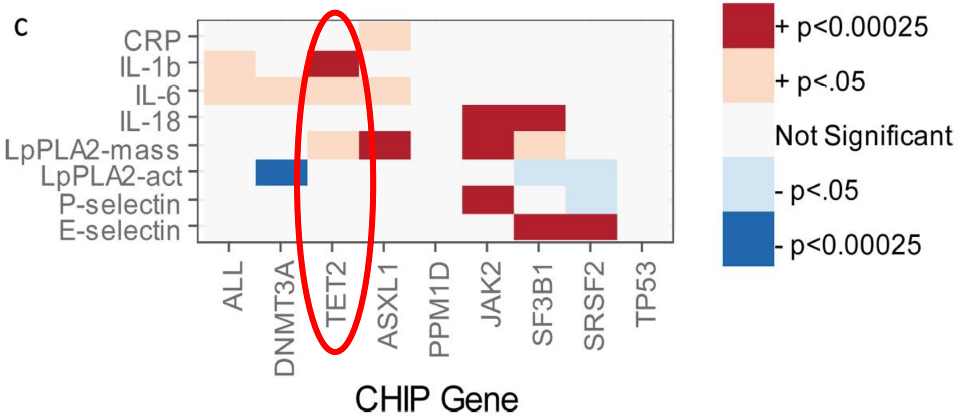
Extended Context:
Evidence for increased IL-1 levels in human Tet2+/- clonal hematopoiesis?

Article | Published: 14 October 2020

Inherited causes of clonal haematopoiesis in 97,691 whole genomes

Alexander G. Bick, Joshua S. Weinstock, [...]Pradeep Natarajan

Nature **586**, 763–768 (2020) | Cite this article



Up to **22,092 individuals from 10 cohorts** were utilized for **this analysis (blood samples).** A set of makers previously implicated in mediating cardiometabolic disease were analyzed including: CD-40, CRP, E-Selectin, ICAM-1, IL-1b, IL-6, IL-10, IL-18, 8-epi PGF2a, Lp-PLA2 mass and activity, MCP1, MMP9, MPO, OPG, P-selectin, TNF-Alpha, TNF-Alpha Receptor 1, TNF-receptor 2.

Extended Context:
Evidence for efficacy of anti-IL-1b therapy in Tet2+/- cardiovascular patients(?)

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, F. Fonseca, J. Nicolau, W. Koenig, S.D. Anker, J.J.P. Kastelein, J.H. Cornel, P. Pais, D. Pella, J. Genest, R. Cifkova, A. Lorenzatti, T. Forster, Z. Kobalava, L. Vida-Simiti, M. Flather, H. Shimokawa, H. Ogawa, M. Dellborg, P.R.F. Rossi, R.P.T. Troquay, P. Libby, and R.J. Glynn, for the CANTOS Trial Group*

N ENGL J MED 377;12 NEJM.ORG SEPTEMBER 21, 2017

10,061 patients with previous myocardial infarction and a high-sensitivity C-reactive protein level of 2 mg or more per liter.

CONCLUSIONS

Antiinflammatory therapy targeting the interleukin-1β innate immunity pathway with canakinumab at a dose of 150 mg every 3 months led to a **significantly lower rate of recurrent cardiovascular events** than placebo, independent of lipid-level lowering. (Funded by Novartis; CANTOS ClinicalTrials.gov number, NCT01327846.)

TET2-Driven Clonal Hematopoiesis and Response to Canakinumab
An Exploratory Analysis of the CANTOS Randomized Clinical Trial

Eric C. Svensson, MD, PhD; Aviv Madar, PhD; Catarina D. Campbell, PhD; Yunsheng He, PhD; Marc Sultan, PhD; Margaret L. Healey, BS; Huilei Xu, PhD; Katie D'Aco, MS; Anita Fernandez, BS; Clarisse Wache-Mainier, BS; Peter Libby, MD; Paul M. Ridker, MD, MPH; Michael T. Beste, PhD; Craig T. Basson, MD, PhD

JAMA Cardiology May 2022 Volume 7, Number 5

RESULTS A total of 338 patients (8.6%) were identified in this subset with evidence for clonal hematopoiesis. *TET2* were more common than *DNMT3A* (119 variants in 103 patients vs 86 variants in 85 patients)

CONCLUSIONS AND RELEVANCE These results are consistent with observations **of increased risk for cardiovascular events in patients with CHIP** and raise the **possibility that those with *TET2* variants may respond better to canakinumab than those without CHIP**. Future studies are required to further substantiate this hypothesis.

→ VAF responses not reported

Summary hematopoietic «Inflamm-Ageing»:

Evidence that Inflammation is a

- driver of (hematopoietic) ageing via the «microbiome»
- driver of clonal (Tet2+/-) hematopoietic expansion
- potential target to attenuate / reverse hematopoietic (and other tissue?) ageing and clonal expansion
- Secondary effects on tissue homeostasis, microbial defense and cancer evolution TBD

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Patrick Helbling
Stefan Isringhausen


ETH zürich

Emma M.C. Wetter Slack


cnio stop cancer
Centro Nacional de Investigaciones Oncológicas

Fátima Al-Shahrour
Santiago G. Martin


FNSNF Swiss National Science Foundation

StemSysMed
Systems Approach to Hematopoietic Stem Cell Diseases

krebsliga